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Genomic imprinting in the development and evolution of psychotic spectrum conditions

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ABSTRACT

I review and evaluate genetic and genomic evidence salient to the hypothesis that the development and evolution of psychotic spectrum conditions have been mediated in part by alterations of imprinted genes expressed in the brain. Evidence from the genetics and genomics of schizophrenia, bipolar disorder, major depression, Prader-Willi syndrome, Klinefelter syndrome, and other neurogenetic conditions support the hypothesis that the etiologies of psychotic spectrum conditions commonly involve genetic and epigenetic imbalances in the effects of imprinted genes, with a bias towards increased relative effects from imprinted genes with maternal expression or other genes favouring maternal interests. By contrast, autistic spectrum conditions, including Kanner autism, Asperger syndrome, Rett syndrome, Turner syndrome, Angelman syndrome, and Beckwith-Wiedemann syndrome, commonly engender increased relative effects from paternally expressed imprinted genes, or reduced effects from genes favouring maternal interests. Imprinted-gene effects on the etiologies of autistic and psychotic spectrum conditions parallel the diametric effects of imprinted genes in placental and foetal development, in that psychotic spectrum conditions tend to be associated with undergrowth and relatively-slow brain development, whereas some autistic spectrum conditions involve brain and body overgrowth, especially in foetal development and early childhood. An important role for imprinted genes in the etiologies of psychotic and autistic spectrum conditions is consistent with neurodevelopmental models of these disorders, and with predictions from the conflict theory of genomic imprinting.

Key words: schizophrenia, psychosis, autism, genomic imprinting, evolution, genomic conflict.

CONTENTS

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I. INTRODUCTION

Analyses of the genetic basis of major disorders of human social cognition, including schizophrenia, bipolar disorder, major depression, and autism, have been characterised by difficulties in replication and small effect sizes (Abdolmaleky, Thiagalingam & Wilcox, 2005; Bacchelli & Maestrini, 2006; Karayiorgou & Gogos, 2006; Norton, Williams & Owen, 2006). A number of genes have recently been reliably associated with these disorders (e.g. Santangelo & Tsatsanis, 2005; Norton *et al.*, 2006), but there is a growing realization that substantial progress is best facilitated by studies that integrate genetic data with aspects of neurophysiology, neuroanatomy, cognition, and behaviour (Goldberg & Weinberger, 2004). The only major discipline largely missing from integrative, genetically-based studies of mental disorders is evolution (but see Crow, 1995*a*,*b*, 1997, 2004; Horrobin, 1998*a*,*b*, 2001). The general absence of evolutionary biology from molecular psychiatry may be due to the history of the field as empirically driven (Keller & Miller, 2006) and a lack of consensus concerning how psychiatric conditions can be understood in terms of dysfunction in adaptive mechanisms, such as components of the 'social brain' in schizophrenia (Burns, 2004, 2006) or cognitive sexual differentiation in autism (Baron-Cohen, Knickmeyer & Belmonte, 2005). The usefulness of evolutionary biology in this field may be gauged by the insight it can provide into the genetic and physiological bases of mental disorders, by directing research along productive pathways.

Herein I review the genetic, epigenetic and genomic evidence salient to a role for genomic imprinting in the development of psychotic spectrum conditions (Marneros & Akiskal, 2006; Badcock & Crespi, 2006; Crespi & Badcock, 2008). I first provide an overview of the phenotypic features and genetic basis of psychotic spectrum conditions. Next, I describe a recently developed model, based on alterations in imprinted genes as important contributing causes to the development of autism and psychosis (Badcock & Crespi, 2006; Crespi & Badcock, 2008). By this hypothesis, psychosis and autism can be broadly characterised as spectra of conditions mediated in part by imbalances towards increased relative expression or activity of maternally expressed and paternally expressed imprinted genes, respectively (Crespi & Badcock, 2008). Third, I describe the features of imprinted genes pertinent to evaluating the hypothesis in the context of Haig's (2000*a*, 2004*a*) conflict theory for the evolution and functions of imprinted genes. The next section is devoted to reviewing evidence regarding the roles of genomic imprinting in polygenic, oligogenic, chromosomal, and single-gene effects in the development and forms of psychosis. A similar analysis for the etiology of autism was published by Badcock & Crespi (2006), and Schanen (2006) provides additional evidence of a role for imprinting effects in the etiology of autism.

II. THE NATURAL HISTORY AND GENETICS OF PSYCHOSIS

Psychosis is literally a disordering of the psyche (Crow, 1995*a*; Tamminga & Holcomb, 2005). In schizophrenia, such disordering commonly involves delusions and auditory hallucinations, loss of coherence and logic in thought and discourse, and emotionality ('affect') inappropriate to social context (Fig. 1A). Delusions usually engender some combination of paranoia, over-interpretation of external events with reference to impact on the self, obsessions, or grandiosity (e.g. Baethge *et al.*, 2005; Niehaus *et al.*, 2005). Auditory hallucinations, a primary symptom found in over

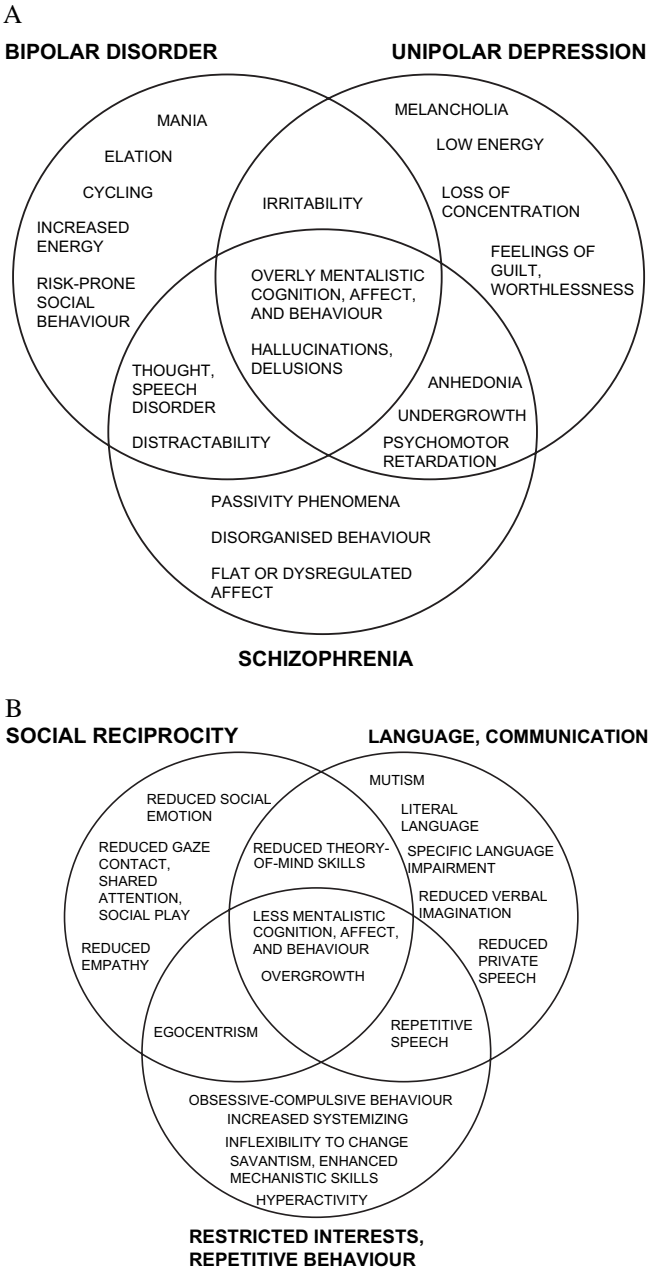

Fig. 1. (A) Depiction of the psychotic spectrum in terms of its three main conditions, schizophrenia, bipolar disorder, and major depression, that grade into one another, and into normality, and exhibit partial overlap in their phenotypic expression and genetic underpinnings. (B) Visualization of the autistic spectrum in terms of three suites of traits, the DSM-IV criteria for autism, that partially overlap in their phenotypic expression and genetic underpinnings.

60% of people diagnosed with schizophrenia, are also common in bipolar disorder, which involves cycling between manic and depressive states (Baethge *et al.*, 2005). Bipolar disorder and major depression also involve other psychotic symptoms, as well as symptoms related to dysregulated emotionality (Boks *et al.*, 2007b).

Schizophrenia, bipolar disorder and major depression are not discrete disorders (Crow, 1995*a*; 1998; Horrobin, 1998*a*; Hamshere *et al.*, 2005; Kempf, Hussain & Potash, 2005; Peralta & Cuesta, 2005; Schürhoff *et al.*, 2005)(Fig. 1A). Their symptoms grade into one another, with some intermediate conditions involving combinations of psychotic, affective and manic features, and they share underlying genetic risk factors to an increasingly recognised degree (Salem & Kring, 1998; van Os *et al.*, 1999; Craddock & Forty, 2006; Blackwood *et al.*, 2007). Specific symptoms of schizophrenia, such as auditory hallucinations and delusions, are also common in non-clinical settings (Bentall, 2003). Indeed, a continuous scale of 'schizotypy', schizophrenia-like cognition, runs from schizophrenia itself into so-called normality (Freedman *et al.*, 2002; Rossi & Daneluzzo, 2002; Mata *et al.*, 2003; Mason *et al.*, 2004), and some schizotypical traits such as belief in supernatural beings (and other aspects of 'magical ideation') are taken for granted in modern society.

Like autistic spectrum conditions (Fig. 1B, Table 1), psychotic spectrum conditions are highly heterogeneous phenotypically (e.g. Niehaus *et al.*, 2005). For example, multivariate analyses of schizophrenia symptoms indicate a useful subdivision of the condition into three main categories: 'positive' symptoms (e.g. hallucination, delusion, and paranoia), 'negative' symptoms (e.g. loss or alteration of emotional affect, loss of will, and loss of pleasure-seeking), and cognitive or 'disorganised' symptoms (e.g. incoherent speech, perseveration) (Tamminga & Holcomb, 2005; Boks *et al.*, 2007*b*). Schizophrenia and bipolar disorder exhibit a lifetime prevalence of 1-3% (Crow, 1993; Horrobin, 1998*a*; Tamminga & Holcomb, 2005), across virtually all cultures and racial groups, and they are considered unique to humans, in contrast to most other major psychiatric conditions which appear to exhibit non-human equivalents (Jablensky *et al.*, 1992; Crow, 1995*a*, 1997; Horrobin, 1998*a*).

Herein, I refer to schizophrenia, bipolar disorder, major depression and several other conditions simply as the psychotic spectrum (Table 1), in keeping with the term 'autistic spectrum' used for Kanner (infantile) autism, Asperger syndrome, Rett syndrome, and some other conditions (Table 1). I thus refer to 'psychosis' throughout this paper in a general sense as disordered cognition, emotionality, or both, commonly involving some component of positive symptoms such as paranoia, delusions, auditory hallucinations, and disordered thought or mood, as found primarily in schizophrenia, schizoaffective disorder, bipolar disorder, and major depression. The 'psychotic-affective spectrum' would be a more accurate term, though less concise. Like the autistic spectrum, conditions on the psychotic spectrum exhibit strong genetic components to their expression, but with many genes involved and different combinations of these genes capable of contributing to the phenotypes (Rapoport *et al.*, 2005; Tamminga & Holcomb, 2005). Autism, schizophrenia, schizotypy, bipolar disorder, and major depression usually exhibit a polygenic and idiopathic (cause unknown) basis (Crespi 2009), but they may also be associated with specific syndromes involving losses or gains of genes or chromosomal regions, or alterations to imprinting (Table 1). 'Autistic' behaviour has

Table 1. The suite of conditions that characterizes the psychotic spectrum and the autistic spectrum

Condition	Cause	References
PSYCHOTIC SPECTRUM		
Schizophrenia	Idiopathic	Tamminga & Holcomb (2005)
Bipolar disorder	Idiopathic	Craddock & Forty (2006)
Major (unipolar) depression	Idiopathic	Craddock & Forty (2006)
Schizotypal personality disorder	Idiopathic	Claridge (1997)
Klinefelter syndrome	47,XXY in males	Boks *et al.* (2007*a*)
Velocardiofacial syndrome	Deletion at 22q11.2	Feinstein *et al.* (2002)
Prader-Willi syndrome	Imbalanced imprinting,15q11-q13	Soni *et al.* (2007, 2008)
Dyslexia	Idiopathic	Condray (2005)
AUTISTIC SPECTRUM		
Kanner (infantile) autism	Idiopathic	Happé *et al.*, (2006)
Asperger syndrome	Idiopathic	Frith (2004)
Rett syndrome	Mutations in *MeCP2* gene	LaSalle *et al.*, (2005)
Angelman syndrome	Imbalanced imprinting,15q11-q13	Cohen *et al.* (2005)
Beckwith-Wiedemann syndrome	Imbalanced imprinting, chromosomes 7,11	Kent *et al.* (2008)
Fragile X syndrome	Lost expression of *FMR1* gene	Belmonte & Bourgeron (2006)
Turner syndrome	45,X in females	Skuse (2005)
Williams syndrome region, duplication	Duplication at 7q11.23	Berg *et al.* (2007)
Potocki-Lupski syndrome	Duplication at 17p11.2	Potocki *et al.* (2007)
Specific language impairment	Idiopathic	Conti-Ramsden *et al.* (2006)
Hyperlexia	Idiopathic	Newman *et al.* (2007)

been described for Klinefelter syndrome, velocardiofacial syndrome and Prader-Willi syndrome, but these psychiatric phenotypes apparently reflect personality premorbid for schizophrenia or aspects of negative schizotypy and they are not underlain by autistic-spectrum neurological or physiological traits (Eliez 2007; Feinstein and Singh 2007; Crespi & Badcock 2008). As for autism, the psychotic spectrum can be considered as a highly convergent set of conditions, with strong genetic, epigenetic and environmental heterogeneity yielding a relatively limited range of phenotypes (Keverne, 1999; Seeman *et al.*, 2005; Badcock & Crespi, 2006; Crespi, 2009). By the hypothesis discussed here, one underlying cause of these convergent phenotypes is dysregulation of imprinted genes that influence cognition and behaviour.

III. THE IMPRINTED BRAIN THEORY OF PSYCHOSIS AND AUTISM

Genomic imprinting refers to epigenetic silencing of alleles in an individual according to their parent-of-origin (Haig 2000*b*, 2004*a*,*b*; Burt & Trivers, 2006)(Fig. 2). The conflict theory of imprinting (Haig, 2000*a*,*b*, 2004*b*) posits that such genes are selected to be expressed or silenced depending on their parent-of-origin and their effects on the growth and fitness of mothers, offspring, and other asymmetrically-related kin (Haig, 2000*a*,*b*; de la Casa-Esperón & Sapienza, 2003; Day & Bonduriansky, 2004; Wilkins, 2005). Thus, for a gene that enhances offspring fitness at a cost to mothers and other maternal kin (such as by enhancing foetal growth), the paternally inherited allele should be expressed but the maternal copy should be silenced, *via* methylation or histone modifications (Haig, 2000*a*,*b*). Conversely, maternally inherited alleles that restrain such 'selfish' effects are selected to be expressed, while such paternal alleles are silenced. This differential imprinting of alleles is due ultimately to intragenomic conflict, driven primarily by lower genetic relatedness among a mother's offspring for paternally inherited genes than for maternally inherited

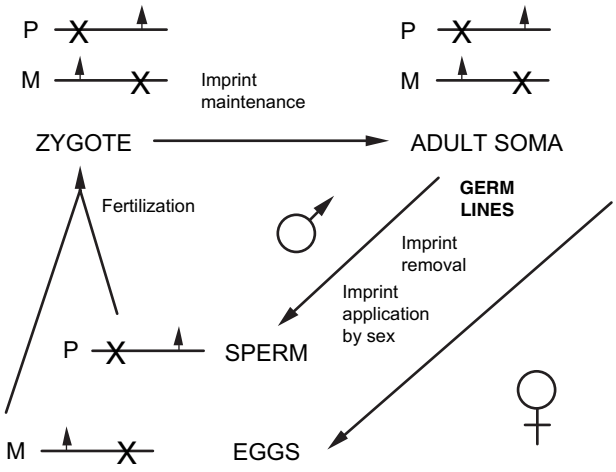

Fig. 2. Depiction of how genomic imprinting involves the expression of a gene or transcript from only the paternally inherited allele or the maternally inherited allele. Imprints are actively maintained during somatic development (or during particular stages of development), then erased and reset (according to the sex of the individual) during gametogenesis. Two hypothetical loci are shown, the left-hand one maternally expressed (with an arrow) and paternally imprinted (as shown by an X), and the other paternally expressed (maternally imprinted).

genes under an evolutionary history that deviates from strict monogamy (Burt & Trivers, 2006).

The conflict theory of genomic imprinting has been supported by an extensive body of genetic and physiological evidence, and it provides the only comprehensive theory for the observed patterns of imprinted gene expression and function in humans, mice, plants and other organisms (Tycko & Morison, 2002; Cattanach, Beechy & Peters, 2004; Haig, 2000*a*,*b*; 2004*a*; Plagge *et al.*, 2004; Weinstein *et al.*, 2004; Chen *et al.*, 2004; Kelsey, 2007). Most studies of genomic imprinting in humans have focused on genes expressed during placental and embryonic development, where many known imprinted genes exert their effects, and many such genes are known to cause placental and foetal growth enhancement or suppression (Goos & Silverman, 2001; McMinn *et al.*, 2006; Angiolini *et al.*, 2006; Wagschal & Feil, 2006). The dynamically balanced, 'tug-of-war' nature of genomically imprinted systems in placentation, with paternally expressed imprinted genes enhancing growth but maternally expressed genes repressing it, generates conditions where disruption of imprinted gene expression may result in functionally opposite disorders of pregnancy, such as foetal growth restriction *versus* foetal overgrowth (Tycko, 2006). Indeed, such diametric conditions are a general property of systems mediated by imprinted genes, which can be perturbed genetically or epigenetically towards increased effects from alleles that are normally either paternally or maternally expressed.

Most known imprinted genes are expressed during placentation, but a considerable number are expressed primarily or entirely in the brain (Isles & Wilkinson, 2000; Tycko & Morison, 2002; Davies, Isles & Wilkinson, 2001, 2005; Davies *et al.* 2007, 2008; Kishino, 2006; Wilkinson, Davies & Isles, 2007). In theory, this pattern of tissue expression fits with a role for genomic conflict in imprinting, given that both the placenta and brain play key roles in the transfer of fitness-limiting resources between individuals that bear genes with partially divergent interests (Haig, 1993, 1996, 1999; Goos & Silverman, 2001; Crespi & Semeniuk, 2004; Burt & Trivers, 2006). Despite the central role of imprinted genes in development of the placenta and foetus, and evidence that the brain represents a strong secondary nexus of imprinted-gene effects on development, previous reviews of brain-expressed imprinted genes (e.g. Davies *et al.*, 2007, 2008) have not evaluated predictions of the conflict theory of imprinting in any comprehensive manner. By analogy with placental conditions showing diametric effects, some cognitive conditions are expected, by this theory, to exhibit phenotypes that engender increased *versus* decreased demands on the mother. Badcock & Crespi (2006) and Crespi & Badcock (2008) describe genetic, physiological, neurological, psychological and behavioural evidence relevant to the hypothesis that the development of autism is mediated in part by imbalances in brain development that lead to increased effects of paternally expressed genes at loci subject to imprinting, relative to maternally expressed ones (Fig. 3). Such paternally expressed genes are expected not just to enhance early growth, but also to drive cognition and behaviour towards more-demanding phenotypes (Haig, 2000*b*; 2004*b*; Baron-Cohen *et al.*, 2005), as seen clearly in Asperger syndrome where reciprocal social behaviour is impaired and self-oriented cognition and behaviour predominate (Rinehart *et al.*, 2002; Fitzgerald, 2004, pp. 30-41; Constantino & Todd, 2005; Badcock & Crespi, 2006), and in Beckwith-Wiedemann syndrome, which is caused by biases towards increased relative effects of paternally expressed imprinted genes, and involves overgrowth and an increased incidence of autism (Eggermann, Eggermann & Schönherr, 2008; Kent *et al.*, 2008).

The psychotic spectrum involves a large suite of developmental, neuroanatomical, cognitive, and behavioural traits, that can be interpreted as diametric opposites to those observed on the autistic spectrum (Crespi & Badcock, 2008). This pattern, and evidence for reduced fitness demands on mothers in the development of relatively schizotypal offspring (Crespi & Badcock, 2008), imply that the etiology of psychosis is underlain in part by imbalances in brain development that lead to increased effects of

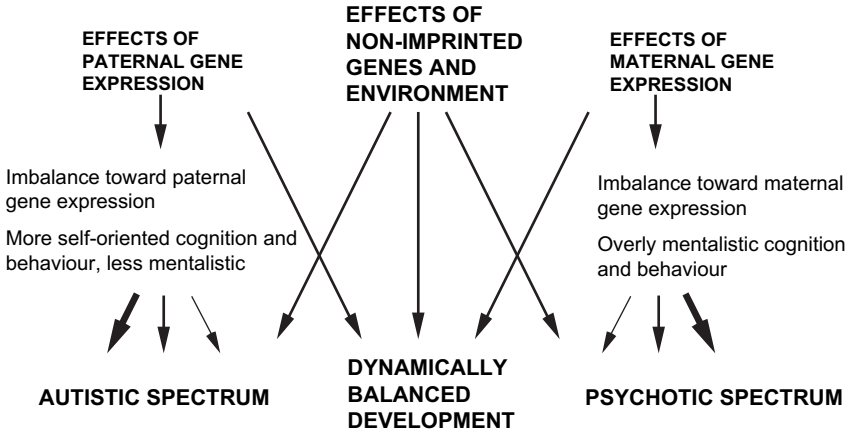

Fig. 3. The imprinted brain model of psychotic spectrum and autistic spectrum conditions, considered in terms of how effects of imprinted genes, non-imprinted genes, and the environment mediate neurodevelopment.

maternally expressed genes at loci subject to imprinting, relative to paternally expressed ones (Fig. 3). As for conditions of gestation that are mediated by imprinting or parent-offspring conflict, relatively large genetic and epigenetic deviations are expected to be pathological and reduce the inclusive fitness of both mother and child; by contrast, small deviations may either benefit the child at a cost to the mother (for imprinted genes with a relative paternal bias in expression), or benefit the mother at a cost to the child (with a maternal bias) (e.g. Naeye, 1981; Moore, 1997; Haig, 1993, 1999; Oudejans *et al.*, 2004; Tycko, 2006; Petry, Ong & Dunger, 2007). The degree to which such imprinted-gene effects on the development of psychotic spectrum conditions represent pathological pleiotropic effects of undergrowth due to maternal-gene biases, or direct effects of dysregulated brain-expressed imprinted genes on neurodevelopment, cognition and behaviour that benefit maternal interests, remains unclear (Abel, 2004; Crespi & Badcock, 2008). The imprinted brain hypothesis is fully compatible with current neurodevelopmental models of autism and schizophrenia (Rapoport *et al.*, 2005; Geschwind & Levitt, 2007), whereby variation in many genes contributes to altered prenatal brain development that manifests during childhood or early adulthood, but it posits a specific role for dysregulation of dynamically balanced maternal-gene effects and paternal-gene effects as brain and behaviour develop (Fig. 3).

The imprinted brain theory of autistic and psychotic spectrum conditions can also be visualised with reference to the concepts of the Kevernian paternal (limbic) brain and maternal (mainly neocortical) brain, the brain regions showing differential expression of paternally expressed imprinted genes and maternal imprinted genes respectively, in chimeric mice (Allen *et al.*, 1995; Keverne *et al.*, 1996; Keverne, 2001; Wilkinson *et al.*, 2007)(Fig. 4). In these mice, cells with exclusively paternal gene expression differentially contribute to development of the limbic system (the hypothalamus, amygdala, and other structures of the emotional 'paternal' brain that mediates basic drives such as hunger, fear and aggression), and cells with exclusively maternal gene expression differentially proliferate in the necortex (the executive 'maternal' brain involved in language, social reciprocity, planning, and behavioural inhibition). By the conceptualization of Crespi & Badcock (2008), increased paternal-brain effects and a relatively normal maternal brain are associated with Asperger syndrome, whereas decreased maternal-brain effects, with relatively normal or increased paternal-brain function, characterize Kanner (infantile) autism, which involves a notable degree of mental retardation. By contrast, positive schizotypy and positive-symptom schizophrenia are associated in this model with increased relative maternal-brain effects and a relatively normal paternal brain, whereas decreased paternal-brain functions, and relatively normal or increased maternal-brain effects, characterize negative schizotypy, negative-symptom schizophrenia, and major depression. This heuristic model represents a considerable over-simplification but it provides a useful framework for conceptualising the roles of imprinted genes in the brain, especially the tendency for paternally-expressed imprinted genes to impact differentially the development and function of the hypothalamus (Davies *et al.*, 2008), and for impaired development and function of the hypothalamus to be associated with the etiology of psychosis in some conditions, such as Prader-Willi syndrome (Davies *et al.*, 2007; Soni *et al.*, 2008)

I have collected and synthesised available information on imprinted-gene effects in psychotic spectrum conditions and their developmental, physiological and neurological bases. The main goal is to evaluate a core prediction of the conflict theory of imprinting for understanding social behaviour and disorders of the human social brain: that brain-expressed imprinted genes mediate, to some degree, the neurodevelopmental underpinnings of schizophrenia and other psychotic-spectrum conditions. In particular, this theory predicts that psychotic spectrum conditions should be associated with some combination of decreased expression or activity of paternally expressed genes, or increased expression or activity of maternally expressed genes. Evaluation of these hypotheses requires consideration of the special nature of imprinted genes.

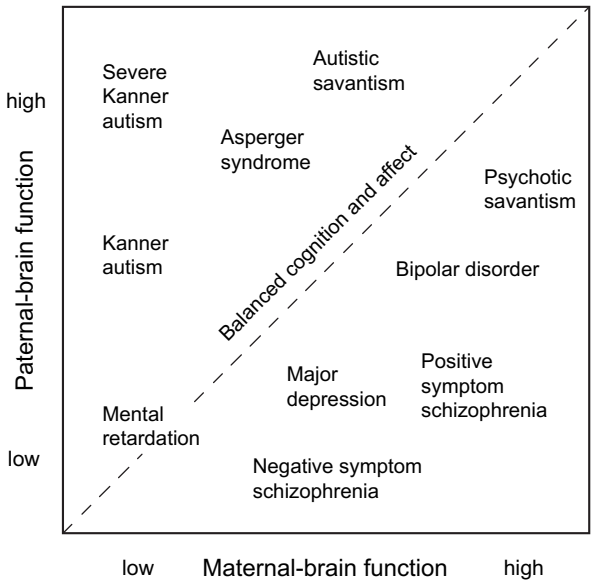

Fig. 4. Depiction of the imprinted brain theory of psychotic spectrum and autistic spectrum conditions, whereby the different conditions can be visualised by their hypothesized positions and degrees of deviation from a line representing normal, balanced cognition and affect. This model is highly conceptual and heuristic. Crespi and Badcock (2008) discuss autistic and psychotic savantism.

IV. THE NATURE OF IMPRINTED GENES

Alterations of imprinted genes may be epigenetic, genetic or genomic in origin (Zogel *et al.*, 2006; Heijmans *et al.*, 2007), and they may take place during neurodevelopment (especially in the foetal stage when many key events in

brain morphogenesis take place) or later, *via* influences on aspects of synaptic transmission, pruning, or plasticity. Such alterations may involve imbalances towards increased phenotypic effects of either maternally expressed or paternally expressed genes, *via* overexpression of these genes or higher activity of their products, or *via* reduced gene expression or activity. For example, a bias towards maternal expression may be due to increased expression of a maternally expressed imprinted gene, decreased expression of a paternally expressed imprinted gene, or both.

Imprinted genes are unusual in several important ways. First, genes may be imprinted only in certain brain regions or cell lineages (Kishino, 2006), and at particular stages during development, such as the foetal stage (e.g. Weinstein, 2001). Imprinting status may also be polymorphic within populations (such that imprinting abnormalities are familial), and paternal *versus* maternal allele expression need not be all or nothing (Weinstein, 2001; de la Casa-Esperón & Sapienza, 2003; Sandovici *et al.*, 2003; Buettner *et al.*, 2004; Croteau *et al.*, 2005). The direction (paternal *versus* maternal) of imprinting can also be specific to multiple isoforms generated from a given gene, such that maternal, paternal, and biallelic expression of different splicing variants can be produced by the same locus (e.g., Weinstein *et al.*, 2007).

Second, most imprinted genes are highly pleiotropic and epistatic in their effects (Morison, Ramsay & Spencer, 2005; Varrault *et al.*, 2006), and many are involved in growth promotion or retardation, often *via* effects on growth factors, growth-factor-binding proteins, or glucose or lipid metabolism (Chen *et al.*, 2005; Charalambous, da Rocha & Ferguson-Smith, 2007). The expression or silencing of imprinted genes may be driven by effects of non-imprinted genes and 'imprinter' genes (genes that apply, maintain, or remove imprints) (Wilkins, 2005), and their developmental and metabolic effects may cause non-imprinted genes to act imprinted, as for *IGFI* (Cattanach *et al.*, 2004) or *HTR2C* (Kishore & Stamm, 2006). Moreover, imprinted and non-imprinted genes can interact in the determination of disease phenotypes, such as in Beckwith-Weidemann syndrome (Murrell *et al.*, 2004). Although imprinted genes are present at low frequency (roughly 1%) among protein-coding genes in the genome, and apparently at about this frequency for genes that generate regulatory, non-coding RNAs (Royo *et al.*, 2006; Royo & Cavaillé, 2008), many such genes exert strong, diverse effects on growth and development from multiple isoforms and promotors (e.g. Riedel, 2004), and within a metabolic pathway 'the influence of a single gene by each of the parental genomes may be sufficient for parent-offspring conflict to be enacted' (Smith, Garfield & Ward, 2006, p. 279).

Third, imprinting patterns are established in male and female gametes each generation, and perpetuated in an allele-specific manner after zygote formation (Fig. 2). Imprints are thus inherited somatically but with a high mutation rate compared to nucleotides, where mutation refers to epigenetic modification of CpG islands (genomic regions with high frequencies of CG dinucleotides) *via* methylation, and effects on histone modifications that modulate gene expression (Jacob & Moley, 2005; Wilkins, 2005). Indeed, genomic imprinting provides a hypothesis for the strong paternal age effects on schizophrenia risk (Malaspina, 2001; Sipos *et al.*, 2004; Malaspina *et al.*, 2005) and autism risk (Lauritsen, Pedersen & Mortensen, 2005; Reichenberg *et al.*, 2006), given that mutations during spermatogenesis appear insufficient to explain such patterns (Farrer *et al.*, 1992; Reik *et al.*, 1993; Tiemann-Boege *et al.*, 2002), and unlike oocytes, spermatogonia undergo many mitotic divisions after imprints are applied (Bestor, 2003). Methylation status can also be affected by diet, such as in L-methionine influences on expression of the *RELN* gene, some epigenetic alterations such as chromatin modifications exhibit environmentally-induced positive and negative feedbacks that result in shifts between alternative states, and some environmentally induced epigenetic modifications can persist across generations (Jacob & Moley, 2005). The genotype of the mother can also influence the epigenotype of her offspring *via* factors present in egg cytoplasm, resulting in parent-of-origin effects that are not due to imprinting (Pickard *et al.*, 2001) but should also engender genomic conflict.

Finally, imprinted genes exert especially important effects on the expression of a wide range of metabolic, reproductive and psychiatric conditions (Nicholls, 2000; Davies *et al.*, 2001; Morison *et al.*, 2005; Charalambous *et al.*, 2007; Crespi & Badcock, 2008) for several reasons: (1) they are functionally haploid, such that mutant alleles are exposed more directly to selection, (2) alterations of imprinting can lead to complete loss of gene function, or doubling of expression, which represent extreme mutational effects, (3) altered expression can be due not just to mutations, but also to epigenetic changes or alterations in the mechanisms of imprint application, maintenance and removal (Wilkins, 2005), (4) such genes are often developmental, such that the effects of altered expression can amplify during growth and differentiation, (5) many imprinted genes are directly involved in systems of cell proliferation, apoptosis, and differentiation, such that the effects of altered expression are extensive, (6) the most common tissue for expression of imprinted genes is the placenta (Tycko & Morison, 2002; Ferguson-Smith *et al.*, 2006), and placental effects on foetal development often have life-long consequences for physiological systems (Gluckman *et al.*, 2005; Isles & Humby, 2006), and (7) imprinted genes are subject to intragenomic conflicts, which may generate tugs-of-war over resources or antagonistic coevolution, both of which can result in deleterious byproducts (Haig, 2004*b*; Burt & Trivers, 2006).

Known imprinted genes have been catalogued by Morison *et al.* (2005), candidate murine imprinted genes from gene-expression studies [which include non-coding DNAs, but also non-imprinted genes regulated by imprinted genes, and so have limited reliability (Ruf *et al.*, 2006)] have been compiled by Nikaido *et al.* (2004), coding genes predicted to be imprinted, from analysis of local genomic structure, are listed by Allen *et al.* (2003), Luedi, Hartemink & Jirtle (2005) and Luedi *et al.* (2007), and the known physiological functions of imprinted genes are described in Tycko & Morison (2002). It is also important to note that parent-of-origin effects on disease risk may be

caused not just by imprinting, but also by effects of mitochondrial DNA, immunological interactions in pregnancy, recombination rates differing between the sexes, maternal effects (Hager, Cheverud & Wolf, 2008) or germline mutations biased by sex. Verification of imprinted gene status, for a given tissue at a given stage of development, requires analyses of gene expression coupled with data on parental origin of the alleles (Luedi *et al.*, 2007).

V. OLIGOGENIC, CHROMOSOMAL AND X-LINKED EFFECTS ON RISK OF PSYCHOSIS AND AUTISM

Oligogenic and chromosomal effects on neurodevelopmental disorders involve gains or losses of a contiguous set of genes. These gains or losses can be associated with imprinting effects given the known or predicted locations and expression patterns of genes subject to imprinting. Table 2 summarises the available information on effects of imprinting, and links to disorders, for three of the main sets of oligogenic, chromosomal and X-linked disorders associated with psychosis and autism: Prader-Willi and Angelman syndromes, Klinefelter and Turner syndromes, and Rett and PPM-X syndromes. These disorders are discussed in detail below.

(1) Prader-Willi and Angelman syndromes

Prader-Willi syndrome (PWS) has three main genetic causes: (1) a paternally inherited deletion of a region on chromosome 15 (15q11-q13) that contains multiple imprinted genes, (2) disomy (two copies) of maternal chromosome 15, or (3) a defect in the Prader-Willi region imprinting centre, which disrupts the application of imprints (Nicholls & Knepper, 2001; Goldstone, 2004; Whittington & Holland, 2004; Bittel & Butler, 2005). The common element in all three cases is loss of expression for (normally) paternally expressed imprinted genes in this region.

Before the usual age of weaning at age two or three, Prader-Willi syndrome involves lack of appetite, poor suckling ability, a weak cry, inactivity, and sleepiness; by contrast, after this age, it involves extreme and unselective overeating, as well as various obsessive-compulsive behaviours (Dykens, Modapp & Finucane, 2000; Holland, Whittington & Hinton, 2003; Whittington & Holland, 2004). Haig & Wharton (2003) have suggested that these features of Prader-Willi syndrome reflect extreme manifestations of traits that benefit the mother by making the baby less demanding on her resources, both before weaning (when food intake and energetic demands are reduced) and after weaning (when ingestion of any solid food available may ease food provisioning). Prader-Willi syndrome also involves growth hormone deficiency and low birth weight (Gillessen-Kaesbach *et al.*, 1995; Goldstone, 2004), which are consistent with increased metabolic effects from maternally expressed imprinted genes, and its primary neurological correlate is dysregulated development of the hypothalamus (Goldstone, 2004, 2006; Hong *et al.*, 2006).

Prader-Willi syndrome engenders a very high incidence (on the order of 50-100%) of psychotic spectrum conditions in adulthood (Boer *et al.*, 2002; Verhoeven, Tuinier & Curfs, 2003; Vogels *et al.*, 2003, 2004), in cases of maternal uniparental disomy as well as paternal deletion (Soni *et al.*, 2007). Soni *et al.* (2008) show that deletion cases are characterised primarily by non-psychotic affective disorders, while disomy cases involve mainly forms of bipolar disorder, sometimes with psychotic symptoms. The genetic differences between disomy and deletion include: (a) higher expression levels of maternally expressed imprinted genes in disomy, for genes in the PWS region, (b) possible haploinsufficiency of non-imprinted genes in this region,

Table 2. Links of psychosis and autism with genetic, genomic, and epigenetic alterations involving imprinted genes at 15q11-q13, the X chromosome, and the *MeCP2* gene

Locus	Link with psychosis	Link with autism
Prader-Willi/ Angelman region at 15q11-q13, with cluster of imprinted genes	High rates of psychosis in Prader-Willi syndrome (due to paternal deletion or maternal duplication of this region) (1-4)	High rates of autism in Angelman syndrome (due to maternal deletion or paternal duplication of this region, notably *UBE3A* loss of expression (5-7)
X chromosome	47,XXX and 47,XXY show high rates of psychosis (8-11)	Turner syndrome (45,X) shows high rates of autism (12-13), low rates of bipolar disorder plus schizophrenia (14)
MeCP2 gene, at Xq28	Some mutations of *MeCP2* in males lead to PPM-X syndrome, which involves psychosis as a core component (15,16)	Many mutations of *MeCP2* in females can lead to Rett syndrome (17,18); *MeCP2* can regulate imprinting (18,19); *MeCP2* alleles have also been linked with idiopathic autism (20-24)

References: (1) Boer *et al.* (2002); (2) Verhoeven *et al.* (2003); (3) Vogels *et al.* (2004); (4) Soni *et al.* (2007, 2008); (5) Peters *et al.* (2004); (6) Trillingsgaard & ØStergaard (2004); (7) Cohen *et al.* (2005); (8) DeLisi *et al.* (1994); (9) DeLisi *et al.* (2005); (10) van Rijn *et al.* (2005); (11) Boks *et al.* (2007*a*); (12) Skuse (2000); (13) Skuse (2005); (14) Mors *et al.* (2001); (15) Cohen *et al.* (2002); (16) Klauck *et al.* (2002); (17) Jedele (2007); (18) LaSalle (2007); (19) Nomura *et al.* (2008); (20) Samaco *et al.* (2004, 2005); (21) Makedonski *et al.* (2005); (22) Shibayama *et al.* (2004); (23) Coutinho *et al.* (2007); (24) Loat *et al.* (2008).

in deletion cases, and (c) complete loss of expression, in disomy, of any paternally expressed genes on chromosome 15 outside the PWS region (Whittington & Holland, 2004; Bittel *et al.*, 2003). Soni *et al.* (2008) suggest that the high rates of affective disorder in Prader-Willi deletion cases are mediated by the absence of paternally expressed imprinted gene product, while the even higher rates of affective and psychotic symptoms in disomy are due to combined effects from loss of paternal gene products and over-expression of one of more maternally expressed imprinted genes, probably *UBE3A*.

The finding of high rates of affective disorders and psychosis in Prader-Willi syndrome, and especially in cases with maternal disomy (which exhibit a greater overall deviation towards maternal-gene influence) supports the hypothesis that excessive effects from maternally expressed imprinted genes, and reduced or absent expression of paternal genes, are involved in the development of psychosis in this syndrome. The roles of specific genes at 15q11-q13 in the development of Prader-Willi syndrome phenotypes remain unclear (Davies *et al.*, 2008), but a role for the necdin gene *NDN* is indicated by the strong expression of this gene in the placenta and hypothalamus (MacDonald & Wevrick 1997; Lee *et al.*, 2005), the functions of necdin in neural development (Lee *et al.*, 2005; Andrieu *et al.*, 2006; Kuwajima, Nishimura & Yoshikawa, 2006) and adipocyte differentiation (Tseng *et al.*, 2005), the phenotypic features of an *NDN*-deficient mouse model (Muscatelli *et al.*, 2000; Andrieu *et al.*, 2006), and its genome-scan and functional linkages with schizophrenia (Fallin *et al.*, 2003; Lee *et al.*, 2005; Le-Niculescu *et al.*, 2007).

The absence of PWS patients with simple single-gene alterations at 15q11-q13, and evidence from mouse models, suggests that the syndrome is underlain not solely by loss of necdin, but by loss of product for two or more paternally expressed genes (Johnstone *et al.*, 2006). Direct evidence for this hypothesis comes from Bischof, Stewart & Wevrick (2007) and Kozlov *et al.* (2007) who found that mice deficient for expression of the paternally expressed imprinted gene *MAGEL2* exhibit neonatal growth retardation, hypotonia, excessive weight gain after weaning, increased adiposity, altered sexual development, and altered circadian rhythms, all traits that recapitulate important features of PWS but are not found in necdin-mutant mouse models of this condition.

A third locus implicated in the development of Prader-Willi syndrome is the HBII-85 cluster of small, non-coding paternally expressed RNAs, which shows loss of expression in several cases resembling Prader-Willi syndrome that are due to paternally inherited translocation breakpoints or deletions localised to this region, with the *NDN* and *MAGEL2* genes apparently unaffected (Wirth *et al.*, 2001; Gallagher *et al.*, 2002; Ding *et al.*, 2005; Sahoo *et al.*, 2008). At least some of the HBII-85 non-coding RNAs appear to regulate alternative mRNA splicing of target genes, and of 104 inferred target genes for these RNAs (Bazeley *et al.*, 2008), five genes exhibit variants that have been associated with schizophrenia (*GRM8*, *IL-2*, *FGFR1*, *CTNNA2/LRRTM1*, and *SLC18A2*)(Takaki *et al.*, 2004; Schwarz *et al.*, 2006; Francks *et al.*, 2007; Jungerius *et al.*, 2007; Talkowski *et al.*, 2008), three genes have been associated with forms of mental retardation (*RPS6KA6*, *CTNND2* and *ZDHHC15*)(Yntema *et al.*, 1999; Medina *et al.*, 2000; Mansouri *et al.*, 2005), and one is an imprinted gene that been associated with risk of Alzheimer's disease (*CTNNA3*)(-Miyashita *et al.*, 2007). These findings suggest that loss of expression of the HBII-85 RNA genes may also be sufficient to cause some or most of the major features of PWS, although the molecular mechanisms require further study. By contrast, loss of expression for imprinted *snoRNA* genes in the *HBII-52* cluster at 15q11-q13 apparently does not play a major role in Prader-Willi syndrome (Runte *et al.*, 2005), despite the observation that one of these RNAs regulates splicing of the serotonin receptor gene *HTR2C* (Kishore & Stamm, 2006), which has been implicated in obesity (e.g. Pooley *et al.*, 2004) and risk of schizophrenia (Castensson *et al.*, 2005).

Fourth, polymorphisms in *UBE3A* and *ATP10C* have been linked with childhood-onset schizophrenia (Sporn *et al.*, 2004), *UBE3A* has been linked with schizophrenia risk (Iossifov *et al.*, 2008) and single-nucleotide polymorphisms of *ATP10C* have been linked with autism (Nurmi *et al.*, 2003). Both the *UBE3A* gene and *ATP10C* at 15q11-q13 are imprinted and maternally expressed in regions of the human brain (Albrecht *et al.*, 1997; Samaco, Hogart & LaSalle, 2005). These observations suggest that the *UBE3A* locus represents a nexus of imprinting conflict that can mediate the expression of both autism and psychosis.

Finally, the presence of psychotic symptoms in a subset of Prader-Willi cases due to paternal deletions has allowed inference of a genetic interval spanning the contiguous *GABRG3* and *OCA2* genes that influences the expression of psychosis (Webb *et al.*, 2008). The *OCA2* gene has been implicated in schizophrenia risk in a recent genome-scan study (Iossifov *et al.*, 2008; see also DeLong 2007), and replicated associations between eye colour (underlain by *OCA2* alleles) and behavioural inhibition (shyness) in childhood (Rosenberg & Kagan, 1987, 1989) suggest pleiotropic effects of this gene on brain and eye development, as for the *PAX6* gene discussed below.

Conditions closely resembling Prader-Willi syndrome can also be caused by a suite of genetic and epigenetic alterations to regions other than 15q11-q13 (Table 3, and Fig. 5). Comparisons of the genetic causes and developmental effects of these diverse alterations with Prader-Willi syndrome mediated by 15q11-q13 provide insight into the molecular-genetic, developmental and physiological etiology of this syndrome, given that different, independent genetic and epigenetic changes result in convergent phenotypes. Thus, the deletions at 1p36, 2q37, 9q34 and 10q26 that result in Prader-Willi phenotypes each contains a gene that is under-expressed in Prader-Willi syndrome due to 15q11-q13 alterations, as does the duplicated region at 3p25.2-p26.2. Most of these genes are expressed in the hypothalamus, and some of them interact with the known paternally expressed imprinted genes *NDN*, *DLK1*, and *HBII-85* snoRNA, or the predicted imprinted genes *NOTCH1* and *SIM2* (Luedi *et al.*, 2007)(Fig. 5); taken together, these findings suggest that Prader-Willi phenotypes are mediated by a suite of alternative modifications to a developmental network centred on the hypothalamus and influenced by altered expression of

Table 3. Evidence that Prader-Willi syndrome and related phenotypes are caused by a wide range of genetic, epigenetic or genomic alterations that affect development of the hypothalamus, the nexus of the paternal brain

Location and alteration causing PWS phenotype	Association with 15q11-q13 or imprinting	Comments
1p36 deletion (1,2)	Gene *GABRD* in deletion region, also down-regulated in PWS mediated by 15q11-q13 (3)	*GABRD* expressed in hypothalamus (4), considered 'good candidate' for psychiatric phenotype of 1p36 deletion subjects (5); *GABRD* upregulated in Fragile X syndrome (6)
2q37 deletion (7)	Gene *HTR2B* in region, also downregulated in PWS mediated by 15q11-q13 (3)	*HTR2B* expressed in hypothalamus, involved in serotonin metabolism and hyperphagia (8)
3p25.2-p26.2 duplication (9)	Gene *OXTR* in region, also downregulated in PWS mediated by 15q11-q13 (3)	*OXTR* expressed throughout brain, involved in social behavior, food intake (10); *OXTR* coexpressed with imprinted *SNRPN* gene at 15q12 (11)
6q16-q21 deletion, translocation (12,13)	*SIM1* gene in region	*SIM1* essential for development of hypothalamus in mice, regulates food intake (14); *SIM1* interacts with *NDN* product necdin (15) and with product of predicted imprinted gene *SIM2* (16); *SIM2* mediates neuroendocrine secretion (17)
9q34 deletion (18)	Gene *NOTCH1* in deletion region, downregulated in 15q11-q13 PWS (3); *EHMT1* gene also in this region, causes major features of 9q34 syndrome (19,20)	*NOTCH1* expressed in hypothalamus (21), regulates neurogenesis (22), interacts with paternally expressed imprinted gene *DLK1* (23); *NOTCH1* variants associated with risk of bipolar disorder and schizophrenia (24); *EHMT1* gene involved in histone methylation processes that regulate imprinting (19,20,25)
10q26 deletion (26,27)	Gene *ADAM8* in region, also downregulated in 15q11-q13 PWS (3); Imprinted *INPP5F_v2* gene in region (28,29)	*ADAM8* essential for function of *CHL1*, which regulates neurite outgrowth (30) and exhibits variants linked with schizophrenia risk (31); *INPP5F_v2* brain-expressed but function unknown
Maternal uniparental disomy 14, *DLK1* (14q32) alteration (32,33)	Lost or reduced expression of paternally-expressed gene *DLK1* (32-35)	*DLK1* and *NDN* coexpressed in mouse development (36); *DLK1* expressed in hypothalamus (37), interacts with *NOTCH1* (23)
Alterations to Xq21.1-Xq21.31 (38)	Region contains gene *RPS6KA6*, one of five X-linked genes predicted to be spliced by a paternally expressed *snoRNA* in HBII-85, at 15q11-q13 (39)	*RPSKA6* (also called *RSK4*) highly expressed in brain and testis, its deletion is implicated in mental retardation (40); mutations of close homolog *RSK2* cause Coffin-Lowry syndrome, which involves mental retardation, growth retardation, and psychosis (41)
Alterations to Xq26-Xq28 region including *FMR1* gene; loss of *FMR1*, FMRP expression in Fragile X syndrome (42)	FMRP protein interacts with product of *CYFIP1* gene at 15q11.2 (42); FMRP involved in function of microRNAs (43); microRNAs at 15q11-q13 and 14q32 are imprinted	Links of phenotype with FMRP, *CYFIP1*, or imprinted microRNAs are speculative
RAI1 gene at 17p11.2; Smith- Magenis syndrome due to reduced RAI1 expression (44,45)	Unknown	Some cases resemble PWS with regard to presence of infantile hypotonia, hyperphagia, short stature, small hands and feet, skin picking, sleep disruption, unstable mood and 'bipolar episodes', and high pain threshold (44-47)

Kleine-Levin syndrome; idiopathic (48,49)	Unknown	Resembles PWS with regard to common presence of hyperphagia, hypersomnia, and psychotic spectrum phenotypes (48,49); etiology involves dysregulated hypothalamus (50)
'Hyperphagic short stature syndrome'; idiopathic (51)	Unknown	Resembles PWS with regard to presence of hyperphagia, short stature, hypotonia, sleep alterations, and learning disability; appears to be due to hypothalamic insufficiency (51)

References: (1) Battaglia (2005); (2) D'Angelo *et al.* (2006); (3) Bittel *et al.* (2007*b*); (4) Pirker *et al.* (2000); (5) Windpassinger *et al.* (2002); (6) Bittel *et al.* (2007*b*); (7) Casas *et al.* (2004); (8) Duxon *et al.* (1997); (9) Bittel *et al.* (2006); (10) Takayanagi *et al.* (2008); (11) H. K. Lee *et al.* (2004); (12) Faivre *et al.* (2002); (13) Varela *et al.* (2006); (14) Michaud *et al.* (2001); (15) Friedman & Fan (2007); (16) Luedi *et al.* (2007); (17) Goshu *et al.* (2004); (18) Cormier-Daire *et al.* (2003); (19) Kleefstra *et al.* (2006); (20) Stewart & Kleefstra (2007); (21) Lindsell *et al.* (1996); (22) Breunig *et al.* (2007); (23) Baladrón *et al.* (2005); (24) Iossifov *et al.* (2008); (25) Fournier *et al.* (2002); (26) Lukusa & Fryns (2000); (27) Courtens *et al.* (2006); (28) Choi *et al.* (2005); (29) Wood *et al.* (2007); (30) Naus *et al.* (2004); (31) Chen *et al.* (2005); (32) Kotzot (2004, 2007); (33) Temple *et al.* (2007); (34) Buiting *et al.* (2008); (35) Kagami *et al.* (2008); (36) Varrault *et al.* (2006); (37) da Roche *et al.* (2007); (38) Gabbett *et al.* (2008); (39) Bazeley *et al.* (2008); (40) Yntema *et al.* (1999); (41) Sheffler *et al.* (2006); (42) Nowicki *et al.* (2007); (43) Plante *et al.* (2006); (44) Dykens & Smith 1998); (45) Bi *et al.* (2006); (46) Girirajan *et al.* (2005); (47) Bersani *et al.* (2007); (48) Gau *et al.* (1996); (49) Arnulf *et al.* (2005); (50) Hong *et al.* (2006); (51) Gilmour *et al.* (2001).

imprinted genes, involving a relative maternal-gene expression bias *via* reduced expression of paternally expressed imprinted genes (Fig. 5).

Given the status of the hypothalamus as the neurological nexus of the paternal brain (Keverne *et al.*, 1996), these patterns provide important links between reduced paternal-gene expression, impaired development of the paternal brain, and Prader-Willi syndrome phenotypes including, in the syndrome itself, a high incidence of psychotic spectrum conditions (Soni *et al.*, 2007, 2008). Psychiatric phenotypes have yet to be investigated in most Prader-Willi phenotypes that are not due to 15q11-q13 alterations, although patients with deletions at 1p36, 6q16-q21 and 9q34 have been reported to exhibit behavioural phenotypes that include tantrums, intolerance to frustration, and self-injury (Cormier-Daire *et al.*, 2003; Battaglia, 2005; Kurosawa *et al.*, 2005; D'Angelo *et al.*, 2006; Varela *et al.*, 2006). Clear psychotic spectrum behaviour is, however, found in two conditions that resemble Prader-Willi syndrome for other morphological and behavioural traits: Smith-Magenis syndrome (Girirajan *et al.*, 2006; Bersani *et al.*, 2007) and Kleine-Levin syndrome (Arnulf *et al.*, 2005). The diversity of causes for ascertained cases of Prader-Willi phenotypes suggests that such phenotypes may grade more or less smoothly into normal development, and represent an important axis of human development underlain in part by variable expression of imprinted, paternally expressed genes in the hypothalamus.

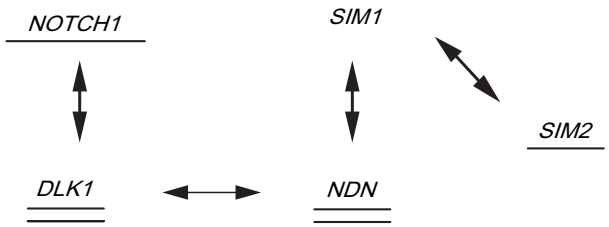

Fig. 5. A network showing patterns of direct gene-product interaction (thick arrows) and gene co-expression (thin arrow) (Varrault *et al.*, 2006) of paternally expressed imprinted genes (double-underlined) and genes that are predicted to be imprinted (single-underlined) (Luedi *et al.* 2007). This network provides evidence that a suite of genes, some imprinted, interact in the development of the hypothalamus and can be dysregulated by multiple independent means to generate Prader-Willi syndrome phenotypes.

Angelman syndrome, the imprinted sister-syndrome to Prader-Willi (Crespi & Badcock 2008), is usually caused by loss or reduction of functional gene product of the gene *UBE3A* at 15q11.2, which is maternally expressed in three brain regions: the cerebellum, hippocampus and olfactory bulb (Albrecht *et al.*, 1997). Like Prader-Willi syndrome, Angelman syndrome exhibits a suite of convergent causes and similar conditions indicative of common dysregulated neurodevelopmental pathways (Williams, Lossie & Driscoll, 2001). In particular, Angelman syndrome shows striking phenotypic overlap for diverse traits with Rett syndrome (Jedele, 2007), and both syndromes involve very high rates of autism (Peters *et al.*, 2004; Trillingsgaard & ØStergaard, 2004; Cohen *et al.*, 2005; Bonati *et al.*, 2007; LaSalle, 2007). *UBE3A* has also been implicated in idiopathic autism (Samaco *et al.*, 2005; see also Kato *et al.*, 2008), as has *MeCP2*, the X-linked gene that directly underlies Rett syndrome, as described below (Shibayama *et al.*, 2004; Nagarajan *et al.*, 2006; Coutinho *et al.*, 2007; Loat *et al.*, 2008). The neurological underpinnings of Angelman and Rett syndrome involve differential effects on the cerebral cortex (leading to acquired microcephaly) and the cerebellum (leading to tremor, abnormal gait, and ataxia); both of these brain regions can be considered as key components of the maternal brain, especially given their correlated evolution in primates (Whiting & Barton, 2003), their strong reciprocal connections and shared functions in the regulation of emotion and cognition (Schmahmann, Weilburg & Sherman, 2007), and their joint expansion in the human lineage (Weaver, 2005).

(2) X chromosome aneuploidies and *MeCP2* alterations

Haig (2006*a*,*b*) predicted that because X-linked genes spend two-thirds of their evolutionary history in females and only one-third in males, non-imprinted X-linked genes are expected to exhibit a bias favouring females, and a bias favouring maternally inherited interests. Thus, like maternally expressed imprinted genes, X chromosome genes are expected to inhibit demand for resources from mothers; this hypothesis is consistent with reduced placental and embryonic growth in mice with 46,XX *versus* 45,X or 46,XY karyotypes (Burgoyne *et al.*, 1995; Ishikawa *et al.*, 2003).

The most common disorders involving sex chromosome aneuploidy in humans are Turner syndrome (usually 45,X) and trisomy (47,XXX) in females (Good *et al.*, 2003; Rovet, 2004), and Klinefelter syndrome in males, which involves one or more extra X chromosomes, usually 47,XXY (Simpson *et al.*, 2003). To the extent that neurodevelopment imbalanced towards a paternal bias (due to reduced expression of X-linked genes) tends to cause autistic spectrum conditions, and maternal biases (due to elevated expression of X-linked genes, as shown by Vawter, Harvey & DeLisi, 2007) tend to cause psychotic spectrum conditions (Badcock & Crespi, 2006; Crespi & Badcock, 2008), Turner syndrome should involve elevated rates of autistic behaviour and conditions, and Klinefelter syndrome should engender higher rates of psychotic spectrum behaviour and conditions.

(*a*) *Turner syndrome and XXX trisomy*

Turner syndrome (usually 45,X) involves notably increased rates of autism, predominantly or exclusively in cases where females retain the maternally inherited X, rather than the paternal X, intact (Skuse *et al.*, 1997; Cresswell & Skuse, 1999; Skuse, 2000, 2005). Skuse *et al.* (1997) attributed these results to the presence of an X-linked imprinted gene whose expression affects the risk of autism, but such a gene or genes has yet to be identified in humans. Alternatively, higher rates of autism in Turner syndrome females with the maternal X intact may be associated with higher rates of pure X monosomy (45,X, as opposed to karyotypes involving additional X-chromosome material) in such females, compared to females with the paternal X intact (Crespi, 2008).

Mors, Mortensen & Ewald (2001) reported a significantly lower incidence of schizophrenia and bipolar disorder (considered together) in Turner females, compared to normal 46,XX females. An increased incidence of schizophrenia has been described in some studies of Turner syndrome females, but these reported increases are apparently due almost exclusively to cases that involve mosaic karyotypes, such that females exhibit some mixture of 45,X, 46,XX, and 47,XXX chromosome complements (Beumont & Mayou, 1971; Fishbain & Vilasuso, 1981; Kunugi, Lee & Nanko, 1999; Donnelly *et al.*, 2000; Prior, Chue & Tibbo, 2000; van Rijn *et al.*, 2005). These findings, and reports of increased rates of schizophrenia in 47,XXX females (DeLisi *et al.*, 1994; Kumra *et al.*, 1998), suggest that psychosis in sex-chromosome anomalous females is due entirely or predominantly to X trisomy (DeLisi *et al.*, 1994; Patwardhan *et al.*, 2002). A higher incidence of schizophrenia in 47,XXX females is also supported by imaging studies showing that such females exhibit three features of brain anatomy characteristic of schizophrenia: (1) reduced brain volume and enlarged ventricles (Warwick *et al.*, 1999; Patwardhan *et al.*, 2002); (2) reduced asymmetry of the prefrontal and temporal lobes (data in Tables 3 and 4 of Warwick *et al.*, 1999), and (3) a reduction in amygdala size (Patwardhan *et al.*, 2002). 47,XXX females also score higher than 46,XX females on tests of schizotypy (Warwick *et al.*, 1999).

(*b*) *Klinefelter syndrome*

Klinefelter syndrome (usually 47,XXY) is associated with impairment of verbal abilities, especially in language processing and working verbal memory (Graham *et al.*, 1988; Fales *et al.*, 2003; Itti *et al.*, 2003, 2006; Simpson *et al.*, 2003; DeLisi *et al.*, 2005). This syndrome also involves a four to tenfold increase in liability to psychosis (Mizukami *et al.*, 1989; DeLisi *et al.*, 1994, 2005; Everman & Stoudemire, 1994; Kebers *et al.*, 2002; van Rijn *et al.*, 2005, 2006a; Boks *et al.*, 2007*a*). Psychosis in Klinefelter syndrome normally involves a relatively high incidence of positive features, such as auditory hallucinations and paranoia, rather than the negative features more common in affected 46,XY males, and it also exhibits a later, female-typical age of onset (Pinabel, Gorwood & Ades, 1997; DeLisi *et al.*, 2005; van Rijn *et al.*, 2005).

As in X trisomy, Klinefelter syndrome individuals exhibit aspects of neuroanatomy similar to those in schizophrenia, including smaller whole-brain volume, reduced or reversed asymmetry of the prefrontal and temporal lobes, a higher incidence of mixed or left-handedness, and a reduced volume of the amygdala (Warwick *et al.*, 1999, 2003; Patwardhan *et al.*, 2002; Itti *et al.*, 2003; DeLisi *et al.*, 2005; van Rijn *et al.*, 2006*a*; Ross *et al.*, 2008). Itti *et al.* (2003) also found that less functionally lateralised Klinefelter's patients exhibited lower scores on tests of verbal ability, and Itti *et al.* (2006) documented smaller left temporal lobes in this condition, which were associated with reduced language ability. Klinefelter syndrome also involves an uneven emotional profile of hyperfunctional emotional experience and reactivity, but hypofunctional ability to identify and verbalise emotions, which resembles the pattern seen in schizophrenia (van Rijn *et al.*, 2005, 2006*b*).

X trisomy and Klinefelter syndrome apparently involve parallel effects on brain anatomy, verbal abilities, and liability to psychosis, which may be due in both cases to the extra X chromosome. Thus, in both XXX and XXY, the presence of an additional X is associated with: (1) impaired verbal abilities, (2) neuroanatomical features similar to those found in schizophrenia, including reduced or reversed lateralization and a smaller amygdala, and (3) notably increased liability to schizophrenia (DeLisi *et al.*, 1994, 2005; Laval *et al.*, 1998; Geschwind *et al.*, 1998; Warwick *et al.*, 2003), which may be related to left-hemisphere deficits mediated by increased dosage of X-linked genes (and perhaps also homologous X-Y genes) that are not inactivated (Williams *et al.*, 2006; Vawter *et al.*, 2007).

Table 4. Data from genome scans showing specific regions that exhibit linkages to psychotic spectrum conditions, and evidence for imprinting or parent-of-origin effects for these same regions. Table 5 shows information regarding regions 1q42, 6p21.3, 6p22.3, 7q31, and 7q35

Region	Association with psychosis	Evidence for imprinting effects
1p36	Schizophrenia and bipolar (1-5)	Imprinted gene *TP73*; *MTHFR* gene regulates methylation
6q16-q26	Schizophrenia and bipolar (6-13)	Maternal parent-of-origin effect in linkage to bipolar disorder (8)
7q21-q22	Schizophrenia and bipolar (14-17); autism (18-21)	Imprinted gene cluster that includes *SGCE* gene; parent-of-origin effects in autism linkage (19)
8q24	Schizophrenia and bipolar (7,11,22-25)	Predicted and confirmed imprinted genes (26)
10p12-p14	Schizophrenia and bipolar (9,17, 27-29); autism (30)	Parent-of-origin effects (for same markers as linked to schizophrenia, bipolar, and autism), in studies of obesity (31-33); gene imprinted in mice (*Sfmbt2*) in this region in humans (34)
10q26	Schizophrenia and bipolar (22,23,35-39); autism (40); handedness (41); homosexuality (42)	Imprinted genes in this region (43,44); maternal parent-of-origin effect in homosexuality linkage (42)
11p13	Schizophrenia and bipolar (45,46); autism (47-49)	Predicted and confirmed imprinted genes (26,50); parent-of-origin effect (51)
11p15.5	Bipolar, major depression (15,52,53); autism (47)	Large imprinted gene cluster
14q32	Schizoaffective bipolar and anxiety (22,54-56)	Imprinted gene cluster including brain-specific RNAs; maternal uniparental disomy of chromosome 14 resembles Prader-Willi syndrome (57,58)
16p13.3	Schizophrenia and bipolar (15,59,60); autism (20,40,61)	Presence of imprinting effects inferred from uniparental disomies (62,63), parent-of-origin effects in other disorders (64-66), the presence of differentially-methylated CpG islands (44), and the EICO database (67)
18p11.2	Schizophrenia and bipolar (5,68-74)	Parent-of-origin effects in schizophrenia and bipolar linkages (68-70), imprinted gene *GNAL* (70)
19q13.3-q13.4	Schizophrenia, schizoaffective and bipolar (12,17,23,73,75-79); autism (30,80)	Cluster of imprinted genes; *DNMT1* 'imprinter' gene
20q13	Schizophrenia and bipolar (7,11,23,81,82)	*GNAS* cluster of imprinted genes

References: (1) Abecasis *et al.* (2004); (2) Kohn *et al.* (2004); (3) Schumacher *et al.* (2005); (4) McGuffin *et al.* (2005); (5) Escamilla *et al.* (2007); (6) Middleton *et al.* (2004); (7) Park *et al.* (2004); (8) Schulze *et al.* (2004); (9) Lambert *et al.* (2005); (10) Levi *et al.* (2005); (11) McQueen *et al.* (2005); (12) Pato *et al.* (2004); (13) Shaltiel *et al.* (2008); (14) Ekelund *et al.* (2000); (15) McInnis *et al.* (2003*a*); (16) Paunio *et al.* (2004); (17) Faraone *et al.* (1998); (18) Smalley *et al.* (2005); (19) Lamb *et al.* (2005); (20) IMGSAC (2001*a*); (21) Barrett *et al.* (1999); (22) Cichon *et al.* (2001); (23) McInnis *et al.* (2003*b*); (24) Dick *et al.* (2003); (25) Walss-Bass *et al.* (2006); (26) Luedi *et al.* (2007); (27) DeLisi *et al.* (2002); (28) Straub *et al.* (2002); (29) Schwab *et al.* (2000); (30) Schellenberg *et al.* (2006); (31) Lindsay *et al.* (2001); (32) Gorlova *et al.* (2003); (33) Dong *et al.* (2005); (34) Kuzmin *et al.* (2008); (35) Kelsoe *et al.* (2001); (36) Ewald *et al.* (2002*a*); (37) Ewald *et al.* (2002*b*); (38) Bulayeva *et al.* (2007); (39) Williams *et al.* (2003); (40) Phillipe *et al.* (1999); (41) van Agtmael *et al.* (2003); (42) Mustanski *et al.* (2005); (43) Choi *et al.* (2005); (44) Strichman-Almashanu *et al.* (2002); (45) Suarez *et al.* (2006); (46) McInnis *et al.* (1996); (47) Duvall *et al.* (2007); (48) Trikalinos *et al.* (2006); (49) Szatmari *et al.* (2007); (50) Luedi *et al.* (2005); (51) Muglia *et al.* (2003); (52) Zandi *et al.* (2003); (53) Zubenko *et al.* (2003); (54) Segurado *et al.* (2003); (55) Ogden *et al.* (2004); (56) Middledorp *et al.* (2008); (57) Kotzot (2004); (58) Falk *et al.* (2005); (59) Yamada *et al.* (2004*a*); (60) Maziade *et al.* (2005); (61) IMGSAC (2001*b*); (62) Yong *et al.* (2002); (63) Eggermann *et al.* (2004); (64) Zerres & Rudnik-Schöneborn (1995); (65) Deichmann *et al.* (1998); (66) Wyszynski & Panhuyson (1999); (67) Nikaido *et al.* (2004); (68) Schwab *et al.* (1998*b*); (69) Kato (2001); (70) Corradi *et al.* (2005); (71) Mukherjee *et al.* (2006); (72) Detera-Wadleigh *et al.* (1999); (73) Fallin *et al.* (2004); (74) Bennett *et al.* (2002); (75) Badenhop *et al.* (2002); (76) Macgregor *et al.* (2004); (77) Hamshere *et al.* (2005); (78) Wijsman *et al.* (2003); (79) Kaufmann *et al.* (1998) (80) Liu *et al.* (2001); (81) Freedman *et al.* (2001); (82) Garver *et al.* (2001).

(*c*) *Rett syndrome and PPM-X syndrome*

The X chromosome harbours the gene *MeCP2* at Xq28, which codes for a methyl-CpG binding protein that regulates the expression of other genes, including the imprinted gene *miR-184* (Bapat & Galande, 2005; Horike *et al.*, 2005; Pescucci, Meloni & Renieri, 2005; Zoghbi, 2005; Nomura *et al.*, 2008). Diverse mutations in the *MeCP2* gene cause the autistic condition Rett syndrome, which involves normal infant development followed by developmental regression at 6-18 months leading to absence of speech, mental retardation, repetitive movements, and other clinical features shared with Angelman syndome and autism (Christodoulou & Weaving, 2003; Glaze, 2004; Neul & Zoghbi, 2004; Rogers, 2004; Weaving *et al.*, 2005). The severity of Rett syndrome is strongly mediated by the degree of skew in X-inactivation, which determines levels of functional *MeCP2* gene product.

Horike *et al.* (2005) identified the gene *DLX5*, which has been reported as imprinted with maternal expression in humans (as was *DLX6*, Okita *et al.*, 2003) as a specific target gene for regulation by *MeCP2*, with *DLX5* expressed biallelically in lymphoblastoid cells of subjects with Rett syndrome, and in the brains of MeCP2-deficient mice, due to apparent loss of imprinting. However, Schüle *et al.* (2007) describe evidence that expression of *DLX5* and *DLX6* is biallelic in normal individuals, and is not affected by levels of *MeCP2* (see also Itaba-Matsumoto *et al.*, 2007).

Makedonski *et al.* (2005) demonstrated that *MeCP2* deficiency leads to increased production of the paternally expressed *UBE3A* antisense transcript, and reduced levels of the maternally expressed gene *UBE3A*. Samaco *et al.* (2005) provided independent support for a link between *MeCP2* expression and *UBE3A*, showing that *UBE3A* levels are significantly reduced in brains of *MeCP2*-deficient mice, as well as in autism, Angelman syndrome and Rett syndrome, and Hogart *et al.* (2007) showed reduced *UBE3A* expression in post mortem brains, for Rett syndrome. These epigenetic disruptions of *UBE3A*, due to reduced *MeCP2* expression, result in relatively paternally-biased imprinted-gene expression, which is predicted for these autistic spectrum conditions under the conflict theory (Badcock & Crespi 2006); these findings may help to explain the phenotypic similarities between Rett syndrome and Angelman syndrome described above. Similar considerations may apply to the autistic condition Fragile X syndrome, which involves reduced expression of the key X-linked gene *FMR1* and thus may generate a bias favouring paternal-gene interests.

In contrast to these effects on autistic spectrum conditions, one mutation in the *MeCP2* gene, *A140V,* can result in PPM-X syndrome (psychosis, pyramidal signs, macroorchidism), which involves manic-depressive psychosis in males (Lindsay *et al.*, 1996; Cohen *et al.*, 2002; Klauck *et al.*, 2002; Kleefstra & Hamel, 2005). The finding that different mutations in the same X-linked gene, involved in the regulation of imprinted genes, can lead to either an autistic condition or psychosis suggests that brain-expressed imprinted genes can play key roles in neural development and psychiatric conditions.

VI. POLYGENIC EFFECTS: GENOME SCAN AND GENETIC ASSOCIATION DATA

Schizophrenia, bipolar disorder and major depression are highly heritable, although various epigenetic and environmental factors mediate their expression (Sullivan, Kendler & Neale, 2003; Craddock, O'Donovan & Owen, 2005; Fanous & Kendler, 2005; Harrison & Weinberger, 2005; Rapoport *et al.*, 2005). The development of these conditions is normally affected by genes at multiple loci, but different genes can contribute within and between human populations. Schizophrenia, bipolar disorder and major depression are known to share susceptibility genes (Park *et al.*, 2004; Kohn & Lerer, 2005; Maziade *et al.*, 2005; Blackwood *et al.*, 2007), although the degree of genetic overlap is as yet unclear.

Two main lines of genomic evidence can be used in evaluating the role of imprinted genes in psychotic spectrum conditions: (1) genome scans that link psychotic spectrum conditions with chromosomal regions harbouring imprinted genes, and (2) genetic association studies, that relate these conditions to variants of specific imprinted genes. As for autism, genome-scan and association studies have often been subject to inconsistency of replication among studies, due to genetic heterogeneity, clinical heterogeneity, and low statistical power (Tager-Flusberg & Joseph, 2003; Bartlett *et al.*, 2005; Veenstra-Vanderweele, Christian & Cook, 2004). Thus, failure of replication in genomic studies cannot be taken as unambiguous falsification unless accompanied by negative results from other approaches or from multiple large, independent scans or association studies. Imprinting can also be implicated in psychosis by parent-of-origin effects, or by showing altered gene expression patterns for brain-expressed imprinted genes, in individuals with psychosis *versus* controls. However, relatively few studies have included tests for parent-of-origin effects (Strauch *et al.*, 1999; Knapp & Strauch, 2004; Shete & Zhou, 2005), and gene-expression studies have yet to target imprinted genes and the developmental and metabolic systems within which they are embedded. It is also difficult to relate parent-of-origin effects directly to biases toward increased relative effects from either maternally or paternally expressed imprinted genes, because it is usually unknown whether mutations or epigenetic alterations lead to decreased or increased gene expression or activity of gene products.

I synthesise three levels of data salient to imprinting effects in the development of psychotic spectrum conditions, in order of decreasing strength of the evidence: (1) regions with imprinted genes and parent-of-origin effects in their linkages to psychotic spectrum conditions, (2) regions with imprinted genes or imprinting effects and linkages to psychosis, but an absence of data on parent-of-origin effects, and (3) regions with parent-of-origin effects in their linkages to psychosis, but an absence of data on a role for imprinted genes. Given that regions with imprinted genes, regions linked with psychosis, and regions showing parent-of-origin effects each encompass a very small proportion of the human genome, coincidences of these genomic patterns are unexpected under a null model of no differential role for imprinting in psychosis; statistical assessment of this prediction requires better knowledge of the loci underlying psychotic spectrum conditions, and of which genes are actually imprinted. Data on imprinting effects in genome-scan and genetic-association studies of psychosis are summarised in Tables 4 and 5, which also list associations of these regions and genes with autism. The strength of the evidence for any given gene or region is in large part a function of the degree to which multiple, independent lines of evidence support a hypothesis of imprinting effects on the development of psychosis.

(1) Regions with imprinted genes and parent-of-origin effects in their linkages to psychosis

The genomic regions at 2p12-q11, 6q16-q21, 14q32 and 18p11 are known to exhibit brain-expressed imprinted

Table 5. A suite of genes associated with psychotic spectrum conditions that are also subject to effects from genomic imprinting

Genes	Evidence for association with psychosis	Main evidence for imprinting effects	Comments
BDNF	Multiple replicated associations with schizophrenia (1,2)	Parent-of-origin effect (3) and bioinformatic prediction (4)	Gene is upregulated in autism (5-7), down-regulated in psychosis (8-10); also linked genetically with autism (11)
CNTNAP2	Deletions are associated with schizophrenia (12)	Parent-of-origin effect in linkage to autism (13)	Gene linked to autism (13, 14)
DISC1	Multiple replicated association studies for schizophrenia, bipolar disorder (15)	Bioinformatic predictions (4,16); interaction with imprinted domain (17)	Not imprinted in humans, in one study (18); gene also associated with Asperger syndrome (19)
DTNBP1	Multiple replicated association studies (e.g. 20, 21)	Imprinting effect with maternal transmission (22)	Effect was sex-specific (22)
FOXP2	One association study (23); cytogenetic evidence (24)	Maternal and paternal uniparental disomies differ in expression of *FOXP2* and in presence of dyspraxia (25)	*FOXP2* has also been associated with autism (26–28); same markers linked with autism and schizophrenia (23,26)
GNAL	Association studies (29)	Differential methylation, parent-of-origin effects (29)	Parent-of-origin effect also found in study of ADHD (30)
GRIK2	One association study (31)	Maternal parent-of- origin effect (31)	Maternal parent-of-origin effect also found in linkage with autism (32)
GRIK3	Association study and copy number variation (33-35)	Parent-of-origin effect (36)	Predicted imprinted in mice (4)
HLA-DRB1	Association studies (37,38)	Parent-of-origin effects in autism linkage (39)	Higher DR4 frequency, lower DR13 frequency in autism (39–42); reverse in schizophrenia (37,38)
LRRTM1	Association study (43)	Imprinted with paternal expression (43)	Also associated with mixed handedness (43)
NECDIN-FEZ1-PCM-DISC1	High rate of psychosis in Prader-Willi syndrome; loss of necdin expression from *NDN* gene (44)	Necdin is imprinted (paternally expressed)	*FEZ1*, *PCM1* and *DISC1*, which have been linked with schizophrenia in genetic association studies (15,45–48), interact with necdin (44)
MAGI2	Association study and functional linkages (49); copy-number variation (50)	Predicted imprinted, maternal expression (16)	Highly expressed in brain, anti-proliferative function consistent with maternal expression (51)
RELN	Genetic association studies (52,53); functional studies (54,55)	(a) parent-of-origin effects in autism linkage (56,57); differential expression (maternal X *versus* paternal X) in Turner syndrome mouse model (58); bioinformatic prediction (59)	*RELN* is also linked genetically with autism (60,61)
RGS4	Genetic and functional studies (62-64)	Bioinformatic prediction (65)	Genetic-association evidence is heterogeneous (64)
SGCE	Mutations cause movement disorder with high incidence of psychosis and depression (66-68)	Imprinted (paternally expressed)	Highly heterogeneous with regard to psychiatric correlates of mutations (67)
UBE3A & *ATP10C*	One study of childhood onset schizophrenia (69) one of schizophrenia, for *UBE3A* (70)	Imprinted (maternally expressed)	Both genes have also been linked with autism (71–74)

References: (1) Neves-Periera *et al.* (2005); (2) Rosa *et al.* (2006); (3) Muglia *et al.* (2003); (4) Luedi *et al.* (2005); (5) Miyazaki *et al.* (2005); (6) Tsai (2005); (7) Connolly *et al.* (2006); (8) Hashimoto *et al.* (2005); (9) Weickert *et al.* (2005); (10) Palomino *et al.* (2006); (11) Nishimura *et al.* (2007); (12) Friedman *et al.* (2008); (13) Arking *et al.* (2008); (14) Alarcón *et al.* (2008); (15) Chubb *et al.* (2008); (16) Luedi *et al.* (2007); (17) Ling *et al.* (2006); (18) Hayesmoore *et al.* (2008); (19) Kilpinen *et al.* (2008); (20) Breen *et al.* (2006); (21) Riley & Kendler (2006); (22) Schwab *et al.* (2006); (23) Sanjuán *et al.* (2006); (24) Moon *et al.* (2006); (25) Feuk *et al.* (2006); (26) Gong *et al.* (2004); (27) Li *et al.* (2005); (28) Marui *et al.* (2005); (29) Corradi *et al.* (2005); (30) Laurin *et al.* (2006); (31) Bah e*t al.* (2004); (32) Jamain *et al.* (2002); (33) Begni *et al.* (2002); (34) Wilson *et al.* (2006); (35) Shibata *et al.* (2006); (36) Shiffer & Heinemann (2007); (37) Wright *et al.* (2001); (38) Li *et al.* (2001); (39) Torres *et al.* (2002); (40) Warren *et al.* (1996); (41) Lee *et al.* (2006); (42) Torres *et al.* (2006); (43) Francks *et al.* (2007); (44) Lee *et al.* (2005); (45) Yamada *et al.* (2004*b*); (46) Gurling *et al.* (2006); (47) Lipska *et al.* (2006); (48) Roberts (2007); (49) Buxbaum *et al.* (2008); (50) Walsh *et al.* (2008); (51) Hu *et al.* (2007); (52) Goldberger *et al.* (2005); (53) Shifman *et al.* (2008); (54) Fatemi (2005); (55) Kundakovic *et al.* (2007); (56) Rampersaud *et al.* (2006); (57) Dutta *et al.* (2007); (58) Davies *et al.* (2006); (59) Nikaido *et al.* (2004); (60) Skaar *et al.* (2005); (61) Serajee *et al.* (2006); (62) Talkowski *et al.* (2006); (63) Levitt *et al.* (2006); (64) Chowdari *et al.* (2008); (65) Allen *et al.* (2003); (66) Lauterbach *et al.* (1994); (67) Doheny *et al.* (2002); (68) DeBerardinis *et al.* (2003); (69) Sporn *et al.* (2004); (70) Iossifov *et al.* (2008); (71) Nurmi *et al.* (2003); (72) Jiang *et al.* (2004); (73) Kato *et al.* (2008); (74) Kim *et al.* (2008).

genes in humans, and thus they represent strong candidates for imprinting effects on the development of psychosis.

(*a*) *2p12 and the* LRRTM1 *gene*

A paternal parent-of-origin effect on both schizophrenia and relative hand skill has been found for 2p12-q11 by Francks *et al.* (2003*b*), who anticipated the imprinted-brain hypothesis for psychosis and autism in stating that their findings, implicating a common, functional, imprinted allele in schizophrenia, suggest that 'lateralized development of the human brain, and complex human cognitive abilities, have been subject to a parental conflict over investment' (p. 3227). The largest schizophrenia linkage meta-analysis to date showed that the 2p11-q14 region was the strongest in the genome, and the only one reaching genome-wide significance (Lewis *et al.*, 2003). The 2p11-q14 region has also been strongly associated with bipolar disorder (Willour *et al.*, 2007; Goes *et al.*, 2007), for linked markers overlapping with those of Francks *et al.* (2003*a*,*b*).

Francks *et al.* (2007) identified *LRRTM1* as a paternally expressed imprinted gene that apparently underlies these linkages of 2p12 with schizophrenia and handedness. This gene is expressed throughout the brain, but expression levels from the risk *versus* protective haplotypes have yet to be investigated; reduced expression would result in a relative maternal gene-expression bias, as predicted under the imprinted brain theory.

(*b*) *6q16-q26 and the* GRIK2 *gene*

The region at 6q16-q21, which shows evidence of a maternal-transmission parent-of-origin effect (Schulze *et al.*, 2004; see also Dick *et al.*, 2003), includes the maternally expressed gene c6orf66 at 6q16.1 that regulates cell proliferation in the brain and other tissues (Okita *et al.*, 2003). The region 6q24-q26 includes several known imprinted genes, including the paternally expressed ZAC1 gene, which plays an important role in embryonic growth and brain development, with strong post-natal expression in GABA (γ-aminobutyric acid)-ergic limbic-system neurons of mice (Valente, Junyent & Auladell, 2005; Varrault *et al.*, 2006). Linkage to schizophrenia as well as bipolar disorder has been found for 6q16-q26 in multiple studies (Cao *et al.*, 1997; Dick *et al.*, 2003; Lerer *et al.*, 2003; McInnis *et al.*, 2003*a*; Middleton *et al.*, 2004; Park *et al.*, 2004; Schulze *et al.*, 2004; Kohn & Lerer, 2005; Lambert *et al.*, 2005; Levi *et al.*, 2005), implying shared susceptibility to psychotic spectrum conditions in this large region.

A candidate gene in this region, *GRIK2* at 6q16 (coding for the glutamate receptor GLUR6), is involved in glutamatergic neurotransmission, exhibits multiple splice variants in the hippocampus (Barbon, Vallini & Barlati, 2001), and is downregulated in the hippocampus in schizophrenia (Benes, Todtenkopf & Kostoulakos, 2001; Porter, Eastwood & Harrison, 1997). Variants of this gene appear to be associated with both psychoses and autism: Phillipe *et al.* (1999) found linkage of autism to 6q16 in a genome scan, and Jamain *et al.* (2002) found evidence for enhanced maternal transmission of *GRIK2* genetic variants in autism in an association study; Shuang *et al.* (2004) and Kim *et al.* (2007) also found associations of *GRIK2* variants with autism, but they did not test for parent-of-origin effects. Bah *et al.* (2004) reported a maternal transmission effect in an association of *GRIK2* with susceptibility to schizophrenia, and Laje *et al.* (2007) found an association between levels of suicidal ideation in major depression and a single-nucleotide polymorphism in this gene, but did not test for parent-of-origin effects.

GRIK3 (at 1p34), which codes for the glutamate receptor GLUR7, shows allelic and copy-number variants associated with schizophrenia (Begni *et al.*, 2002; Wilson *et al.*, 2006; Shibata *et al.*, 2006; but see also Lai *et al.*, 2005) as well as altered expression in the frontal cortex of schizophrenics (Sokolov, 1998; Meador-Woodruff, Davis & Haroutunian, 2001). Schiffer *et al.* (2000) describe evidence of unequal allelic expression of GLUR7 mRNA in human brains that they interpret as possibly indicating an imprinting effect, Schiffer & Heinemann (2007) demonstrate a parent-of-origin effect in their genetic-association study that linked *GRIK3* with major depression and bipolar disorder, and Luedi *et al.* (2005) predicted this gene to be imprinted with maternal expression (in mice) in a bioinformatic study. Another glutamate-receptor gene, *GRIK4* (at 11q22), has recently been linked genetically with schizophrenia and bipolar disorder (Pickard *et al.*, 2006), but parent-of-origin effects were not evaluated in this case. The associations of *GRIK2*, *GRIK3* and *GRIK4* with psychosis support a role for disrupted glutamatergic neurotransmission in these disorders (Pickard *et al.*, 2006), as in autism (Carlsson, 1998; Szatmari *et al.*, 2007).

(*c*) *14q32 and the* DLK1 *gene*

The region 14q32 has been implicated in bipolar disorder with paternal inheritance (Cichon *et al.*, 2001) as well as showing linkage with bipolar and schizoaffective disorder (Segurado *et al.*, 2003; Ogden *et al.*, 2004), anxiety (Middeldorp *et al.*, 2008), and reading disability and attention deficit hyperactivity (ADHD) (Gayán *et al.*, 2005). This region contains a small cluster of imprinted genes including the paternally expressed gene *DLK1*, the maternally expressed *GTL2* gene, the paternally expressed *DIO3* gene, several other imprinted genes (Tierling *et al.*, 2006), and a large set of brain-specific, maternally expressed snoRNAs and microRNAs (Cavaillé *et al.*, 2002; Seitz *et al.*, 2004*a*,*b*; Croteau *et al.*, 2005; Tierling *et al.*, 2006). The *DLK1* gene is less than 1Mb from the linkage peak of Cichon *et al.* (2001).

Functional links of the 14q32 region to psychosis are suggested by three findings: First, expression of *DLK1* and dopamine beta-hydroxylase (DBH) is tightly correlated in neuroblastoma cells, and *DBH* genotype is associated with paranoid ideation in patients with major depression (Wood *et al.*, 2002). Second, *DLK1* expression is associated with differentiation of dopaminergic midbrain neurons (Christophersen *et al.*, 2007), and such neurons have been postulated to play a central role in the etiology of schizophrenia (Seeman *et al.*, 2005; Laviolette, 2007). Finally, the deiodinase gene *DIO3* is paternally expressed in mice and it appears to be also imprinted in humans (Hernandez *et al.*,

2004); the product of this gene inactivates thyroid hormones (with knockouts leading to hypothyroidism in mice) (Hernandez *et al.*, 2006), and hypothyroidism represents a notable physiological cause of psychosis (Heinrich & Grahm, 2003), as described in more detail below for the *GNAS* locus. The suite of imprinted genes at 14q32 has also been demonstrated to undergo interactions directly indicative of genomic conflict (Davis *et al.*, 2005), as for the *IGF1-H19* region (Lewis & Redrup, 2005).

Maternal uniparental disomies of chromosome 14 (UPD14) exhibit a distinctive phenotype that resembles Prader-Willi syndrome for several traits, including low birth weight, poor neonatal suckling, delayed motor development, obesity, and in a few cases skin picking or skill with jigsaw puzzles (Berends *et al.*, 1999; Hordijk *et al.*, 1999; Manzoni *et al.*, 2000; Shimoda *et al.*, 2002; Kotzot, 2004, 2007; Falk *et al.*, 2005). Maternal UPD14 can also involve language and developmental delay (Worley *et al.*, 2001; Kotzot, 2004), hypothyroidism (Manzoni *et al.*, 2000), and higher verbal than non-verbal IQ (Manzoni *et al.*, 2000). These traits in maternal UPD14 are apparently related to reduced expression of paternally expressed genes at 14q32, with *DLK1* as a primary candidate for phenotypic effects (Sutton & Shaffer, 2000; Temple *et al.*, 2007; Buiting *et al.*, 2008; Kagami *et al.*, 2008).

(*d*) *18p11.2 and the* GNAL *gene*

This region has also been repeatedly associated in genome scans with schizophrenia and bipolar disorder (Schwab *et al.*, 1998*b*; Detera-Wadleigh *et al.*, 1999; Kato, 2001; Segurado *et al.*, 2003; Fallin *et al.*, 2004; Lin *et al.*, 2005; Escamilla *et al.*, 2007 and references therein), as well as exhibiting linkages to a psychosis endophenotype in bipolar disorder and schizophrenia (Mukherjee *et al.*, 2006), prepulse inhibition (Palmer *et al.*, 2003) and dyslexia (Fisher *et al.*, 2002*a*), which exhibits strong neuroanatomical and cognitive links to psychosis (Shapleske *et al.*, 1999; Heim *et al.*, 2004; Bersani *et al.*, 2006; Edgar *et al.*, 2006). Paternal and maternal parent-of-origin effects have been reported by most studies in these linkages to schizophrenia and bipolar disorder (see Stine *et al.*, 1995; Gershon *et al.*, 1996; Schwab *et al.*, 1998*b*; Nöthen *et al.*, 1999; Turecki *et al.*, 1999; Kato, 2001; Corradi *et al.*, 2005; Mulle *et al.*, 2007).

Corradi *et al.* (2005) describe evidence (including the presence of differentially methylated regions) that the *GNAL* gene at 18p11.2 exhibits imprinting, and is responsible for these parent-of-origin effects. This hypothesis is supported by the finding that most of the linkages of 18p11.2 to psychiatric conditions centre at or near a single genetic marker, D18S53, which is directly adjacent (0.5 cM) to the *GNAL* locus (Schwab *et al.*, 1998*b*; Turecki *et al.*, 1999; Fisher *et al.*, 2002*a*). Allelic variation at the *GNAL* locus has been associated with major depression in females (Zill et al., 2002) and with ADHD (Laurin *et al.* 2006), and Bickeböller, Kistler & Scholz (1997) found a possible association with bipolar disorder; the former two studies also reported evidence for parent-of-origin effects. By contrast, Zill et al. (2003) found no evidence of association in a study of patients with bipolar disorder.

The *GNAL* locus codes for two transcripts, Gαolf and XLGαolf, that localise to diverse brain regions (Belluscio *et al.*, 1998), including several regions associated with psychosis, such as the prefrontal cortex, nucleus accumbens, and striatum, as well as exhibiting expression in the olfactory bulb (Zill *et al.*, 2002; Corradi *et al.*, 2005). Activity of *GNAL* transcripts is functionally coupled to the dopamine D1 and adenosine A2a receptors, which modulate dopaminergic neurotransmission and show functional and genetic links with psychosis (Lara *et al.*, 2006; Ottoni *et al.*, 2005; Lara, 2002; Abdolmaleky *et al.*, 2005; Corradi *et al.*, 2005; Dmitrzak-Weglarz *et al.*, 2006; Ravyn & Bostwick, 2006). The Gαolf transcript is also upregulated in the striatum in response to psychostimulants (in mice, Corvol *et al.*, 2007) and antidepressants (in rats, Taoka *et al.*, 2006), which implicates its cAMP-signalling effects in affective and psychotic conditions (Hattori *et al.*, 2005; Avissar & Schreiber, 2006).

Most details of the parental and tissue expression patterns and molecular functions of *GNAL* transcripts remain to be elucidated. The Gαolf protein shares extensive homology with the *GNAS* transcript Gαs, and it likewise influences dopaminergic neurotransmission *via* the cAMP pathway (Vuoristo *et al.*, 2000). Mice homozygous for a null mutation of Gαolf exhibit greatly-impaired olfaction, most are 'unable to nurse and die within two days of birth' (Belluscio *et al.*, 1998, p. 69), and survivors are hyperactive; adult females exhibit impaired maternal behaviour, apparently due to olfactory deficits (Belluscio *et al.*, 1998). This study concluded that Gαolf plays a key role in olfactory signal transduction, as well as influencing behaviour *via* the dopaminergic system. These findings are of interest because deficits and alterations in olfaction are a well-documented characteristic of schizophrenia (Moberg *et al.*, 2006).

(2) Regions with imprinting effects and linkages to psychosis

The genomic regions at 1q42, 1p36, 6p21.3, 6p22.3, 7q21-q22, 7q31, 7q35, 8q24, 10p12-p14, 10q26, 11p13, 11p15.5, 16p13.3, 19q13.3-q13.4, and 20q13 have been linked with psychotic spectrum conditions and also exhibit known imprinted genes, parent-of-origin effects, or genes directly influenced by imprinted genes (Tables 4 and 5).

(*a*) *1q42 and the* DISC1 *gene*

The *DISC1* gene exhibits one of the best-replicated associations with psychotic spectrum conditions including schizophrenia, bipolar disorder and depression (Chubb *et al.*, 2008), as well as showing linkage in one study with Asperger syndrome (Kilpinen *et al.*, 2008). Luedi *et al.* (2007) have predicted *DISC1* to be imprinted with maternal expression based on bioinformatics, but the presence or absence of parent-of-origin effects has not been reported for this gene, and Hayesmoore *et al.* (2008) demonstrated that *DISC1* is not imprinted in adult human brain. These findings indicate that the bioinformatics prediction appears inaccurate in this case, but independent evidence from chromosome-capture experiments indicates that *DISC1*

expression may be affected by trans-acting chromosomal regulation mediated by the imprinted *IGF2-H19* locus (Zhao *et al.*, 2006). Similar considerations apply to the *NF1* gene, which has been linked with autism (Mbarek *et al.*, 1999; Marui *et al.*, 2004); this gene is not known to be imprinted, but its expression is modulated by an inter-chromosomal interaction with the paternal allele of the *IGF2-H19* imprinted domain (Ling *et al.*, 2006). These findings suggest that *DISC1* and *NF1* comprise part of an 'extended genotype' for these imprinted genes (Smits & Kelsey, 2006), which may influence the risk of disease.

(*b*) *1p36 and the* TP73 *gene*

The 1p36 region has been linked in genome scans to schizophrenia (Abecasis *et al.*, 2004; Kohn *et al.*, 2004; Escamilla *et al.*, 2007), dyslexia (Grigorenko *et al.*, 2001; Tzenova *et al.*, 2004), speech disorder (Smith *et al.*, 2005), bipolar disorder (Schumacher *et al.*, 2005), and major depression (McGuffin *et al.*, 2005). The three independent linkages to schizophrenia and dyslexia exhibit their highest logarithm of odds (LOD) scores at the same marker, D1S507, at 1p36.21 (Grigorenko *et al.*, 2001; Tzenova *et al.*, 2004; Kohn *et al.*, 2004), or very close nearby (Abecasis *et al.*, 2004; Smith *et al.*, 2005; McGuffin *et al.*, 2005), and Stefansson *et al.* (2002) also found suggestive evidence of a peak in this region for schizophrenia.

Two genes directly involved in imprinting effects are also found in the 1p36 region: *TP73*, an imprinted gene at 1p36.32 that is maternally expressed in humans, and *MTHFR* at 1p36.22, which regulates folate and homocysteine metabolism, and thus affects methylation of imprinted genes.

TP73 is transcribed from multiple promotors and exhibits multiple isoforms with opposing pro-apoptotic and anti-apoptotic effects (A. F. Lee *et al.*, 2004; Ramadan *et al.*, 2005; Cabrera-Socorro *et al.*, 2006; Boominathan, 2007). It is tightly coexpressed with reelin (the *RELN* gene product) in Cajal-Retzuis cells in the developing foetal neocortex of mice (Meyer *et al.*, 2002; Cabrera-Socorro *et al.*, 2006), which may explain the maternal-expression status of RELN reported in the Expression-based Imprint Candidate Organizer (EICO) database of putative imprinted genes (Nikaido *et al.*, 2004). The gene product of *TP73* trans-activates target genes of the key apoptosis-related gene *TP53*, which has been linked with schizophrenia (Ni *et al.*, 2005).

Mice deficient in p73 proteins exhibit increased apoptosis in cortical and hippocampal neurons, impaired olfaction, and chronic inflammation (Yang *et al.*, 2000; Cabrera-Socorro *et al.*, 2006). Terminal deletions at 1p36 (many of which include the *TP73* gene) lead to monosomy for this region and represent the most common terminal deletion in humans (Heilstedt *et al.*, 2003). Such deletions result in mental retardation, delayed myelinisation, hypothyroidism, hearing loss, and impaired vision (as well as epilepsy, hypotonia, language impairment and heart defects) (Heilstedt *et al.*, 2003; Battaglia, 2005; D'Angelo *et al.*, 2006). D'Angelo *et al.* (2006) also noted that terminal deletions at 1p36.33 are associated with a suite of physiological and behavioural traits similar to Prader-Willi syndrome, and Moon *et al.* (2006) reported that alterations in copy number of chromosomal segments at 1p36.33 are found relatively commonly in schizophrenia. The set of phenotypes found in human 1p36 deletion resembles those seen in p73-deficient mice, and such disruptions may be due in part to reduced expression of reelin and a dramatic size reduction of the (transthyretin-secreting) choroid plexus (Meyer *et al.*, 2004; Cabrera-Socorro *et al.*, 2006).

TP73 gene products also regulate two maternally expressed, imprinted genes at 11p15.5, *CDKN1C* and *KCNQ1* (Blint *et al.*, 2002), which may account for the growth retardation commonly seen in 1p36 deletion. Wu *et al.* (1999) note a lack of apparent differences between paternal *versus* maternal deletions at 1p36, but their study did not take account of the fact that only some such deletions include the *TP73* gene. Individuals with 1p36 deletions have not been examined for neuroanatomical, psychiatric or formal language-related phenotypes; individuals with maternal deletions including *TP73* may be expected to differ from others for such traits.

MTHFR codes for the enzyme methylenetetrahydrofolate reductase, which exhibits functional polymorphisms that have been associated with schizophrenia, bipolar disorder, depression, and autism, with some gender-specific effects (Lewis *et al.*, 2005; McGuffin *et al.*, 2005; Muntjewerff *et al.*, 2005; Sazci *et al.*, 2005; James *et al.*, 2006; Zintzaras, 2006). Each of these conditions is associated with the TT genotype of the C677T polymorphism, which reduces the availability of folate metabolites for methylation and may thereby cause defects in the expression of imprinted genes and other genes regulated by methylation of promotor regions (Zogel *et al.*, 2006; Axume *et al.*, 2007). The effects of these polymorphisms on psychiatric conditions may be mediated in part by maternal folate status during pregnancy, which also affects the methylation status of imprinted genes (Shields *et al.*, 1999; Ingrosso *et al.*, 2003; Picker & Coyle, 2005; Zogel *et al.*, 2006). MTHFR deficiency has also been shown in a case study to lead to a condition that mimics Angelman syndrome (Williams *et al.*, 2001), and transmission ratio disruption for this gene suggests effects of the A1298C genotype on embryonic survival (Infante-Rivard & Weinberg, 2005).

(*c*) *6p21.3 and* HLA-DRB1 *gene*

Schizophrenia and autism involve dysregulation of the neuroimmune and immune systems (Wright *et al.*, 1996*b*, 2001; Benasich, 2002; Torres *et al.*, 2002; Engstrom *et al.*, 2003; Cohly & Panja, 2005; Croen *et al.*, 2005; Ashwood, Wills & Van de Water, 2006). In particular, these conditions involve strongly altered ratios of cytokines and other immune-system components that are indicative of Th1 (cell-mediated) *versus* Th2 (humoral) systems of immunity (Schwarz *et al.*, 2001; Hu *et al.*, 2006; Molloy *et al.*, 2006; Riedel *et al.*, 2007), and significantly altered frequencies of immune and autoimmune diseases in affected individuals and relatives (Comi *et al.*, 1999; Holden & Pakula, 1999; Sweeten *et al.*, 2003; Boulanger & Shatz, 2004; Ashwood *et al.*, 2006; Ashdown *et al.*, 2006; Eaton *et al.*, 2006).

Differences in autoimmune disorders include a strikingly decreased frequency of rheumatoid arthritis in schizophrenics (Eaton, Hayward & Ram, 1992; Torrey & Yolken, 2001; Gorwood *et al.*, 2004) and an increased frequency in families with autistic members (Comi *et al.*, 1999; Sweeten *et al.*, 2003). Gorwood *et al.* (2004) also found a significantly decreased level of paranoid ideation, a measure of positive schizotypy, in rheumatoid arthritis patients.

Immune-disorder effects in autism, schizophrenia, and rheumatoid arthritis appear to be mediated at least in part by class II Human Leukocyte Antigen (HLA) loci at 6p21.3, with notable effects from HLA-DR4 and HLA-DR13 alleles at the locus *HLA-DRB1*. Thus, autism is strongly associated with an increased frequency of DR4 alleles, especially in the linked haplotype combination B44-SC3-DR4 (Warren *et al.*, 1992, 1996; Torres *et al.*, 2002, 2006; Lee *et al.*, 2006; but see also Guerini *et al.*, 2006); autism also involves a significantly reduced frequency of DR13 alleles at the *HLA-DRB1* locus (Torres *et al.*, 2002). There is evidence for a decreased frequency of the DR4 allele in schizophrenia in some populations (in patients and their mothers; Wright *et al.*, 1996*a*, 1998; Arinami *et al.*, 1998; reviewed in Wright *et al.*, 2001) although some studies did not replicate this difference (Hawi *et al.*, 1999; Akaho *et al.*, 2000; Li *et al.*, 2001). Moreover, one study noted strong preferential transmission of the DR13 allele in schizophrenia (Li *et al.*, 2001), such that this allele is positively associated with the disorder. The *HLA-DRB1* locus also exhibits significantly differential expression in the central nervous system and in blood for schizophrenia patients *versus* controls (Glatt *et al.*, 2005).

One means of analysing the robustness of these associations is by using epidemiological and genetic data that link these same HLA alleles with rheumatoid arthritis, as this autoimmune disorder is found at much lower rates in schizophrenia, but shows evidence of a higher frequency in autism (and in relatives), as noted above. In rheumatoid arthritis, DR4 exhibits an increased frequency (Wright *et al.*, 2001; Newton *et al.*, 2004; Kapitány *et al.*, 2005; Roudier, 2006), as do the A2-B44 and A2-B44-DR4 haplotypes (McDermott *et al.*, 1986; Ollier *et al.*, 1986) and the autism-associated B44-SC30-DR4 haplotype (Fraser *et al.*, 1990). A hypervariable-region sequence HRV-3, found preferentially in DR4 haplotypes, is also strongly associated with both autism and rheumatoid arthritis (Warren *et al.*, 1996). These findings are consistent with patterns of genetic and epidemiological connection between autism, schizophrenia, rheumatoid arthritis, and DR4 alleles of the DRB1 locus, although further studies involving analysis of extended haplotypes, and epidemiological analyses targeted at the apparent associations, are clearly needed.

Parent-of-origin effects have been noted in the inheritance of DR4 and DR13 alleles in autism (Torres *et al.*, 2002), and 6p21.3 harbours four potentially imprinted genes (Nikaido *et al.*, 2004). Interpretation of these parent-of-origin effects is complicated by the presence of maternal-foetal immunological interactions, especially given that non-inherited maternal alleles may also influence offspring phenotypes (Johnson, 2003; Hsieh *et al.*, 2006); in this case (Torres *et al.*, 2002), DR4 alleles were preferentially inherited from the father, and fewer DR13 alleles than expected were inherited from the mother. Analyses of the effects of genes in the 6p21.3 region are also complicated by strong linkage disequilibrium in this region (Blomhoff *et al.*, 2006), such that it is difficult to ascribe phenotypic effects to particular alleles, and also by evidence for recent positive selection at this locus for some human populations (Raymond *et al.*, 2005; Windsor *et al.*, 2005; Voight *et al.*, 2006). Moreover, phylogenetic analyses of the suite of alleles at *HLA-DRB1* indicates that this locus has diversified very recently compared to other class II HLA loci (which generally predate the chimpanzee-human split)(von Salomé, Gyllensten & Bergström, 2007), and DR4 has evolved very recently (within the past 250,000 years), with its allelic variants evolving especially rapidly (Bergström *et al.*, 1998; Hohjoh *et al.*, 2003).

(*d*) *6p22.3 and the* DTNBP1 *gene*

The dysbindin gene *DTNBP1* at 6p22.3 exhibits a well-replicated genetic and functional association with the risk of schizophrenia (Riley & Kendler, 2006), and genetic variants of this gene have also been linked with bipolar disorder (Breen *et al.*, 2006; Pae *et al.*, 2006). Schwab *et al.* (2006) describe evidence for a sex-specific imprinting effect in the association of this gene with schizophrenia in an abstract; previous studies of this gene have not reported tests for parent-of-origin effects. The report by Schwab *et al.* (2006) is partially corroborated by the presence of an allele-specific protein-DNA interaction involving *DTNBP1* (Maynard *et al.*, 2008), but further studies are required for definitive inferences.

(*e*) *7q21-q22 and the* SGCE, MAGI2, *and* RELN *genes*

The region 7q21-q22 has been linked to schizophrenia (Ekelund *et al.*, 2000; Paunio *et al.*, 2004; see also Moises *et al.*, 1995, Blouin *et al.*, 1998, Faraone *et al.*, 1998), bipolar disorder (McInnis *et al.*, 2003a), and autism (IMGSAC, 2001*a*; Lamb *et al.*, 2005; Smalley *et al.*, 2005). In addition, a chromosomal breakpoint at 7q21 (0.5 Mb from the imprinted region here) was associated with childhood-onset schizophrenia and paranoia in a case study (Yan *et al.*, 2000). Dysregulation of three imprinted or putatively imprinted genes in this region may underlie these genetic associations with psychosis.

First, mutations or cytogenetic abnormalities involving the paternally expressed imprinted gene *SGCE* at 7q21 (Piras *et al.*, 2000; Grabowski *et al.*, 2003; Okita *et al.*, 2003) are associated with one form of the movement disorder myoclonus dystonia. This disorder, when due to functional mutations of *SGCE* (which cause a maternal gene-expression bias, since paternal-gene activity is reduced), engenders high rates of psychotic symptoms including paranoia and hallucinations, in addition to anxiety, panic attacks, and depression (Lauterbach *et al.*, 1994; Doheny *et al.*, 2002; DeBerardinis *et al.*, 2003).

Second, the gene *MAGI2*, about 15 Mb distant from SGCE at 7q21, is predicted as imprinted and maternally expressed in humans by Luedi *et al.* (2007), a report that is supported in part by the presence of an allele-specific

protein-DNA interaction involving this gene (Maynard *et al.*, 2008). *MAGI2* is highly expressed in the brain, where it exerts anti-proliferative effects *via* regulation of the *PTEN* and *NRG1-ERBB* growth-signalling pathways (Hu *et al.*, 2007; Buxbaum *et al.*, 2008). *MAGI2* alleles have been associated with schizophrenia risk by Buxbaum *et al.* (2008), and Walsh *et al.* (2008) reported an association between disruption of this gene *via* a duplication and a case of schizophrenia, in an analysis of copy number variants.

Third, the gene *RELN*, at 7q22, codes for the extracellular matrix protein reelin which is secreted by GABA-ergic interneurons, and its expression is regulated *via* promotor methylation by *DNMT1*, a methyltransferase 'imprinter' gene that may itself be subject to genomic conflicts over expression pattern (Veldic *et al.*, 2005; Wilkins, 2005; Grayson *et al.*, 2006). Reelin is dysregulated in both schizophrenia and autism, primarily *via* changes in its methylation status (Dong *et al.*, 2005a; Fatemi, 2005; Fatemi *et al.*, 2005; Grayson *et al.*, 2005; Guidotti *et al.*, 2005), and it has also been linked *via* genetic association studies with schizophrenia (Goldberger *et al.*, 2005; Shifman *et al.*, 2008) and autism (Persico *et al.*, 2001; Zhang *et al.*, 2002; Bonora *et al.*, 2003; Devlin *et al.*, 2004; Bartlett *et al.*, 2005; Skaar *et al.*, 2005; Serajee *et al.*, 2006; Li *et al.*, 2008). Three lines of evidence suggest imprinting effects in *RELN* expression: (1) the EICO database of potentially imprinted genes (Nikaido *et al.*, 2004), (2) parent-of-origin effects in linkage of *RELN* with autism (Dutta *et al.*, 2007; Rampersaud *et al.*, 2007), and (3) studies of a mouse model for Turner syndrome in which *RELN* is differentially expressed between mice with a paternal *versus* maternal X chromosome (Davies *et al.*, 2006); however, there is no direct evidence of imprinting for this gene.

(*f*) *7q31 and the* FOXP2 *gene*

This region has been linked with autism and the related condition Specific Language Impairment (O'Brien *et al.*, 2003; Schellenberg *et al.*, 2006), and with schizophrenia (Detera-Wadleigh *et al.*, 1999). Genetic mapping and mutational studies of a three-generation pedigree of the 'KE' family, who exhibit autosomal dominant speech and language impairment, led to the identification of *FOXP2* at 7q31.2 as the causative gene for Specific Language Impairment (Fisher & Marcus, 2006). Allelic variants of *FOXP2* have been linked with autism in some studies (Newbury *et al.*, 2002; Gong *et al.*, 2004; Li *et al.*, 2005; Marui *et al.*, 2005), but other studies have found no evidence of association (Wassink *et al.*, 2002; Gauthier *et al.*, 2003). This gene may thus play a minor role in the etiology of autism, or its role may be restricted to effects on language skills that are also commonly affected in autism.

Sanjuán *et al.* (2006) found significant differences in *FOXP2* genetic variants between controls and schizophrenia patients with auditory hallucinations; this effect may be mediated by interleukin-2 (*IL-2*), given that *FOXP2* binds to the *IL-2* promoter (Wang *et al.*, 2003) and *IL-2* has been linked with schizophrenia genetically and physiologically (Schwarz *et al.*, 2006). The polymorphic sites linked to schizophrenia in the study of Sanjuán *et al.* (2006), rs1456031 and rs2396753, were the same two sites linked to autism by Gong *et al.* (2004), and they have not been genotyped in other studies. Further studies using these two polymorphic sites are required for robust interpretation of these associations. The only other evidence salient to an association between *FOXP2* and schizophrenia is data from Moon *et al.* (2006, their Table 3) suggesting that increased copy number of chromosomal segments at 7q31.2, including *FOXP2*, may be relatively common in this disorder.

Feuk *et al.* (2006) found that a lack of paternally inherited *FOXP2* is associated with reduced expression of some isoforms of this gene, and speech and language impairment, in patients with maternal uniparental disomy for chromosome 7. By contrast, paternal uniparental disomy of this chromosome does not lead to reduced *FOXP2* expression, or impaired speech and language. These authors suggest that imprinting effects may mediate this difference, but they also note that there is no evidence regarding differential expression or methylation of the paternal and maternal copies of this gene. There are no imprinted genes known from this region, although imprinted-gene clusters are found at 7q21.3 and 7q32.3. Crespi (2007) suggested that human speech and language may have evolved partially in the context of genomic conflict over resources provided by parents to young children, given the preliminary evidence for imprinting effects on the expression of *FOXP2* (Feuk *et al.*, 2006) and its interaction partner *FOXP1* (Nikaido *et al.*, 2004), recent positive selection on *FOXP2* in the human lineage (Enard *et al.*, 2002), and the apparent role of this gene in the evolution of speech.

Polymorphisms in a second gene in the 7q31 region, the metabotropic glutamate receptor *GRM8*, have been associated with schizophrenia (Takaki *et al.*, 2004) and autism (Serajee *et al.*, 2003; but see also Li *et al.*, 2008). *GRM8* haplotypes were also associated with variation in language and stereotypy phenotypes in autism, and such linkages were highly significant for maternal transmission but there was no evidence of association for paternal transmission (Serajee *et al.*, 2003). These data are suggestive of imprinting. *GRM8* is not known to be imprinted, but it is a short distance (3Mb) from the imprinted-gene cluster at 7q32. Different polymorphic markers were used in each study, and Takaki *et al.* (2004) did not test for parent-of-origin effects.

(*g*) *7q35 and the* CNTNAP2 *gene*

Deletions of the gene *CNTNAP2* has been linked with schizophrenia in three unrelated subjects (Friedman *et al.*, 2007), and allelic variants of this gene have recently been linked with autism (Alarcón *et al.*, 2008; Arking *et al.*, 2008). Arking *et al.* (2008) reported a strong parent-of-origin effect, such that the 'common variant [was] a disease variant only when inherited through the female germline' (Arking *et al.*, 2008, p. 162), and both studies also found that the associations with autism were notably-stronger for male than female patients. The *CNTNAP2* gene is strongly expressed in anterior brain regions of humans (but not rodents)(Abrahams *et al.*, 2007), and it is down-regulated in a variety of cancers (McAvoy *et al.*, 2007). Imprinted genes or parent-of-origin effects have apparently not been reported for the region harbouring this gene.

(*h*) *Parent-of-origin effects at 8q24*

The region at 8q24.3 has been associated with schizophrenia (Walss-Bass *et al.*, 2006), with the highest LOD score at D8S1836, surrounded by a cluster of four genes predicted to be imprinted (Luedi *et al.*, 2007), and within 3Mb of the known, brain-expressed imprinted gene *KCNK9*. Linkages to bipolar disorder have been reported for 8q24.13 (Cichon *et al.*, 2001; Park *et al.*, 2004) and 8q24.22 (Dick *et al.*, 2003; McInnis *et al.*, 2003*b*); Cichon *et al.* (2001) and McInnis *et al.* (2003*b*) did not find evidence for parent-of-origin effects for these sites, the other studies did not test for such effects, and there are no known or predicted imprinted genes in these regions.

(*i*) *Parent-of-origin effects at 10p12-p14*

Markers in this region have been linked with schizophrenia (Schwab *et al.*, 1998a; Straub *et al.*, 2002, for D10S1423), schizophrenia and schizoaffective disorder (DeLisi *et al.*, 2002, for D10S189), bipolar disorder (Lambert *et al.*, 2005, for D10S197), and autism (Lamb *et al.*, 2005, for D10S189), but these studies did not test the markers for parent-of-origin effects; Arking *et al.* (2008) also found linkage of 10p13-p14 to autism. Significant parent-of-origin effects have, however, been reported for these same markers in studies of obesity or body mass index: at D10S189 (Lindsay *et al.*, 2001), D10S1423 (Gorlova *et al.*, 2003), and D10S197 (Dong *et al.*, 2005*b*). The gene *Sfmbt2* at 10p14, about 0.5 Mb from D10S189, is imprinted with paternal expression in mouse placenta and embryos (Kuzmin *et al.*, 2008), and the predicted imprinted gene *GATA3* is a further 0.9 Mb from D10S189. *Sfmbt2* has yet to be studied in humans, but in mice it is one of 11 genes strongly upregulated in response to treatment with the mood-stabilizing drug sodium valproate, a standard treatment for bipolar disorder (Chetcuti *et al.*, 2006).

(*j*) *10q26 and the* INPP5F *gene*

This region has been linked with schizophrenia and bipolar disorder (Cichon *et al.*, 2001; Kelsoe *et al.*, 2001; Ewald *et al.*, 2002*a*,*b*; Lerer *et al.*, 2003; McInnis *et al.*, 2003*b*; Williams *et al.*, 2003; Bulayeva *et al.*, 2007), and with ADHD (Fisher *et al.*, 2002*b*), autism (Philippe *et al.*, 1999), and handedness (Van Agtmael *et al.*, 2003). Mustanski *et al.* (2005) reported linkage of 10q26 to homosexuality with a maternal parent-of-origin effect, but Cichon *et al.* (2001) and McInnis *et al.* (2003*b*) tested for, but did not find, significant parent-of-origin effects. Homosexuality, schizophrenia and schizotypy appear to engender significant increases in mixed handedness and left handedness, although some results are inconclusive (e.g. Blanchard *et al.*, 2006; Narr *et al.*, 2007). Many of the studies cited above (Philippe *et al.*, 1999; Cichon *et al.*, 2001; Kelsoe *et al.*, 2001; Ewald *et al.*, 2002*b*; McInnis *et al.*, 2003*b*; Mustanski *et al.*, 2005) note linkages to the same genetic marker, D10S217 at 10q26.2, although in some cases few markers were used. Patients with subterminal deletions of 10q (which includes deletion of D10S217) exhibit low birth weight and behavioural problems that 'suggest the diagnosis of pediatric bipolar disorder' (Courtens *et al.*, 2006).

Evidence for imprinting effects at 10q26 comes from Choi *et al.* (2005), who found that an isoform of the inositol phosphatase gene *INPP5F* was paternally expressed in brain tissue of mice, and from Wood *et al.* (2007), who showed paternal expression for this gene in humans (in foetal brain and other tissues). Stopkova *et al.* (2004) independently suggested that the *INPP5F*(=*SAC2*) gene at 10q26.11 might be associated with schizophrenia and bipolar disorder, based on its genomic location and function in the PI3K (phosphatidylinositol 3-kinase) growth-signalling pathway (see Kalkman, 2006). Strichman-Almashanu *et al.* (2002) reported a differentially methylated region in humans at 10q26.3 and a 'similarly-methylated region' at 10q26.11 (near *INPP5F*), and Hou (2003) suggested that 10q26 trisomy involves effects from imprinting, based on apparent higher survival in trisomy from paternal than maternal translocations. Finally, Luedi *et al.* (2005) noted that the murine analog of the human homeobox gene *NKX6-2*, at 10q26 near 10S217, exhibits high expression in the brain and is predicted to be imprinted with maternal expression, based on their bioinformatic analysis.

(*k*) *11p13 and the* BDNF *and* PAX6 *genes*

This region has been associated in genome scans with schizophrenia (Suarez *et al.*, 2006) bipolar disorder (McInnes *et al.*, 1996), and autism (Trikalinos *et al.*, 2006; Duvall *et al.*, 2007; Szatmari *et al.*, 2007). The region is of particular interest because it harbours the *BDNF* gene, for brain-derived neurotrophic factor, a neuronal growth factor involved in neurodevelopment as well as dopaminergic and serotoninergic transmission (Guillin, Demily & Thibaut, 2007), and the *PAX6* gene, a transcription factor that regulates development of the brain, eye, and pancreas (Mo & Zecevic, 2007; Davis *et al.*, 2008).

Imprinting effects on *BDNF* are suggested based on several lines of evidence: (1) bioinformatics sequence analysis predicting it to be imprinted in mice (Luedi *et al.*, 2005), (2) parent-of-origin effects for *BDNF* in its linkage to schizophrenia (Muglia *et al.*, 2003), (3) paternally biased transmission of the *BDNF* Val66Met polymorphism in ADHD (Kent *et al.*, 2005), although Schimmelmann *et al.* (2007) could not replicate this finding, (4) regulation of expression of BDNF by the gene *MeCP2* (Wade, 2004), and (5) the presence of two imprinted genes, *AWT1* (the Wilm's tumour gene) and *WAT-AS* at 11p13, about 4.6 Mb distant (Naumova, Greenwood & Morgan, 2001; Hancock *et al.*, 2007). However, there is no direct evidence of imprinting involving this gene.

BDNF is overexpressed in autism, at least among children (Miyazaki *et al.*, 2005; Tsai, 2005; Connolly *et al.*, 2006; Hashimoto *et al.*, 2006; Nishimura *et al.*, 2007) but it exhibits reduced expression in schizophrenia in almost all studies (Weickert *et al.*, 2003, 2005; Angelucci, Brenè & Mathé, 2005; Hashimoto *et al.*, 2005; Palomino *et al.*, 2006; Buckley *et al.*, 2007; Guillin *et al.*, 2007; see also Peet, 2004). Polymorphisms within the *BDNF* gene have been associated genetically with autism in the single such study conducted to date (Nishimura *et al.*, 2007). Many studies have reported associations of *BDNF* genetic variants with schizophrenia (Sklar *et al.*, 2002; Neves-Periera *et al.*, 2005; Rosa *et al.*, 2006; Qian *et al.*, 2007) and bipolar disorder (Lohoff *et al.*, 2005; Craddock & Forty, 2006) and a promotor polymorphism variant that reduces expression has been linked

with bipolar disorder (Okada *et al.*, 2006). By contrast, other studies show a lack of association and recent meta-analyses yielded mixed results (Gratacos *et al.*, 2007; Xu *et al.*, 2007).

PAX6, about 4Mb distant from *BDNF*, is predicted as imprinted with maternal expression by Luedi *et al.* (2007); *PAX6*, and the predicted-imprinted gene *WIT1*, flank the known imprinted gene *WT1*. Loss of function mutations of *PAX6* have been associated with autism in conjunction with ocular disorders involving the iris, and WAGR (Wilms tumour, Aniridia, ambiguous Genitalia, mental Retardation) syndrome, due to deletion of multiple genes in this region, also involves high rates of autism (Davis *et al.*, 2008). Phenotypic variation in iris characteristics, apparently due in part to allelic variation in *PAX6* and involving pleiotropic effects on brain and eye development, has also been associated with cognitive traits on the autistic spectrum (Larsson, Pedersen & Stattin, 2007). Loss of expression of a maternally expressed imprinted gene is predicted to be associated with autism under the imprinted brain theory (Badcock & Crespi, 2006; Crespi & Badcock, 2008), as it results in a bias towards increased effects from paternal genes. *PAX6* is coexpressed with the schizophrenia-linked gene *OLIG2* (Georgieva *et al.*, 2006) in the human brain (Mo & Zecevic, 2007), but it has yet to be examined with regard to the risk of psychotic-spectrum conditions.

(*i*) *11p15.5 and the* CDKN1C *gene*

This location has been linked in genome scans with bipolar disorder (McInnis *et al.*, 2003*a*; Zandi *et al.*, 2003; see also Craddock & Lendon, 1999), major depression (Zubenko *et al.*, 2003), autism (Duvall *et al.*, 2007) and dyslexia (Hsiung *et al.*, 2004). The region also contains a large cluster of imprinted genes, some of which are expressed in the brain, as well as genes implicated in psychosis or autism but not known to be subject to imprinting; these include *SCT* (Alamy *et al.*, 2004; Köves *et al.*, 2004; Toda *et al.*, 2006), *HRAS* (see Hsiung *et al.*, 2004), *TH* (the gene for tyrosine hydroxylase) (e.g. Seeman *et al.*, 2005) and *DRD4* (Lung, Tzeng & Shu, 2002; Xing *et al.*, 2003; Abdolmaleky *et al.*, 2005). *DRD4* shows evidence of maternal transmission of repeat-allele markers in bipolar disorder (Muglia *et al.*, 2002) and paternal transmission in ADHD (Hawi *et al.*, 2005), but no direct evidence of imprinting.

The maternally expressed imprinted gene *CDKN1C* at 11p15.5 represents a 'rheostat for embryonic growth' (Andrews *et al.*, 2007, p. 8), and its protein product p57kip2 regulates *Nurr1*, a nuclear receptor essential for the maturation of midbrain dopamine cells; in turn, *Nurr1* regulates the expression of *BDNF* (Volpicelli *et al.*, 2007). *Nurr1* levels are reduced in prefrontal cortex in schizophrenia and bipolar disorder (Xing *et al.*, 2006), and mice with reduced *Nurr1* levels have been proposed as an animal model for schizophrenia (Rojas *et al.*, 2007).

(*m*) *16p13.3 and the* GRIN2A *gene*

This region has been linked with bipolar disorder and schizophrenia (McInnis *et al.*, 2003*a*; Yamada *et al.*, 2004*a*; Maziade *et al.*, 2005; Cassidy *et al.*, 2007), as well as autism (Phillipe *et al.*, 1999; IMGSAC, 2001*a*,*b*; Liu *et al.*, 2001) and ADHD (Smalley *et al.*, 2002; Ogdie *et al.*, 2003). Smalley *et al.* (2005) also highlight this region as one of four jointly implicated in autism and ADHD. Rubenstein-Taybi syndrome, which is due to deletions or translocations involving 16p13.3, also exhibits a high incidence of bipolar-disorder symptoms (Hellings *et al.*, 2002). The presence of imprinted genes on chromosome 16, and in this specific region, is suggested by the placental growth-restriction effects of maternal uniparental disomies (Yong *et al.*, 2002; Eggermann *et al.*, 2004), by the presence of parent-of-origin effects or differentially methylated CpG islands at 16p12-p13 (Zerres & Rudnik-Schöneborn, 1995; Deichmann *et al.*, 1998; Wyszynski & Panhuysen, 1999; Strichman-Almashanu *et al.*, 2002), and by the bioinformatic predictions of Luedi *et al.* (2007) for imprinting of eight genes at 16p13.3.

A candidate gene for these genome scan findings is the N-methyl-d-aspartate (NMDA) receptor subunit gene *GRIN2A*; mouse knockouts of this gene exhibit strongly altered learning and memory (Bannerman *et al.*, 2004; see also de Quervain & Papassotiropoulos, 2006). This gene is found at 16p13.3, and variants have been associated with autism (Barnby *et al.*, 2005), ADHD (Turic *et al.*, 2004), schizophrenia (Iwayama-Shigeno *et al.*, 2005; Tang *et al.*, 2006) and bipolar disorder (Itokawa *et al.*, 2003). None of these studies discusses the presence or absence of parent-of-origin effects.

(*n*) *19q13.3-q13.4: imprinted and 'imprinter' genes*

Badenhop *et al.* (2002) linked 19q12-q13 with bipolar disorder in a genome scan, Macgregor *et al.* (2004) provided evidence for 19q13 linkage with schizophrenia, and 19q13 has also been strongly linked with Specific Language Impairment (SLI Consortium, 2002).

An important cluster of imprinted genes is found at 19q13.4, including *PEG3*, *APeg3*, *ITUP1* and *ZIM2*, which are expressed in the brain (Yamaguchi *et al.*, 2002; J. Kim *et al.*, 2004; Maegawa *et al.*, 2004; Glasgow *et al.*, 2005). *PEG3* and *APeg3* are known to affect oxytocin and vasopressin production, and affiliative mother-offspring interactions, in rodents (Li *et al.*, 1999; Glasgow *et al.*, 2005; Isles & Holland, 2005). In humans, GABA modulates the release of oxytocin in the brain, oxytocin mediates aspects of learning, memory, and affiliative behaviour (Depue & Morrone-Strupinsky, 2005), oxytocin levels affect dopaminergic and glutamatergic regulation of prepulse inhibition, and reduced oxytocin receptor expression has been proposed as a primary correlate of social-behaviour deficits in schizophrenia (Feifel & Reza, 1999; Liu, Pappas & Carter, 2005). Vasopressin also regulates aspects of human social behaviour, emotion, and cognition, in part *via* interaction with the dopaminergic and serotoninergic systems, and alterations of the vasopressinergic system are associated with schizophrenia and autism (Jentsch, Arguello & Anzivino, 2003; Matsuoka *et al.*, 2005), and affect prepulse inhibition in animal models (Egashira *et al.*, 2005). Autism has been associated with genetic variation in the vasopressin receptor gene *AVPR1a* (Yirmiya *et al.*, 2006), and the oxytocin receptor gene *OXTR* (Wu *et al.*, 2005; see also Ylisaukko-oja

et al., 2006), apparently *via* their effects on social behaviour. The importance of oxytocin and vasopressin in modulating social interaction, their genetic and physiological links with autism and schizophrenia, and the effects of imprinted genes on their expression suggest that these neuropeptides play a role in these two conditions.

The 'imprinter' gene *DNMT1* at 19q13.3 codes for a methyltransferase involved in the maintenance of the methylation patterns that regulate the expression of imprinted and non-imprinted genes (see Wilkins, 2005). Like *MeCP2* and the related genes *MBD1, 2* and *3*, *DNMT1*, it is highly expressed in the brain (Tucker, 2001). Wilkins (2005) describes the forms of genomic conflict that can be associated with the application and removal of imprints regulating gene expression, depending upon the *cis*- and *trans*- arrangements of genes that are paternally or maternally expressed. Such conflicts involving 'imprinter' genes represent a potential arena for epigenetic disruption distinct from that involving imprinted genes themselves (see Burt & Trivers, 1998; Reik & Walter, 2001; Wilkins & Haig, 2001, 2002). Other methyltransferase genes such as *MBD3* have been suggestively implicated in autism (Wimpory, Nicholas & Nash, 2002).

DNMT1 is upregulated in cortical GABAergic interneurons in schizophrenia and bipolar disorder, which results in hypermethylation and decreased expression of reelin and GAD67 (glutamic acid decarboxylase) in prefrontal cortex and hippocampus (Dong *et al.*, 2005*a*; Grayson *et al.*, 2005; Noh *et al.*, 2005; Veldic *et al.*, 2005; Grayson *et al.*, 2006). Such epigenetic dysregulation may influence the development and symptoms of psychosis (Grayson *et al.*, 2005), given that it involves changes in gene expression that 'impinge on several pathways, including expression of imprinted genes, cell-cycle control, growth factor/receptor signal transduction, and mobilization of retroelements' (Jackson-Grusby *et al.*, 2001, p. 31). The degree to which imprinting conflict over gene expression mediates or potentiates such effects remains to be addressed. However, Bestor (2003) provides evidence that genomic conflict drives the remarkably high levels of Dnmt1o (a protein produced from *DNMT1*) in oocytes, and may be involved in cases of Beckwith-Wiedemann syndrome due to loss of imprinting for the gene *KCNQT1OT1*. Other 'imprinter' genes, many of which are found in genomic locations linked with schizophrenia or mood disorders in genome scans (Abdolmaleky *et al.*, 2004), may be subject to similar effects.

(*o*) *20q13 and the* GNAS *locus*

This region has been linked with bipolar disorder (McInnis *et al.*, 2003; Park *et al.*, 2004; McQueen *et al.*, 2005) and schizophrenia (Freedman *et al.*, 2001; Garver *et al.*, 2001) in genome scans, and it also contains a cluster of imprinted genes at the *GNAS* locus. *GNAS* is a complex imprinted locus whose expression involves use of multiple promotors to produce several gene products, some maternally and some paternally expressed (Weinstein *et al.*, 2004, 2007; J. Liu *et al.*, 2005; Peters *et al.*, 2006). These alternatively imprinted transcripts exert divergent, opposing effects on energy metabolism, providing strong support for the conflict theory of imprinting (Plagge *et al.*, 2004; Chen *et al.*, 2005; Weinstein *et al.*, 2007). Further support for the presence of genomic conflict mediated by alleles at this locus comes from effects of paternal inactivation of *GNAS* in proximal renal tubule, which are explicable in terms of maternal-foetal conflict over calcium used in bone mineralisation (Haig, 2004*a*).

Three lines of evidence implicate the *GNAS* locus in the etiologies of schizophrenia and autism, and their constituent phenotypes.

First, the *GNAS* locus codes for a protein product, Gαs, predominantly from the maternal allele in some tissues (including the pituitary and proximal renal tubules) and from both alleles in other tissues (Weinstein *et al.*, 2001). *GNAS* alleles have been linked to schizophrenia in a case-control study (Minoretti *et al.*, 2006). In particular, the TT genotype of the T393C polymorphism, which is associated with relatively high Gαs expression, increases risk of schizophrenia with negative symptoms. These data, and the development of mouse mutants that constitutively express this transcript as a model for sensorimotor gating deficits in schizophrenia (Gould *et al.*, 2004), suggest that higher levels of this maternally-biased imprinted gene are associated with schizophrenia in this case.

Multiple studies have documented higher levels of Gαs in patients with bipolar disorder than in controls, but lower levels in unipolar depression (Avissar & Schreiber, 2006). Proximate mechanisms for such effects of Gαs expression on psychiatric phenotypes may involve altered levels of neuronal apoptosis in the brain (Minoretti *et al.*, 2006), dysregulation of dopamine D1 receptor activity (Jin, Wang & Friedman, 2001; Gould *et al.*, 2004), effects on the hypothalamic-pituitary-adrenal axis (HPA) axis (Goldman & Mitchell, 2004; Strawn *et al.*, 2004), and dysregulation of the cAMP signalling system more generally (Hattori *et al.*, 2005).

Second, the *GNAS* locus also generates the maternally expressed transcript that codes for NESP55, a neuroendocrine secretory protein of unknown molecular function (Eder *et al.*, 2004). NESP55 is highly expressed in various brain regions, including the hypothalamus, serotoninergic neurons of the dorsal raphe nucleus, and the locus coeruleus, whose activity mediates the norepinephrine-adrenergic system (Ischia *et al.*, 1997; S. J. Kim *et al.*, 2000; Plagge *et al.*, 2004). This protein functions as a specific antagonist of the *5-HT1B* serotonin receptor, leading to reduced anxiety in a mouse model (Ischia *et al.*, 1997; Grimaldi *et al.*, 1999). NESP55 knockout mice (which have reduced maternal-gene expression) show normal growth patterns, but are hyperactive and also show abnormally high avoidance of novel environments (Plagge *et al.*, 2005). One interpretation of this pattern is that these mice are exhibiting two autistic phenotypes: aversion to novelty is a core feature of this disorder (e.g. Gomot *et al.*, 2006), and hyperactivity is notably common in autism, especially in childhood (Gillberg & Billstedt, 2000; Lee & Ousley, 2006). However, differences in cognition and behaviour between humans and mice severely limit the strength of such inferences, and loss of NESP55 expression in humans is not associated with any obvious phenotypic effects (S. J. Kim

et al., 2000; Liu *et al.*, 2000). *GNAS* also interacts with *FMR1*, the causative gene for the autism spectrum condition Fragile X syndrome (see Fig. 1 in Bittel, Kibiryeva & Butler, 2007*a*), although the nature of the interaction is unknown.

Third, some mutations and epigenetic alterations at the *GNAS* locus lead to disordered thyroid metabolism (Bastepe & Jüppner, 2005; Germain-Lee *et al.*, 2005; Linglart *et al.*, 2005), including hypothyroidism due to altered expression of a *GNAS* transcript in the thyroid (Germain-Lee *et al.*, 2002). Hypothyroidism (due to multiple causes), and hyperparathyroidism, pseudohypoparathyroidism and pseudopseudohypoparathyroidism (due in some cases to alterations at the *GNAS* locus) have been causally linked with forms of psychosis (Hay & Jolley, 1974; Hay, Jolley & Jones, 1974; Preskorn & Reveley, 1978; Arnold, 2003; Heinrich & Grahm, 2003), including Capgras syndrome, the delusional misidentification of others as imposters (Hirstein & Ramachandran, 1997), which is found most commonly in paranoid schizophrenia (Mann & Foreman, 1996; Oyebode & Sargeant, 1996). However, although psychosis is a relatively common feature of hypothyroidism (Heinrich & Grahm, 2003), it is not characteristic of the two main human disorders of *GNAS* dysregulation, McCune-Albright syndrome and Albright hereditary osteodystrophy, and the nature of functional links between the expression levels of different *GNAS* transcripts, thyroid disorders, and psychosis requires further study.

(3) Parent-of-origin effects in linkages to psychosis

Genome scans for bipolar disorder have inferred linkages with maternal parent-of-origin effects for 1q41 and 13q12 (McInnis *et al.*, 2003*b*), 2p24-p21 and 2q31-q32 (Cichon *et al.*, 2001), and 22q13.1 (Petronis *et al.*, 2002). By contrast, paternal parent-of-origin effects have been found for 16q21-q23 (Cichon *et al.*, 2001), 18p11 (Kato, 2001; see also Corradi *et al.*, 2005), and 18q21-q22 (McMahon *et al.*, 2001; McInnis *et al.*, 2003*b*; Schulze *et al.*, 2003). Luedi *et al.* (2007) also present evidence for linkage of predicted imprinted genes with schizophrenia, bipolar disorder, and autism, including putative imprinting of the schizophrenia-linked genes *OLIG2* (Georgieva *et al.*., 2006) and *DGCR6* (Liu *et al.*, 2002), the autism-linked gene *CENTG2* (Wassink *et al.*, 2005), and the gene *NR3C1*, which has been associated with major depression (Zobel *et al.*, 2008).

Lan *et al.* (2007) reviewed genetic models for inheritance of bipolar disorder, and found evidence consistent with strong parent-of-origin effects. By contrast, DeLisi *et al.* (2000) reported an absence of evidence for parent-of-origin effects in the inheritance of schizophrenia, although they noted 'a trend for more maternal than paternal inheritance' at $P < 0.08$. Scans for schizophrenia have detected maternal parent-of-origin effects for 18p11 (Schwab *et al.*, 1998*b*) and 22q12 (DeLisi *et al.*, 2002); the latter authors suggest that their discovery of an imprinting effect at this locus indicates that this disorder is primarily epigenetic (due to altered gene expression) rather than a result of variation in DNA sequence.

VIII. DISCUSSION

Evidence for effects of imprinted genes and genomic conflicts on the etiologies of psychotic and autistic spectrum conditions includes: (1) the contrast between high rates of psychotic spectrum conditions in Prader-Willi syndrome and high rates of autism in Angelman, Beckwith-Wiedemann, and Rett syndromes, (2) high rates of psychotic spectrum conditions in Klinefelter syndrome and XXX trisomy, but elevated rates of autism in Turner syndrome, and (3) imprinted-gene effects and parent-of-origin effects in the development of psychosis and autism identified or inferred from genome scans and genetic-association studies. These diverse findings are broadly consistent with the hypothesis that psychotic spectrum conditions commonly involve genetic and epigenetic imbalances towards increased relative effects of genes favouring maternal interests (*via* reduced expression of paternally expressed genes, increased expression of maternally expressed genes, both effects, or increased expression of X-linked genes), while autistic spectrum conditions more commonly entail the opposite: increased relative effects of paternally expressed genes.

The hypothesis that imprinted genes contribute to the etiologies of psychosis and autism is consistent with current neurodevelopmental models for these conditions, in that autism involves constrained overgrowth of the body, head or both (Courchesne & Pierce, 2005; Redcay & Courchesne, 2005; Mraz *et al.*, 2007; Sacco *et al.*, 2007; van Daalen *et al.*, 2007; Webb *et al.*, 2007; Kent *et al.*, 2008), whereas schizophrenia is characterised by effects of slow development, undergrowth, and altered patterns of apoptosis and synaptic pruning (Rapoport *et al.*, 2005; Kalkman, 2006). Such diametric patterns are directly parallel to those generated by dysregulation of imprinted gene effects in placentation and foetal development, where biases towards paternal expression of imprinted genes enhance growth and maternal biases reduce it (Haig, 2004*a*,*b*; McMinn *et al.*, 2006; Angiolini *et al.*, 2006). An important difference between imprinting effects on growth in the placenta and brain, however, is that imprinting effects on brain development are expected to involve local and regional effects on brain structure and function, as well as influences on general growth (Crespi & Badcock, 2008). In particular, reduced effects from paternally expressed genes are expected to engender impaired development and function of limbic-system regions (Keverne *et al.*, 1996; Davies *et al.*, 2007), and possibly also reduced cerebral lateralization, both of which have been associated with the expression of psychosis in a suite of studies (Crespi & Badcock 2008). The simplest neuroanatomical correlates of psychotic spectrum conditions are reduced functionality of the hypothalamus, the core of the paternal brain, in Prader-Willi syndrome, and reduced hemispheric lateralization in schizophrenia (e.g. Ceccherini-Nelli, Turpin-Crowther & Crow, 2007), as apparently mediated in part by the paternally expressed gene *LRRTM1* (Francks *et al.*, 2007). By contrast, in Angelman and Rett syndromes the cerebral cortex and cerebellum are differentially affected, leading to differential loss of maternal-brain functions and high rates of mental retardation.

Whereas imprinted-gene conflicts in placental development may sometimes be physiologically straightforward, as in the *IGF2-IGF2R* system that regulates growth in mice (e.g. Smith *et al.*, 2006), or conflicts regarding production and sharing of body heat in neonatal rodents (Haig, 2008), conflicts in brain development are likely to be considerably more complex, and they may only be recognisable as such once the functions of brain-expressed imprinted genes are much better understood. The degree to which risks of autistic or psychotic spectrum conditions are mediated directly by such imprinted-gene expression effects on neurological function and childhood or adult behaviour, as opposed to indirectly *via* secondary effects on early growth of the brain and body, also remains to be investigated (Crespi & Badcock, 2008; Goos & Ragsdale, 2008).

There is at present no substantiated alternative to Haig's conflict theory that offers an evolutionary or developmental explanation or basis for the genomic imprinting effects that are observed in psychotic and autistic spectrum conditions (Davies *et al.*, 2007; Wilkinson *et al.*, 2007). The primary logical basis of this hypothesis is that considerable evidence implicates imprinted genes in conflicts over maternal resources, a substantial proportion of imprinted genes exert brain-specific effects, and conflicts over maternal resources should involve not just placentation and foetal development, but also cognition and behaviour throughout childhood (Crespi & Badcock 2008). The main evidence contra-indicating the hypothesis that imprinted genes, and genes regulating imprinting, partially mediate the risk of such conditions is that few of the genes that have been linked thus far with schizophrenia, bipolar disorder, major depression, or autism are imprinted. It is difficult to evaluate this observation, given that few genes have been definitively associated with these conditions as yet, only a small proportion of genetic-association and genome-scan studies of these conditions has tested for parent-of-origin effects, and only a proportion of imprinted genes, or genes controlled by imprinted genes, have been identified as such (Luedi *et al.*, 2005, 2007; Royo *et al.*, 2006). However, where imprinted-gene effects have been documented and characterised, as in Prader-Willi syndrome, Beckwith-Wiedemann syndrome, Angelman syndrome, and *SGCE* and *LRRTM1* mutations, they exhibit notably-strong effects on the expression of psychosis or autism, and there is no reason to expect the absence of comparable yet smaller effects from genetic, genomic and epigenetic alterations throughout the genome. The possibility of such pervasive, convergent effects, varying in magnitude, is supported by the multiple, independent causes of Prader-Willi syndrome phenotypes described here, and by the presence of psychotic spectrum *versus* autistic spectrum conditions in pairs of genomic sister-syndromes mediated by deletions *versus* duplications of the same genomic region, as in Smith-Magenis syndrome, Williams syndrome, and Velocardiofacial syndrome (Crespi & Badcock, 2008).

The main implications of this review are threefold. First, and most generally, these findings, taken together, suggest an important role for genomic conflict in the evolution of human cognitive architecture, given that psychotic and autistic spectrum phenotypes appear to reflect diametrically altered development of the human social brain (Crespi & Badcock 2008). Neurodevelopment, like placental and foetal development, may thus proceed under a dynamic balance between the conflicting interests of maternally and paternally imprinted genes, with the development of any given individual mediated in part by genetic and epigenetic variation affecting their position on a spectrum from maternal-gene bias, to balanced development, to paternal-gene bias (Fig. 3). Whereas small deviations from balanced development are expected, under the conflict theory of imprinting, to benefit either the mother or the child at some cost to the other, larger deviations become more likely to be maladaptive for both, and contribute to the deleterious clinical phenotypes of autistic and psychotic spectrum conditions.

Second, consideration of a role for imprinted genes in neurodevelopmental conditions should motivate a focus on the further recognition and functional characterisation of imprinted brain-expressed genes, especially imprinted genes active in early foetal development, and genes such as *DNMT1*, *DNMT3a* and *MeCP2* that can regulate imprinting effects (Wilkins, 2005; Horsthemke & Buiting, 2008). A notable strength of the imprinted brain hypothesis is that it makes clear, falsifiable, *a priori* predictions about the expected effects on cognitive and behavioural phenotypes of alterations in imprinted genes, towards either a maternal or a paternal bias.

Third, future genome scans and genetic-association studies of psychotic and autistic spectrum conditions should include an emphasis on analyzing genetic and epigenetic variants in brain-expressed imprinted genes. A primary motivation for an enhanced focus on imprinted genes in neurodevelopmental disorders is that such genes are known to be especially important in brain development (Davies *et al.*, 2007, 2008; Wilkinson *et al.*, 2007), they are more-readily subject to major dysregulation than non-imprinted genes, and the well-supported conflict theory of imprinting predicts that their dysregulation should impact strongly upon the development and function of the human social brain (Crespi & Badcock, 2008). The conflict theory of imprinting thus provides a conceptual link of evolutionary theory with genes, genomes, development, and behaviour that should help to guide research in understanding the major disorders of human social cognition.

IX. CONCLUSIONS

(1) Disorders mediated by imprinted genes tend to exhibit diametric phenotypes, because dysregulated epigenesis may tip gene expression towards increased relative effects from either maternally or paternally imprinted genes. Examples include placental and foetal overgrowth *versus* undergrowth, Beckwith-Wiedemann syndrome *versus* Silver-Russell syndrome, and Angelman syndrome *versus* Prader-Willi syndrome. In each case, a paternal imprinted-gene bias leads to relatively increased growth and demands on the mother, and a maternal bias leads to relatively decreased growth and demands.

(2) Previous studies have implicated increased relative effects of paternally expressed imprinted genes in some

autism spectrum conditions. By the conflict theory of genomic imprinting, psychotic spectrum conditions (including schizophrenia, bipolar disorder, and major depression) should be mediated in part by increased relative effects from maternal imprinted-gene expression (or other maternal-gene interests), given that these conditions involve many phenotypes that are notably diametric to those observed on the autism spectrum.

(3) The high incidence of psychosis in Prader-Willi syndrome can be attributed to a bias towards decreased relative effects of paternally expressed imprinted genes. By contrast, high rates of autism in Angelman syndrome and Beckwith-Wiedemann syndrome may be associated with a bias towards increased relative effects from paternally expressed imprinted genes. Klinefelter syndrome (47,XXY) and 47,XXX trisomy involve increased rates of psychosis, which contrast with the relatively high rates of autism observed in Turner syndrome (45,X). These effects of X chromosome aneuploidy on psychosis and autism may be mediated by genomic conflict effects, given that X-linked genes are, like maternally expressed imprinted genes, expected to favour matrilineal interests.

(4) Genome-scan and genetic-association studies demonstrate that parent-of-origin and imprinted-gene effects are commonly found in analyses of the genetic basis of schizophrenia and bipolar disorder. In some cases (e.g. the genes *SGCE* and *GNAS*) these disorders can be traced to increased expression of maternal genes, or reduced expression of paternal genes, each of which creates a bias towards effects of imprinted genes with maternal expression. In other cases (e.g. *BDNF, CNTNAP2, DISC1, GRIK2, GRM8, FOXP2, HLA-DRB1, MeCP2, RELN* and *UBE3A*), genetic variants of the same gene have been linked with both autism and psychosis. This pattern is consistent with diametric genetic and epigenetic effects in autism and psychosis to the extent that gene expression is differentially altered in these two sets of disorders, as for *BDNF*, a brain growth factor which tends to be over-expressed in autism and under-expressed in schizophrenia compared to controls.

(5) The conflict theory of imprinting provides a clear conceptual link of evolutionary biology with genes, development, and behaviour that should help to guide empirical research aimed at understanding the causes of the major disorders of human social cognition, including schizophrenia, bipolar disorder, major depression, and autism. The primary implication of this theory, and its empirical support to date, is that increased emphasis on the recognition and analysis of brain-expressed imprinted genes is vital to further progress in understanding human neurodevelopment, behaviour and evolution.

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XI. REFERENCES

Abdolmaleky, H. M., Faraone, S. V., Glatt, S. J. & Tsuang, M. T. (2004). Meta-analysis of association between the T102C polymorphism of the 5HT2a receptor gene and schizophrenia. *Schizophrenia Research* **67**, 53–62.

Abdolmaleky, H. M., Thiagalingam, S. & Wilcox, M. (2005). Genetics and epigenetics in major psychiatric disorders: dilemmas, achievements, applications, and future scope. *American Journal of Pharmacogenomics* **5**, 149–160.

Abecasis, G. R., Burt, R. A., Hall, D., Bochum, S., Doheny, K. F., Lundy, S. L., Torrington, M., Roos, J. L., Gogos, J. A. & Karayiorgou, M. (2004). Genomewide scan in families with schizophrenia from the founder population of Afrikaners reveals evidence for linkage and uniparental disomy on chromosome 1. *American Journal of Human Genetics* **74**, 403–417.

Abel, K. M. (2004). Foetal origins of schizophrenia: testable hypotheses of genetic and environmental influences. *British Journal of Psychiatry* **184**, 383–385.

Abrahams, B. S., Tentler, D., Perederiy, J. V., Oldham, M. C., Coppola, G. & Geschwind, D. H. (2007). Genome-wide analyses of human perisylvian cerebral cortical patterning. *Proceedings of the National Academy of Sciences of the United States of America* **104**, 17849–17854.

Akaho, R., Matsushita, I., Narita, K., Okazaki, Y., Okabe, Y., Matsushita, M., Hohjoh, H., Tokunaga, K. & Sasaki, T. (2000). Support for an association between HLA-DR1 and schizophrenia in the Japanese population. *American Journal of Medical Genetics, B* **96**, 725–727.

Alamy, S. S., Jarskog, L. F., Sheitman, B. B. & Lieberman, J. A. (2004). Secretin in a patient with treatment-resistant schizophrenia and prominent autistic features. *Schizophrenia Research* **66**, 183–186.

Alarcón, M., Abrahams, B. S., Stone, J. L., Duvall, J. A., Perederiy, J. V., Bomar, J. M., Sebat, J., Wigler, M., Martin, C. L., Ledbetter, D. H., Nelson, S. F., Cantor, R. M. & Geschwind, D. H. (2008). Linkage, association, and gene-expression analyses identify CNTNAP2 as an autism-susceptibility gene. *American Journal of Human Genetics* **82**, 150–159.

Albrecht, U., Sutcliffe, J. S., Cattanach, B. M., Beechey, C. V., Armstrong, D., Eichele, G. & Beaudet, A. L. (1997). Imprinted expression of the murine Angelman syndrome gene, Ube3a, in hippocampal and Purkinje neurons. *Nature Genetics* **17**, 75–78.

Allen, E., Horvath, S., Tong, F., Kraft, P., Spiteri, E., Riggs, A. D. & Marahrens, Y. (2003). High concentrations of long interspersed nuclear element sequence distinguish monoallelically expressed genes. *Proceedings of the National Academy of Sciences of the United States of America* **100**, 9940–9945.

Allen, N. D., Logan, K., Lally, G., Drage, D. J., Norris, M. L. & Keverne, E. B. (1995). Distribution of parthenogenetic cells in the mouse brain and their influence on brain development and behavior. *Proceedings of the National Academy of Sciences of the United States of America* **92**, 10782–10786.

Andrews, S. C., Wood, M. D., Tunster, S. J., Barton, S. C., Surani, M. A. & John, R. M. (2007). Cdkn1c (p57Kip2) is the major regulator of embryonic growth within its imprinted domain on mouse distal chromosome 7. *BMC Developmental Biology* **7**, 53.

Andrieu, D., Meziane, H., Marly, F., Angelats, C., Fernandez, P. A. & Muscatelli, F. (2006). Sensory defects in Necdin deficient mice result from a loss of sensory neurons correlated within an increase of developmental programmed cell death. *BMC Developmental Biology* **6**, 56.

Angelucci, F., Brenè, S. & Mathé, A. A. (2005). BDNF in schizophrenia, depression and corresponding animal models. *Molecular Psychiatry* **10**, 345–352.

Angiolini, E., Fowden, A., Coan, P., Sandovici, I., Smith, P., Dean, W., Burton, G., Tycko, B., Reik, W., Sibley, C. & Constância, M. (2006). Regulation of placental efficiency for nutrient transport by imprinted genes. *Placenta* **27** Suppl A, s98–s102.

Arinami, T., Otsuka, Y., Hamaguchi, H., Itokawa, M., Aoki, J., Shibuya, H., Okubo, Y., Iwawaki, A., Ota, K., Enguchi, H., Tagaya, H., Yano, S., Shimizu, H. & Toru, M. (1998). Evidence supporting an association between the DRB1 gene and schizophrenia in Japanese. *Schizophrenia Research* **32**, 81–86.

Arking, D. E., Cutler, D. J., Brune, C. W., Teslovich, T. M., West, K., Ikeda, M., Rea, A., Guy, M., Lin, S., Cook, E. H. & Chakravarti, A. (2008). A common genetic variant in the neurexin superfamily member CNTNAP2 increases familial risk of autism. *American Journal of Human Genetics* **82**, 160–164.

Arnold, L. M. (2003). Gender differences in bipolar disorder. *Psychiatric Clinics of North America* **26**, 595–620.

Arnulf, I., Zeitzer, J. M., File, J., Farber, N. & Mignot, E. (2005). Kleine-Levin syndrome: a systematic review of 186 cases in the literature. *Brain* **128**, 2763–2776.

Ashdown, H., Dumont, Y., Ng, M., Poole, S., Boksa, P. & Luheshi, G. N. (2006). The role of cytokines in mediating effects of prenatal infection on the fetus: implications for schizophrenia. *Molecular Psychiatry* **11**, 47–55.

Ashwood, P., Wills, S. & Van de Water, J. (2006). The immune response in autism: a new frontier for autism research. *Journal of Leukocyte Biology* **80**, 1–15.

Avissar, S. & Schreiber, G. (2006). The involvement of G proteins and regulators of receptor-G protein coupling in the pathophysiology, diagnosis and treatment of mood disorders. *Clinica Chimica Acta* **366**, 37–47.

Axume, J., Smith, S. S., Pogribny, I. P., Moriarty, D. J. & Caudill, M. A. (2007). The MTHFR 677TT genotype and folate intake interact to lower global leukocyte DNA methylation in young Mexican American women. *Nutrition Research* **27**, 1365–1317.

Bacchelli, E. & Maestrini, E. (2006). Autism spectrum disorders: molecular genetic advances. *American Journal of Medical Genetics, C* **142**, 13–23.

Badcock, C. & Crespi, B. (2006). Imbalanced genomic imprinting in brain development: an evolutionary basis for the aetiology of autism. *Journal of Evolutionary Biology* **19**, 1007–1032.

Badenhop, R. F., Moses, M. J., Scimone, A., Mitchell, P. B., Ewen-White, K. R., Rosso, A., Donald, J. A., Adams, L. J. & Schofield, P. R. (2002). A genome screen of 13 bipolar affective disorder pedigrees provides evidence for susceptibility loci on chromosome 3 as well as chromosomes 9, 13 and 19. *Molecular Psychiatry* **7**, 851–859.

Baethge, C., Baldessarini, R. J., Freudenthal, K., Streeruwitz, A., Bauer, M. & Bschor, T. (2005). Hallucinations in bipolar disorder: characteristics and comparison to unipolar depression and schizophrenia. *Bipolar Disorder* **7**, 136–145.

Bah, J., Quach, H., Ebstein, R. P., Segman, R. H., Melke, J., Jamain, S., Rietschel, M., Modai, I., Kanas, K., Karni, O., Lerer, B., Gourion, D., Krebs, M. O., Etain, B., Schürhoff, F., Szöke, A., Leboyer, M. & Bourgeron, T. (2004). Maternal transmission disequilibrium of the glutamate receptor GRIK2 in schizophrenia. *Neuroreport* **15**, 1987–1991.

Baladrón, V., Ruiz-Hidalgo, M. J., Nueda, M. L., Díaz-Guerra, M. J., García-Ramírez, J. J., Bonvini, E., Gubina, E., & Laborda, J. (2005) Dlk acts as a negative regulator of Notch1 activation through interactions with specific EGF-like repeats. *Experimental Cell Research* **303**, 343–359.

Bannerman, D. M., Deacon, R. M. J., Brady, S., Bruce, A., Sprengel, R., Seeburg, P. H. & Rawlins, J. N. P. (2004). A comparison of GluR-A-deficient and wild-type mice on a test battery assessing sensorimotor, affective, and cognitive behaviors. *Behavioral Neuroscience* **118**, 643–647.

Bapat, S. & Galande, S. (2005). Association by guilt: identification of DLX5 as a target for MeCP2 provides a molecular link between genomic imprinting and Rett syndrome. *Bioessays* **27**, 676–680.

Barbon, A., Vallini, I. & Barlati, S. (2001). Genomic organization of the human GRIK2 gene and evidence for multiple splicing variants. *Gene* **274**, 187–197.

Barnby, G., Abbott, A., Sykes, N., Morris, A., Weeks, D. E., Mott, R., Lamb, J., Bailey, A. J. & Monaco, A. P. (2005). Candidate-gene screening and association analysis at the autism-susceptibility locus on chromosome 16p: evidence of association at GRIN2A and ABAT. *American Journal of Human Genetics, B* **76**, 950–966.

Baron-Cohen, S., Knickmeyer, R. C. & Belmonte, M. K. (2005). Sex differences in the brain: implications for explaining autism. *Science* **310**, 819–823.

Barrett, S., Beck, J. C., Bernier, R., Bisson, E., Braun, T. A., Casavant, T. L., Childress, D., Folstein, S. E., Garcia, M., Gardiner, M. B., Gilman, S., Haines, J. L., Hopkins, K., Landa, R., Meyer, N. H., Mullane, J. A., Nishimura, D. Y., Palmer, P., Piven, J., Purdy, J., Santangelo, S. L., Searby, C., Sheffield, V., Singleton, J., Slager, S. (1999). An autosomal genomic screen for autism. Collaborative linkage study of autism. American Journal of Medical Genetics, *B* **88**, 609–615.

Bartlett, C. W., Gharani, N., Millonig, J. H. & Brzustowicz, L. M. (2005). Three autism candidate genes: a synthesis of human genetic analysis with other disciplines. *International Journal of Developmental Neuroscience* **23**, 221–234.

Bastepe, M. & Jüppner, H. (2005). GNAS locus and pseudohypoparathyroidism. *Hormone Research* **63**, 65–74.

Battaglia, A. (2005). Del 1p36 syndrome: a newly emerging clinical entity. *Brain & Development* **27**, 358–361.

Bazeley, P. S., Shepelev, V., Talebizadeh, Z., Butler, M. G., Fedorova, L., Filatov, V. & Fedorov, A. (2008). snoTARGET shows that human orphan snoRNA targets locate close to alternative splice junctions. *Gene* **408**, 172–179.

Begni, S., Popoli, M., Moraschi, S., Bignotti, S., Tura, G. B. & Gennarelli, M. (2002). Association between the ionotropic glutamate receptor kainate 3 (GRIK3) ser310ala polymorphism and schizophrenia. *Molecular Psychiatry* **7**, 416–418.

Belluscio, L., Gold, G. H., Nemes, A. & Axel, R. (1998). Mice deficient in G(olf) are anosmic. *Neuron* **20**, 69–81.

Belmonte, M. K. & Bourgeron, T. (2006). Fragile X syndrome and autism at the intersection of genetic and neural networks. *Nature Neuroscience* **9**, 1221–1225.

Benasich, A. A. (2002). Impaired processing of brief, rapidly presented auditory cues in infants with a family history of autoimmune disorder. *Developmental Neuropsychology* **22**, 351–372.

Benes, F. M., Todtenkopf, M. S. & Kostoulakos, P. (2001). GluR5, 6,7 subunit immunoreactivity on apical pyramidal cell dendrites in hippocampus of schizophrenics and manic depressives. *Hippocampus* **11**, 482–491.

Bennett, P., Seurado, R., Jones, I., Bort, S., McCandless, F., Lambert, D., Heron, J., Comerford, C., Middle, F., Corvin,

A., Pelios, G., Kirov, G., Larsen, B., Mulcahy, T., Williams, N., O'Connell, R., O'Mahony, E., Payne, A., Owen, M., Holmans, P., Craddock, N. & Gill, M. (2002). The Wellcome trust UK-Irish bipolar affective disorder sibling-pair genome screen: first stage report. *Molecular Psychiatry* **7**, 189–200.

Bentall, R. (2003) *Madness Explained: Psychosis and Human Nature*. Allen Lane, London.

Berends, M. J., Hordijk, R., Scheffer, H., Oosterwijk, J. C., Halley, D. J. & Sorgedrager, N. (1999). Two cases of maternal uniparental disomy 14 with a phenotype overlapping with the Prader-Willi phenotype. *American Journal of Medical Genetics* **84**, 76–79.

Berg, J. S., Brunetti-Pierri, N., Peters, S. U., Kang, S. H., Fong, C. T., Salamone, J., Freedenberg, D., Hannig, V. L., Prock, L. A., Miller, D. T., Raffalli, P., Harris, D. J., Erickson, R. P., Cunniff, C., Clark, G. D., Blazo, M. A., Peiffer, D. A., Gunderson, K. L., Sahoo, T., Patel, A., Lupski, J. R., Beaudet, A. L. & Cheung, S. W. (2007). Speech delay and autism spectrum behaviors are frequently associated with duplication of the 7q11.23 Williams-Beuren syndrome region. *Genetics in Medicine* **9**, 427–441.

Bergström, T. F., Josefsson, A., Erlich, H. A. & Gyllensten, U. (1998). Recent origin of HLA-DRB1 alleles and implications for human evolution. *Nature Genetics* **18**, 237–242.

Bersani, G., Maneschi, M. L., Tarolla, E. & Pancheri, P. (2006). Dyslexia as a possible aspect of neurocognitive impairment in schizophrenia. *Schizophrenia Research* **82**, 265–266.

Bersani, G., Russo, D., Limpido, L. & Marconi D. (2007). Mood disorder in a patient with Smith-Magenis syndrome: a case report. *Neuro Endocrinology Letters* **28**, 7–10.

Bestor, T. H. (2003). Imprinting errors and developmental asymmetry. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* **358**, 1411–1415.

Beumont, P. J. & Mayou, R. (1971). Schizophrenia and XO-XX-XXX mosaicism. *British Journal of Psychiatry* **118**, 349–350.

Bi, W., Saifi, G. M., Girirajan, S., Shi, X., Szomju, B., Firth, H., Magenis, R. E., Potocki, L., Elsea, S. H. & Lupski, J. R. (2006). RAI1 point mutations, CAG repeat variation, and SNP analysis in non-deletion Smith-Magenis syndrome. *American Journal of Medical Genetics, A* **140**, 2454–2463.

Bickeböller, H., Kistler, M. & Scholz, M. (1997). Investigation of the candidate genes ACTHR and golf for bipolar illness by the transmission/disequilibrium test. *Genetic Epidemiology* **14**, 575–580.

Bischof, J. M., Stewart, C. L. & Wevrick, R. (2007). Inactivation of the mouse Magel2 gene results in growth abnormalities similar to Prader-Willi syndrome. *Human Molecular Genetics* **16**, 2713–2719.

Bittel, D. C. & Butler, M. G. (2005). Prader-Willi syndrome: clinical genetics, cytogenetics and molecular biology. *Expert Reviews in Molecular Medicine* **7**, 1–20.

Bittel, D. C., Kibiryeva, N. & Butler, M. G. (2007a). Whole genome microarray analysis of gene expression in subjects with fragile X syndrome. *Genetics in Medicine* **9**, 464–472.

Bittel, D. C., Kibiryeva, N., Sell, S. M., Strong, T. V., Butler, M. G. (2007b) Whole genome microarray analysis of gene expression in Prader-Willi syndrome. *American Journal of Medical Genetics, A* **143**, 430–442.

Bittel, D. C., Kibiryeva, N., Talebizadeh, Z. & Butler, M. G. (2003). Microarray analysis of gene/transcript expression in Prader-Willi syndrome: deletion versus UPD. *Journal of Medical Genetics* **40**, 568–574.

Blackwood, D. H., Pickard, B. J., Thomson, P. A., Evans, K. L., Porteous, D. J. & Muir, W. J. (2007). Are some genetic risk factors common to schizophrenia, bipolar disorder and depression? Evidence from DISC1, GRIK4 and NRG1. *Neurotoxicity Research* **11**, 73–83.

Blanchard, R., Cantor, J. M., Bogaert, A. F., Breedlove, S. M. & Ellis, L. (2006). Interaction of fraternal birth order and handedness in the development of male homosexuality. *Hormones and Behavior* **49**, 405–414.

Blint, E., Phillips, A. C., Kozlov, S., Stewart, C. L. & Vousden, K. H. (2002). Induction of p57(KIP2) expression by p73beta. *Proceedings of the National Academy of Sciences of the United States of America* **99**, 3529–3534.

Blomhoff, A., Olsson, M., Johansson, S., Akselsen, H. E., Pociot, F., Nerup, J., Kockum, I., Cambon-Thomsen, A., Thorsby, E., Undlien, D. E. & Lie, B. A. (2006). Linkage disequilibrium and haplotype blocks in the MHC vary in an HLA haplotype specific manner assessed mainly by DRB1*03 and DRB1*04 haplotypes. *Genes and Immunity* **7**, 130–140.

Blouin, J. L., Dombroski, B. A., Nath, S. K., Lasseter, V. K., Wolyniec, P. S., Nestadt, G., Thornquist, M., Ullrich, G., McGrath, J., Kasch, L., Lamacz, M., Thomas, M. G., Gehrig, C., Radhakrishna, U., Snyder, S. E., Balk, K. G., Neufeld, K., Swartz, K. L., DeMarchi, N., Papadimitriou, G. N., Dikeos, D. G., Stefanis, C. N., Chakravarti, A., Childs, B., Housman, D. E., Kazazian, H. H., Antonarakis, S. & Pulver, A. E. (1998). Schizophrenia susceptibility loci on chromosomes 13q32 and 8p21. *Nature Genetics* **20**, 70–73.

Boer, H., Holland, A., Whittington, J., Butler, J., Webb, T. & Clarke, D. (2002). Psychotic illness in people with Prader Willi syndrome due to chromosome 15 maternal uniparental disomy. *Lancet* **359**, 135–136.

Boks, M. P., De Vette, M. H., Sommer, I. E., Van Rijn, S., Giltay, J. C., Swaab, H. & Kahn, R. S. (2007a). Psychiatric morbidity and X-chromosomal origin in a Klinefelter sample. *Schizophrenia Research* **93**, 399–402.

Boks, M. P., Leask, S., Vermunt, J. K. & Kahn, R. S. (2007b). The structure of psychosis revisited: The role of mood symptoms. *Schizophrenia Research* **93**, 178–185.

Bonati, M. T., Russo, S., Finelli, P., Valsecchi, M. R., Cogliati, F., Cavalleri, F., Roberts, W., Elia, M. & Larizza, L. (2007). Evaluation of autism traits in Angelman syndrome: a resource to unfold autism genes. *Neurogenetics* **8**, 169–178.

Bonora, E., Beyer, K. S., Lamb, J. A., Parr, J. R., Klauck, S. M., Benner, A., Paolucci, M., Abbott, A., Ragoussis, I., Poustka, A., Bailey, A. J. & Monaco, A. P. (2003). Analysis of reelin as a candidate gene for autism. *Molecular Psychiatry* **8**, 885–892.

Boominathan, L. (2007). Some facts and thoughts: p73 as a tumor suppressor gene in the network of tumor suppressors. *Molecular Cancer* **6**, 27.

Boulanger, L. M. & Shatz, C. J. (2004). Immune signalling in neural development, synaptic plasticity and disease. *Nature Reviews Neuroscience* **5**, 521–531.

Breen, G., Prata, D., Osborne, S., Munro, J., Sinclair, M., Li, T., Staddon, S., Dempster, D., Sainz, R., Arroyo, B., Kerwin, R. W., St Clair, D. & Collier, D. (2006). Association of the dysbindin gene with bipolar affective disorder. *American Journal of Psychiatry* **163**, 1636–1638.

Breunig, J. J., Silbereis, J., Vaccarino, F. M., Sestan, N. & Rakic, P. (2007). Notch regulates cell fate and dendrite morphology of newborn neurons in the postnatal dentate gyrus. *Proceedings of the*

National Academy of Sciences of the United States of America **104**, 20558–20563.

Buckley, P. F., Pillai, A., Evans, D., Stirewalt, E. & Mahadik, S. (2007). Brain derived neurotropic factor in first-episode psychosis. *Schizophrenia Research* **91**, 1–5.

Buettner, V. L., Longmate, J. A., Barish, M. E., Mann, J. R. & Singer-Sam, J. (2004). Analysis of imprinting in mice with uniparental duplication of proximal chromosomes 7 and 15 by use of a custom oligonucleotide microarray. *Mammalian Genome* **15**, 199–209.

Buiting, K., Kanber, D., Martín-Subero, J. I., Lieb, W., Terhal, P., Albrecht, B., Purmann, S., Gross, S., Lich, C., Siebert, R., Horsthemke, B. & Gillessen-Kaesbach, G. (2008). Clinical features of maternal uniparental disomy 14 in patients with an epimutation and a deletion of the imprinted DLK1/GTL2 gene cluster. *Human Mutation* (in press).

Bulayeva, K. B., Glatt, S. J., Bulayev, O. A., Pavlova, T. A. & Tsuang, M. T. (2007). Genome-wide linkage scan of schizophrenia: a cross-isolate study. *Genomics* **89**, 167–177.

Burgoyne, P. S., Thornhill, A. R., Boudrean, S. K., Darling, S. M., Bishop, C. E. & Evans, E. P. (1995). The genetic basis of XX-XY differences present before gonadal sex differentiation in the mouse. *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences* **350**, 253–260.

Burns, J. K. (2004). An evolutionary theory of schizophrenia: cortical connectivity, metarepresentation, and the social brain. *Behavioral and Brain Sciences* **27**, 831–885.

Burns, J. K. (2006). Psychosis: A costly by-product of social brain evolution in Homo sapiens. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **30**, 797–814.

Burt, A. & Trivers, R. (1998). Genetic conflicts in genomic imprinting. *Proceedings of the Royal Society of London, Series B, Biological Sciences* **265**, 2393–2397.

Burt, A. & Trivers, R. (2006). *Genes in Conflict: The Biology of Selfish Genetic Elements*. Harvard University Press, Cambridge, MA.

Buxbaum, J. D., Georgieva, L., Young, J. J., Plescia, C., Kajiwara, Y., Jiang, Y., Moskvina, V., Norton, N., Peirce, T., Williams, H., Craddock, N. J., Carroll, L., Corfas, G., Davis, K. L., Owen, M. J., Harroch, S., Sakurai, T. & O'Donovan, M. C. (2008). Molecular dissection of NRG1-ERBB4 signaling implicates PTPRZ1 as a potential schizophrenia susceptibility gene. *Molecular Psychiatry* **13**, 162–172.

Cabrera-Socorro, A., Pueyo Morlans, M., Suarez Sola, M. L., Gonzalez Delgado, F. J., Castañeyra-Perdomo, A., Marin, M. C. & Meyer, G. (2006). Multiple isoforms of the tumor protein p73 are expressed in the adult human telencephalon and choroid plexus and present in the cerebrospinal fluid. *European Journal of Neuroscience* **23**, 2109–2118.

Cao, Q., Martinez, M., Zhang, J., Sanders, A. R., Badner, J. A., Cravchik, A., Markey, C. J., Beshah, E., Guroff, J. J., Maxwell, M. E., Kazuba, D. M., Whiten, R., Goldin, L. R., Gershon, E. S. & Gejman, P. V. (1997). Suggestive evidence for a schizophrenia susceptibility locus on chromosome 6q and a confirmation in an independent series of pedigrees. *Genomics* **43**, 1–8.

Carlsson, M. L. (1998). Hypothesis: is infantile autism a hypoglutamatergic disorder? Relevance of glutamate - serotonin interactions for pharmacotherapy. *Journal of Neural Transmission* **105**, 525–535.

Casas, K. A., Mononen, T. K., Mikail, C. N., Hassed, S. J., Li, S., Mulvihill, J. J., Lin, H. J., Falk, R. E. (2004). Chromosome 2q terminal deletion: report of 6 new patients and review of phenotype-breakpoint correlations in 66 individuals. *American Journal of Medical Genetics, A* **130**, 331–339.

Castensson, A., Aberg, K., McCarthy, S., Saetre, P., Andersson, B. & Jazin, E. (2005). Serotonin receptor 2C (HTR2C) and schizophrenia: examination of possible medication and genetic influences on expression levels. *American Journal of Medical Genetics, B* **134**, 84–89.

Cattanach, B. M., Beechey, C. V. & Peters, J. (2004). Interactions between imprinting effects in the mouse. *Genetics* **168**, 397–413.

Cavaillé, J., Seitz, H., Paulsen, M., Ferguson-Smith, A. C. & Bachellerie, J. P. (2002). Identification of tandemly-repeated C/D snoRNA genes at the imprinted human 14q32 domain reminiscent of those at the Prader-Willi/Angelman syndrome region. *Human Molecular Genetics* **11**, 1527–1538.

Ceccherini-Nelli, A., Turpin-Crowther, K. & Crow, T. J. (2007). Schneider's first rank symptoms and continuous performance disturbance as indices of dysconnectivity of left- and right-hemispheric components of language in schizophrenia. *Schizophrenia Research* **90**, 203–213.

Charalambous, M., Da Rocha, S. T. & Ferguson-Smith, A. C. (2007). Genomic imprinting, growth control and the allocation of nutritional resources: consequences for postnatal life. *Current Opinion in Endocrinology, Diabetes and Obesity* **14**, 3–12.

Chen, M., Gavrilova, O., Liu, J., Xie, T., Deng, C., Nguyen, A. T., Nackers, L. M., Lorenzo, J., Shen, L. & Weinstein, L. S. (2005). Alternative Gnas gene products have opposite effects on glucose and lipid metabolism. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 7386–7391.

Chen, M., Haluzik, M., Wolf, N. J., Lorenzo, J., Dietz, K. R., Reitman, M. L. & Weinstein, L. S. (2004). Increased insulin sensitivity in paternal Gnas knockout mice is associated with increased lipid clearance. *Endocrinology* **145**, 4094–4102.

Chetcuti, A., Adams, L. J., Mitchell, P. B. & Schofield, P. R. (2006). Altered gene expression in mice treated with the mood stabilizer sodium valproate. *International Journal of Neuropsychopharmacology* **9**, 267–276.

Choi, J. D., Underkoffler, L. A., Wood, A. J., Collins, J. N., Williams, P. T., Golden, J. A., Schuster, E. F., Jr, Loomes, K. M. & Oakey, R. J. (2005). A novel variant of Inpp5f is imprinted in brain, and its expression is correlated with differential methylation of an internal CpG island. *Molecular and Cellular Biology* **25**, 5514–5522.

Chowdari, K. V., Bamne, M., Wood, J., Talkowski, M. E., Mirnics, K., Levitt, P., Lewis, D. A. & Nimgaonkar, V. L. (2008). Linkage disequilibrium patterns and functional analysis of RGS4 polymorphisms in relation to schizophrenia. *Schizophrenia Bulletin* **34**, 118–126.

Christodoulou, J. & Weaving, L. S. (2003). MECP2 and beyond: phenotype-genotype correlations in Rett syndrome. *Journal of Child Neurology* **18**, 669–674.

Christophersen, N. S., Grønborg, M., Petersen, T. N., Fjord-Larsen, L., Jørgensen, J. R., Juliusson, B., Blom, N., Rosenblad, C. & Brundin, P. (2007). Midbrain expression of Delta-like 1 homologue is regulated by GDNF and is associated with dopaminergic differentiation. *Experimental Neurology* **204**, 791–801.

Chubb, J. E., Bradshaw, N. J., Soares, D. C., Porteous, D. J. & Millar, J. K. (2008). The DISC locus in psychiatric illness. *Molecular Psychiatry* **13**, 36–64.

Cichon, S., Schumacher, J., Müller, D. J., Hürter, M., Windemuth, C., Strauch, K., Hemmer, S., Schulze, T. G., Schmidt-Wolf, G., Albus, M., Borrmann-Hassenbach, M.,

Franzek, E., Lanczik, M., Fritze, J., Kreiner, R., Reuner, U., Weigelt, B., Minges, J., Lichtermann, D., Lerer, B., Kanyas, K., Baur, M. P., Wienker, T. F., Maier, W., Rietschel, M., Propping, P. & Nöthen, M. M. (2001). A genome screen for genes predisposing to bipolar affective disorder detects a new susceptibility locus on 8q. *Human Molecular Genetics* **10**, 2933–2944.

Claridge, G. (1997). *Schizotypy: Implications for Illness and Health*. Oxford University Press, Oxford.

Cohen, D., Lazar, G., Couvert, P., Desportes, V., Lippe, D., Mazet, P. & Héron, D. (2002). MECP2 mutation in a boy with language disorder and schizophrenia. *American Journal of Psychiatry* **159**, 148–149.

Cohen, D., Pichard, N., Tordjman, S., Baumann, C., Burglen, L., Excoffier, E., Lazar, G., Mazet, P., Pinquier, C., Verloes, A. & Héron, D. (2005). Specific genetic disorders and autism: clinical contribution towards their identification. *Journal of Autism and Developmental Disorders* **35**, 103–116.

Cohly, H. H. & Panja, A. (2005). Immunological findings in autism. *International Review of Neurobiology* **71**, 317–341.

Comi, A. M., Zimmerman, A. W., Frye, V. H., Law, P. A. & Peeden, J. N. (1999). Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. *Journal of Child Neurology* **14**, 388–394.

Condray, R. (2005). Language disorder in schizophrenia as a developmental learning disorder. *Schizophrenia Research* **73**, 5–20.

Connolly, A. M., Chez, M., Streif, E. M., Keeling, R. M., Golumbek, P. T., Kwon, J. M., Riviello, J. J., Robinson, R. G., Neuman, R. J. & Deuel, R. M. (2006). Brain-derived neurotrophic factor and autoantibodies to neural antigens in sera of children with autistic spectrum disorders, Landau-Kleffner syndrome, and epilepsy. *Biological Psychiatry* **59**, 354–363.

Constantino, J. N. & Todd, R. D. (2005). Intergenerational transmission of subthreshold autistic traits in the general population. *Biological Psychiatry* **57**, 655–660.

Conti-Ramsden, G., Simkin, Z. & Botting, N. (2006). The prevalence of autistic spectrum disorders in adolescents with a history of specific language impairment (SLI). *Journal of Child Psychology and Psychiatry* **47**, 621–628.

Cormier-Daire, V., Molinari, F., Rio, M., Raoul, O., De Blois, M. C., Romana, S., Vekemans, M., Munnich, A. & Colleaux, L. (2003). Cryptic terminal deletion of chromosome 9q34: a novel cause of syndromic obesity in childhood? *Journal of Medical Genetics* **40**, 300–303.

Corradi, J. P., Ravyn, V., Robbins, A. K., Hagan, K. W., Peters, M. F., Bostwick, R., Buono, R. J., Berrettini, W. H. & Furlong, S. T. (2005). Alternative transcripts and evidence of imprinting of GNAL on 18p11.2. *Molecular Psychiatry* **10**, 1017–1025.

Corvol, J. C., Valjent, E., Pascoli, V., Robin, A., Stipanovich, A., Luedtke, R. R., Belluscio, L., Girault, J. A. & Herve, D. (2007). Quantitative changes in Galphaolf protein levels, but not D1 receptor, alter specifically acute responses to psychostimulants. *Neuropsychopharmacology* **32**, 1109–1121.

Courchesne, E. & Pierce, K. (2005). Brain overgrowth in autism during a critical time in development: implications for frontal pyramidal neuron and interneuron development and connectivity. *International Journal of Developmental Neuroscience* **23**, 153–170.

Courtens, W., Wuyts, W., Rooms, L., Pera, S. B. & Wauters, J. (2006). A subterminal deletion of the long arm of chromosome 10: a clinical report and review. *American Journal of Medical Genetics, A* **140**, 402–409.

Coutinho, A. M., Oliveira, G., Katz, C., Feng, J., Yan, J., Yang, C., Marques, C., Ataíde, A., Miguel, T. S., Borges, L., Almeida, J., Correia, C., Currais, A., Bento, C., Mota-Vieira, L., Temudo, T., Santos, M., Maciel, P., Sommer, S. S. & Vicente, A. M. (2007). MECP2 coding sequence and 3'UTR variation in 172 unrelated autistic patients. *American Journal of Medical Genetics, B* **144**, 475–483.

Craddock, N. & Forty, L. (2006). Genetics of affective (mood) disorders. *European Journal of Human Genetics* **14**, 660–668.

Craddock, N. & Lendon, C. (1999). Chromosome Workshop: chromosomes 11, 14, and 15. *American Journal of Medical Genetics* **88**, 244–254.

Craddock, N., O'Donovan, M. C. & Owen, M. J. (2005). The genetics of schizophrenia and bipolar disorder: dissecting psychosis. *Journal of Medical Genetics* **42**, 193–204.

Crespi, B. J. (2007). Sly FOXP2: genomic conflict in the evolution of language. *Trends in Ecology & Evolution* **22**, 174–175.

Crespi, B. J. (2008). Turner syndrome and the evolution of human sexual dimorphism. *Evolutionary Applications* (in press).

Crespi, B. J. (2009). Evolutionary genetics of affective disorders. In: *Depression: Translational Approaches to Understanding and Treating* (eds. Pariante, C. & Nesse, R. M.). Oxford University Press, Oxford, (in press).

Crespi, B. & Badcock, C. (2008). Autism and psychosis as diametrical disorders of the social brain. *Behavioral and Brain Sciences* **31**, 241–261.

Crespi, B. & Semeniuk, C. (2004). Parent-offspring conflict in the evolution of vertebrate reproductive mode. *American Naturalist* **163**, 635–653.

Creswell, C. S. & Skuse, D. H. (1999). Autism in association with Turner syndrome: genetic implications for male vulnerability to pervasive developmental disorders. *Neurocase* **5**, 101–108.

Croen, L. A., Grether, J. K., Yoshida, C. K., Odouli, R. & Van de Water, J. (2005). Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study. *Archives of Pediatrics & Adolescent Medicine* **159**, 151–157.

Croteau, S., Roquis, D., Charron, M. C., Frappier, D., Yavin, D., Loredo-Osti, J. C., Hudson, T. J. & Naumova, A. K. (2005). Increased plasticity of genomic imprinting of Dlk1 in brain is due to genetic and epigenetic factors. *Mammalian Genome* **16**, 127–135.

Crow, T. J. (1993). Sexual selection, Machievellian intelligence, and the origins of psychosis. *Lancet* **342**, 594–598.

Crow, T. J. (1995*a*). A continuum of psychosis, one human gene, and not much else: The case for homogeneity. *Schizophrenia Research* **17**, 135–145.

Crow, T. J. (1995*b*). A Darwinian approach to the origins of psychosis. *British Journal of Psychiatry* **167**, 12–25.

Crow, T. J. (1997). Is schizophrenia the price that *Homo sapiens* pays for language? *Schizophrenia Research* **28**, 127–141.

Crow, T. J. (1998). From Kraepelin to Kretschmer leavened by Schneider: The transition from categories to psychosis to dimensions of variation intrinsic to Homo sapiens. *Archives of General Psychiatry* **55**, 502–504.

Crow, T. J. (2004). Auditory hallucinations as primary disorders of syntax: an evolutionary theory of the origins of language. *Cognitive Neuropsychiatry* **9**, 125–145.

D'Angelo, C. S., Da Paz, J. A., Kim, C. A., Bertola, D. R., Castro, C. I. E., Varela, M. C. & Koiffmann, C. P. (2006). Prader-Willi-like phenotype: investigation of 1p36 deletion in 41 patients with delayed psychomotor development, hypotonia, obesity and/or hyperphagia, learning disabilities and behavioral problems. *European Journal of Medical Genetics* **49**, 451–460.

Da Rocha, S. T., Tevendale, M., Knowles, E., Takada, S., Watkins, M. & Ferguson-Smith, A. C. (2007). Restricted

co-expression of Dlk1 and the reciprocally imprinted non-coding RNA, Gtl2: implications for cis-acting control. *Developmental Biology* **306**, 810–823.

Davies, W., Isles, A. R., Humby, T. & Wilkinson, L. S. (2008). What are imprinted genes doing in the brain? *Epigenetics* **2**, 201–206.

Davies, W., Isles, A., Song, J., Burrmann, D., Burgoyne, P. & Wilkinson, L. (2006). X-linked parent-of-origin effects in brain: Implications for sex-specific neurobiology. *XIV World Congress on Psychiatric Genetics, Abstract*.

Davies, W., Isles, A. R. & Wilkinson, L. S. (2001). Imprinted genes and mental dysfunction. *Annals of Medicine* **33**, 428–436.

Davies, W., Isles, A. R. & Wilkinson, L. S. (2005). Imprinted gene expression in the brain. *Neuroscience and Biobehavioral Reviews* **29**, 421–430.

Davies, W., Lynn, P. M., Relkovic, D. & Wilkinson, L. S. (2007). Imprinted genes and neuroendocrine function. *Frontiers in Neuroendocrinology* **29**, 413–427.

Davis, E., Caiment, F., Tordoir, X., Cavaillé, J., Ferguson-Smith, A., Cockett, N., Georges, M. & Charlier, C. (2005). RNAi-mediated allelic trans-interaction at the imprinted Rtl1/Peg11 locus. *Current Biology* **15**, 743–749.

Davis, L. K., Meyer, K. J., Rudd, D. S., Librant, A. L., Epping, E. A., Sheffield, V. C. & Wassink, T. H. (2008). Pax6 3' deletion results in aniridia, autism and mental retardation. *Human Genetics* **123**, 371–378.

Day, T. & Bonduriansky, R. (2004). Intralocus sexual conflict can drive the evolution of genomic imprinting. *Genetics* **167**, 1537–1546.

DeBerardinis, R. J., Conforto, D., Russell, K., Kaplan, J., Kollros, P. R., Zackai, E. H. & Emanuel, B. S. (2003). Myoclonus in a patient with a deletion of the epsilon-sarcoglycan locus on chromosome 7q21. *American Journal of Medical Genetics* **121**, 31–36.

Deichmann, K. A., Heinzmann, A., Forster, J., Dischinger, S., Mehl, C., Brueggenolte, E., Hildebrandt, F., Moseler, M. & Kuehr, J. (1998). Linkage and allelic association of atopy and markers flanking the IL4-receptor gene. *Clinical and Experimental Allergy* **28**, 151–155.

de la Casa-Esperón, E. & Sapienza, C. (2003). Natural selection and the evolution of genome imprinting. *Annual Review of Genetics* **37**, 349–370.

DeLisi, L. E., Friedrich, U., Wahlstrom, J., Boccio-Smith, A., Forsman, A., Eklund, K. & Crow, T. J. (1994). Schizophrenia and sex chromosome anomalies. *Schizophrenia Bulletin* **20**, 495–505.

DeLisi, L. E., Maurizio, A. M., Svetina, C., Ardekani, B., Szulc, K., Nierenberg, J., Leonard, J. & Harvey, P. D. (2005). Klinefelter's syndrome (XXY) as a genetic model for psychotic disorders. *American Journal of Medical Genetics, B* **135**, 15–23.

DeLisi, L. E., Razi, K., Stewart, J., Relja, M., Shields, G., Smith, A. B., Wellman, N., Larach, V. W., Loftus, J., Vita, A., Comazzi, M. & Crow, T. J. (2000). No evidence for a parent-of-origin effect detected in the pattern of inheritance of schizophrenia. *Biological Psychiatry* **48**, 706–709.

DeLisi, L. E., Shaw, S. H., Crow, T. J., Shields, G., Smith, A. B., Larach, V. W., Wellman, N., Loftus, J., Nanthakumar, B., Razi, K., Stewart, J., Comazzi, M., Vita, A., Heffner, T. & Sherrington, R. (2002). A genome-wide scan for linkage to chromosomal regions in 382 sibling pairs with schizophrenia or schizoaffective disorder. *American Journal of Psychiatry* **159**, 803–812.

DeLong, R. (2007). GABA(A) receptor alpha5 subunit as a candidate gene for autism and bipolar disorder: a proposed endophenotype with parent-of-origin and gain-of-function features, with or without oculocutaneous albinism. *Autism* **11**, 135–147.

de Quervain, D. J. & Papassotiropoulos, A. (2006). Identification of a genetic cluster influencing memory performance and hippocampal activity in humans. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 4270–4274.

Depue, R. A. & Morrone-Strupinsky, J. V. (2005). A neurobehavioral model of affiliative bonding: implications for conceptualizing a human trait of affiliation. *Behavioral and Brain Sciences* **28**, 313–350.

Detera-Wadleigh, S. D., Badner, J. A., Berrettini, W. H., Yoshikawa, T., Goldin, L. R., Turner, G., Rollins, D. Y., Moses, T., Sanders, A. R., Karkera, J. D., Esterling, L. E., Zeng, J., Ferraro, T. N., Guroff, J. J., Kazuba, D., Maxwell, M. E., Nurnberger, J. I., & Gershon, E. S. (1999). A high-density genome scan detects evidence for a bipolar-disorder susceptibility locus on 13q32 and other potential loci on 1q32 and 18p11.2. *Proceedings of the National Academy of Sciences of the United States of America* **96**, 5604–5609.

Devlin, B., Bennett, P., Dawson, G., Figlewicz, D. A., Grigorenko, E. L., McMahon, W., Minshew, N., Pauls, D., Smith, M., Spence, M. A., Rodier, P. M., Stodgell, C. & Schellenberg, G. D. (2004). CPEA Genetics Network. Alleles of a reelin CGG repeat do not convey liability to autism in a sample from the CPEA network. *American Journal of Medical Genetics, B* **126**, 46–50.

Dick, D. M., Foroud, T., Flury, L., Bowman, E. S., Miller, M. J., Rau, N. L., Moe, P. R., Samavedy, N., El-Mallakh, R., Manji, H., Glitz, D. A., Meyer, E. T., Smiley, C., Hahn, R., Widmark, C., McKinney, R., Sutton, L., Ballas, C., Grice, D., Berrettini, W., Byerley, W., Coryell, W., DePaulo, R., MacKinnon, D. F., Gershon, E. S., Kelsoe, J. R., McMahon, F. J., McInnis, M., Murphy, D. L., Reich, T., Scheftner, W. & Nurnberger, J. I., Jr (2003). Genomewide linkage analyses of bipolar disorder: a new sample of 250 pedigrees from the National Institute of Mental Health Genetics Initiative. *American Journal of Human Genetics* **73**, 107–114.

Ding, F., Prints, Y., Dhar, M. S., Johnson, D. K., Garnacho-Montero, C., Nicholls, R. D. & Francke, U. (2005). Lack of Pwcr1/MBII-85 snoRNA is critical for neonatal lethality in Prader-Willi syndrome mouse models. *Mammalian Genome* **16**, 424–431.

Dmitrzak-Weglarz, M., Rybakowski, J. K., Slopien, A., Czerski, P. M., Leszczynska-Rodziewicz, A., Kapelski, P., Kaczmarkiewicz-Fass, M. & Hauser, J. (2006). Dopamine receptor D1 gene -48A/G polymorphism is associated with bipolar illness but not with schizophrenia in a Polish population. *Neuropsychobiology* **53**, 46–50.

Doheny, D. O., Brin, M. F., Morrison, C. E., Smith, C. J., Walker, R. H., Abbasi, S., Müller, B., Garrels, J., Liu, L., De Carvalho Aguiar, P., Schilling, K., Kramer, P., De Leon, D., Raymond, D., Saunders-Pullman, R., Klein, C., Bressman, S. B., Schmand, B., Tijssen, M. A. J., Ozelius, L. J. & Silverman, J. M. (2002). Phenotypic features of myoclonus-dystonia in three kindreds. *Neurology* **59**, 1187–1196.

Dong, E., Agis-Balboa, R. C., Simonini, M. V., Grayson, D. R., Costa, E. & Guidotti, A. (2005*a*). Reelin and glutamic acid decarboxylase67 promoter remodeling in an epigenetic methionine-induced mouse model of schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 12578–12583.

Dong, C., Li, W. D., Geller, F., Lei, L., Li, D., Gorlova, O. Y., Hebebrand, J., Amos, C. I., Nicholls, R. D. & Price, R. A. (2005*b*). Possible genomic imprinting of three human obesity-related genetic loci. *American Journal of Human Genetics* **76**, 427–437.

Donnelly, S. L., Wolpert, C. M., Menold, M. M., Bass, M. P., Gilbert, J. R., Cuccaro, M. L., Delong, G. R. & Pericak-Vance, M. A. (2000). Female with autistic disorder and monosomy X (Turner syndrome): parent-of-origin effect of the X chromosome. *American Journal of Medical Genetics* **96**, 312–316.

Dutta, S., Guhathakurta, S., Sinha, S., Chatterjee, A., Ahmed, S., Ghosh, S., Gangopadhyay, P. K., Singh, M. & Usha, R. (2007). Reelin gene polymorphisms in the Indian population: a possible paternal 5'UTR-CGG-repeat-allele effect on autism. *American Journal of Medical Genetics, B* **144**, 106–112.

Duvall, J. A., Lu, A., Cantor, R. M., Todd, R. D., Constantino, J. N. & Geschwind, D. H. (2007). A quantitative trait locus analysis of social responsiveness in multiplex autism families. *American Journal of Psychiatry* **164**, 656–662.

Duxon, M. S., Flanigan, T. P., Reavley, A. C., Baxter, G. S., Blackburn, T. P. & Fone, K. C. (1997). Evidence for expression of the 5-hydroxytryptamine-2B receptor protein in the rat central nervous system. *Neuroscience* **76**, 323–329.

Dykens, E. M. & Smith, A. C. (1998). Distinctiveness and correlates of maladaptive behaviour in children and adolescents with Smith-Magenis syndrome. *Journal of Intellectual Disability Research*. **42**, 481–489.

Dykens, E. M., Hodapp, R. M. & Finucane, B. M. (2000). *Genetics and Mental Retardation Syndromes: A New Look at Behavior and Interventions*. Brookes Publishing Company, Baltimore, MD.

Eaton, W. W., Byrne, M., Ewald, H., Mors, O., Chen, C. Y., Agerbo, E. & Mortensen, P. B. (2006). Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. *American Journal of Psychiatry* **163**, 521–528.

Eaton, W. W., Hayward, C. & Ram, R. (1992). Schizophrenia and rheumatoid arthritis: a review. *Schizophrenia Research* **6**, 181–192.

Eder, S., Leierer, J., Klimaschewski, L., Wilhelm, A., Volknandt, W., Laslop, A. & Fischer-Colbrie, R. (2004). Secretion and molecular forms of NESP55, a novel genomically imprinted neuroendocrine-specific protein from AtT-20 cells. *Neuro-Signals* **13**, 298–307.

Edgar, J. C., Yeo, R. A., Gangestad, S. W., Blake, M. B., Davis, J. T., Lewine, J. D. & Cañive, J. M. (2006). Reduced auditory M100 asymmetry in schizophrenia and dyslexia: applying a developmental instability approach to assess atypical brain asymmetry. *Neuropsychologia* **44**, 289–299.

Egashira, N., Tanoue, A., Higashihara, F., Fuchigami, H., Sano, K., Mishima, K., Fukue, Y., Nagai, H., Takano, Y., Tsujimoto, G., Stemmelin, J., Griebel, G., Iwasaki, K., Ikeda, T., Nishimura, R. & Fujiwara, M. (2005). Disruption of the prepulse inhibition of the startle reflex in vasopressin V1b receptor knockout mice: reversal by antipsychotic drugs. *Neuropsychopharmacology* **30**, 1996–2005.

Eggermann, T., Curtis, M., Zerres, K. & Hughes, H. E. (2004). Maternal uniparental disomy 16 and genetic counseling: new case and survey of published cases. *Genetic Counseling* **15**, 183–190.

Eggermann, T., Eggermann, K. & Schönherr, N. (2008). Growth retardation versus overgrowth: Silver-Russell syndrome is genetically opposite to Beckwith-Wiedemann syndrome. *Trends in Genetics* (in press).

Ekelund, J., Lichtermann, D., Hovatta, I., Ellonen, P., Suvisaari, J., Terwilliger, J. D., Juvonen, H., Varilo, T., Arajärvi, R., Kokko-Sahin, M. L., Lönnqvist, J. & Peltonen, L. (2000). Genome-wide scan for schizophrenia in the Finnish population: evidence for a locus on chromosome 7q22. *Human Molecular Genetics* **9**, 1049–1057.

Eliez, S. (2007). Autism in children with 22q11.2 deletion syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry* **46**, 433–434.

Enard, W., Przeworski, M., Fisher, S. E., Lai, C. S. L., Wiebe, V., Kitano, T., Monaco, A. P. & Pääbo, S. (2002). Molecular evolution of FOXP2, a gene involved in speech and language. *Nature* **418**, 869–872.

Engstrom, H. A., Ohlson, S., Stubbs, E. G., Maciulis, A., Caldwell, V., Odell, J. D. & Torres, A. R. (2003). Decreased expression of CD95 (Fas/APO-1) on CD4+ T-lymphocytes from participants with autism. *Journal of Developmental and Physical Disabilities* **15**, 155–163.

Escamilla, M. A., Ontiveros, A., Nicolini, H., Raventos, H., Mendoza, R., Medina, R., Munoz, R., Levinson, D., Peralta, J. M., Dassori, A. & Almasy, L. (2007). A genome-wide scan for schizophrenia and psychosis susceptibility loci in families of Mexican and Central American ancestry. *American Journal of Medical Genetics, B* **144**, 193–199.

Everman, D. B. & Stoudemire, A. (1994). Bipolar disorder associated with Klinefelter's syndrome and other chromosomal abnormalities. *Psychosomatics* **35**, 35–40.

Ewald, H., Flint, T., Kruse, T. A. & Mors, O. (2002*a*). A genome-wide scan shows significant linkage between bipolar disorder and chromosome 12q24.3 and suggestive linkage to chromosomes 1p22-21, 4p16, 6q14-22, 10q26 and 16p13.3. *Molecular Psychiatry* **7**, 734–744.

Ewald, H., Flint, T. J., Jorgensen, T. H., Wang, A. G., Jensen, P., Vang, M., Mors, O. & Kruse, T. A. (2002*b*). Search for a shared segment on chromosome 10q26 in patients with bipolar affective disorder or schizophrenia from the Faroe Islands. *American Journal of Medical Genetics* **114**, 196–204.

Faivre, L., Cormier-Daire, V., Lapierre, J. M., Colleaux, L., Jacquemont, S., Geneviéve, D., Saunier, P., Munnich, A., Turleau, C., Romana, S., Prieur, M., De Blois, M. C. & Vekemans, M. (2002). Deletion of the SIM1 gene (6q16.2) in a patient with a Prader-Willi-like phenotype. *Journal of Medical Genetics* **39**, 594–596.

Fales, C. L., Knowlton, B. J., Holyoak, K. J., Geschwind, D. H., Swerdloff, R. S. & Gonzalo, I. G. (2003). Working memory and relational reasoning in Klinefelter syndrome. *Journal of the International Neuropsychological Society* **9**, 839–846.

Falk, M. J., Curtis, C. A., Bass, N. E., Zinn, A. B. & Schwartz, S. (2005). Maternal uniparental disomy chromosome 14: case report and literature review. *Pediatric Neurology* **32**, 116–120.

Fallin, M. D., Lasseter, V. K., Wolyniec, P. S., Mcrath, J. A., Nestadt, G., Valle, D., Liang, K. & Pulver, A. E. (2003). Genomewide linkage scan for schizophrenia susceptibility loci among Ashkenazi Jewish families shows evidence of linkage on chromosome 10q22. *American Journal of Human Genetics* **73**, 601–611.

Fallin, M. D., Lasseter, V. K., Wolyniec, P. S., McGrath, J. A., Nestadt, G., Valle, D., Liang, K. Y. & Pulver, A. E. (2004). Genomewide linkage scan for bipolar-disorder susceptibility loci among Ashkenazi Jewish families. *American Journal of Human Genetics* **75**, 204–219.

Fanous, A. H. & Kendler, K. S. (2005). Genetic heterogeneity, modifier genes, and quantitative phenotypes in psychiatric illness: searching for a framework. *Molecular Psychiatry* **10**, 6–13.

Faraone, S. V., Matise, T., Svrakic, D., Pepple, J., Malaspina, D., Suarez, B., Hampe, C., Zambuto, C. T., Schmitt, K., Meyer, J., Markel, P., Lee, H., Harkavy Friedman, J., Kaufmann, C., Cloninger, C. R. & Tsuang, M. T. (1998). Genome scan of European-American schizophrenia pedigrees: results of the

NIMH Genetics Initiative and Millennium Consortium. *American Journal of Medical Genetics* **81**, 290–295.

Farrer, L. A., Cupples, L. A., Kiely, D. K., Conneally, P. M. & Myers, R. H. (1992). Inverse relationship between age at onset of Huntington disease and paternal age suggests involvement of genetic imprinting. *American Journal of Human Genetics* **50**, 528–535.

Fatemi, S. H. (2005). Reelin glycoprotein in autism and schizophrenia. *International Review of Neurobiology* **71**, 179–187.

Fatemi, S. H., Snow, A. V., Stary, J. M., Araghi-Niknam, M., Reutiman, T. J., Lee, S., Brooks, A. I. & Pearce, D. A. (2005). Reelin signaling is impaired in autism. *Biological Psychiatry* **57**, 777–787.

Feifel, D. & Reza, T. (1999). Oxytocin modulates psychotomimetic-induced deficits in sensorimotor gating. *Psychopharmacology* **141**, 93–98.

Feinstein, C., Eliez, S., Blasey, C. & Reiss, A. L. (2002). Psychiatric disorders and behavioral problems in children with velocardiofacial syndrome: usefulness as phenotypic indicators of schizophrenia risk. *Biological Psychiatry* **51**, 312–318.

Feinstein, C. & Singh, S. (2007). Social phenotypes in neurogenetic syndromes. *Child and Adolescent Psychiatric Clinics of North America* **16**, 631–647.

Ferguson-Smith, A. C., Moore, T., Detmar, J., Lewis, A., Hemberger, M., Jammes, H., Kelsey, G., Roberts, C. T., Jones, H. & Constancia, M. (2006). Epigenetics and imprinting of the trophoblast – a workshop report. *Placenta* **27** Suppl A, s122–s126.

Feuk, L., Kalervo, A., Lipsanen-Nyman, M., Skaug, J., Nakabayashi, K., Finucane, B., Hartung, D., Innes, M., Kerem, B., Nowaczyk, M. J., Rivlin, J., Roberts, W., Senman, L., Summers, A., Szatmari, P., Wong, V., Vincent, J. B., Zeesman, S., Osborne, L. R., Cardy, J. O., Kere, J., Scherer, S. W. & Hannula-Jouppi, K. (2006). Absence of a paternally inherited FOXP2 gene in developmental verbal dyspraxia. *American Journal of Human Genetics* **79**, 965–972.

Fishbain, D. A. & Vilasuso, A. (1981). Manic-depressive illness associated with Turner's syndrome mosaicism. *Journal of Nervous and Mental Disease* **169**, 459–461.

Fisher, S. E., Francks, C., Marlow, A. J., MacPhie, I. L., Newbury, D. F., Cardon, L. R., Ishikawa-Brush, Y., Richardson, A. J., Talcott, J. B., Gayán, J., Olson, R. K., Pennington, B. F., Smith, S. D., DeFries, J. C., Stein, J. F. & Monaco, A. P. (2002*a*). Independent genome-wide scans identify a chromosome 18 quantitative-trait locus influencing dyslexia. *Nature Genetics* **30**, 86–91.

Fisher, S. E., Francks, C., McCracken, J. T., McGough, J. J., Marlow, A. J., MacPhie, I. L., Newbury, D. F., Crawford, L. R., Palmer, C. G., Woodward, J. A., Del'Homme, M., Cantwell, D. P., Nelson, S. F., Monaco, A. P. & Smalley, S. L. (2002*b*). A genomewide scan for loci involved in attention-deficit/hyperactivity disorder. *American Journal of Human Genetics* **70**, 1183–1196.

Fisher, S. E. & Marcus, G. F. (2006). The eloquent ape: genes, brains and the evolution of language. *Nature Reviews.Genetics* **7**, 9–20.

Fitzgerald, M. (2004). *Autism and Creativity: Is there a Link between Autism in Men and Exceptional Ability?* Brunner-Routledge, New York.

Fournier, C., Goto, Y., Ballestar, E., Delaval, K., Hever, A. M., Esteller, M. & Feil, R. (2002). Allele-specific histone lysine methylation marks regulatory regions at imprinted mouse genes. *EMBO Journal* **21**, 6560–6570.

Francks, C., DeLisi, L. E., Fisher, S. E., Laval, S. H., Rue, J. E., Stein, J. F. & Monaco, A. P. (2003*a*). Confirmatory evidence for linkage of relative hand skill to 2p12-q11. *American Journal of Human Genetics* **72**, 499–502.

Francks, C., DeLisi, L. E., Shaw, S. H., Fisher, S. E., Richardson, A. J., Stein, J. F. & Monaco, A. P. (2003*b*). Parent-of-origin effects on handedness and schizophrenia susceptibility on chromosome 2p12-q11. *Human Molecular Genetics* **12**, 3225–3230.

Francks, C., Maegawa, S., Laurén, J., Abrahams, B. S., Velayos-Baeza, A., Medland, S. E., Colella, S., Groszer, M., McAuley, E. Z., Caffrey, T. M., Timmusk, T., Pruunsild, P., Koppel, I., Lind, P. A., Matsumoto-Itaba, N., Nicod, J., Xiong, L., Joober, R., Enard, W., Krinsky, B., Nanba, E., Richardson, A. J., Riley, B. P., Martin, N. G., Strittmatter, S. M., Möller, H. J., Rujescu, D., St Clair, D., Muglia, P., Roos, J. L., Fisher, S. E., Wade-Martins, R., Rouleau, G. A., Stein, J. F., Karayiorgou, M., Geschwind, D. H., Ragoussis, J., Kendler, K. S., Airaksinen, M. S., Oshimura, M., DeLisi, L. E. & Monaco, A. P. (2007). LRRTM1 on chromosome 2p12 is a maternally suppressed gene that is associated paternally with handedness and schizophrenia. *Molecular Psychiatry* **12**, 1129–1139.

Fraser, P. A., Stern, S., Larson, M. G., Marcus-Bagley, D., Awdeh, Z., Glass, D. N. & Alper, C. A. (1990). HLA extended haplotypes in childhood and adult onset HLA-DR4-associated arthropathies. *Tissue Antigens* **35**, 56–59.

Freedman, R., Adler, L. E., Olincy, A., Waldo, M. C., Ross, R. G., Stevens, K. E. & Leonard, S. (2002). Input dysfunction, schizotypy, and genetic models of schizophrenia. *Schizophrenia Research* **54**, 25–32.

Freedman, R., Leonard, S., Olincy, A., Kaufmann, C. A., Malaspina, D., Cloninger, C. R., Svrakic, D., Faraone, S. V. & Tsuang, M. T. (2001). Evidence for the multigenic inheritance of schizophrenia. *American Journal of Medical Genetics* **105**, 794–800.

Friedman, E. R. & Fan, C. M. (2007). Separate necdin domains bind ARNT2 and HIF1alpha and repress transcription. *Biochemical and Biophysical Research Communications* **363**, 113–118.

Friedman, J. I., Vrijenhoek, T., Markx, S., Janssen, I. M., van der Vliet, W. A., Faas, B. H., Knoers, N. V., Cahn, W., Kahn, R. S., Edelmann, L., Davis, K. L., Silverman, J. M., Brunner, H. G., Van Kessel, A. G., Wijmenga, C., Ophoff, R. A. & Veltman, J. A. (2008). CNTNAP2 gene dosage variation is associated with schizophrenia and epilepsy. *Molecular Psychiatry* **13**, 261–266.

Frith, U. (2004). Emanuel Miller lecture: confusions and controversies about Asperger syndrome. *Journal of Child Psychology and Psychiatry* **45**, 672–686.

Gabbett, M. T., Peters, G. B., Carmichael, J. M., Darmanian, A. P. & Collins, F. A. (2008). Prader-Willi syndrome phenocopy due to duplication of Xq21.1-q21.31, with array CGH of the critical region. *Clinical Genetics*. **73**, 353–359.

Gallagher, R. C., Pils, B., Albalwi, M. & Francke, U. (2002). Evidence for the role of PWCR1/HBII-85 C/D box small nucleolar RNAs in Prader-Willi syndrome. *American Journal of Human Genetics* **71**, 669–678.

Garver, D. L., Holcomb, J., Mapua, F. M., Wilson, R. & Barnes, B. (2001). Schizophrenia spectrum disorders: an autosomal-wide scan in multiplex pedigrees. *Schizophrenia Research* **52**, 145–160.

Gau, S. F., Soong, W. T., Liu, H. M., Hou, J. W., Tsai, W. Y., Chiu, Y. N., Yeh, Y. C., Wang, P. J. & Wang, T. R. (1996). Kleine-Levin syndrome in a boy with Prader-Willi syndrome. *Sleep* **19**, 13–17.

Gauthier, J., Joober, R., Mottron, L., Laurent, S., Fuchs, M., De Kimpe, V. & Rouleau, G. A. (2003). Mutation screening of FOXP2 in individuals diagnosed with autistic disorder. *American Journal of Medical Genetics* **118**, 172–175.

Gayán, J., Willcutt, E. G., Fisher, S. E., Francks, C., Cardon, L. R., Olson, R. K., Pennington, B. F., Smith, S. D., Monaco, A. P. & DeFries, J. C. (2005). Bivariate linkage scan for reading disability and attention-deficit/hyperactivity disorder localizes pleiotropic loci. *Journal of Child Psychology and Psychiatry and Allied Disciplines* **46**, 1045–1056.

Georgieva, L., Moskvina, V., Peirce, T., Norton, N., Bray, N. J., Jones, L., Holmans, P., Macgregor, S., Zammit, S., Wilkinson, J., Williams, H., Nikolov, I., Williams, N., Ivanov, D., Davis, K. L., Haroutunian, V., Buxbaum, J. D., Craddock, N., Kirov, G., Owen, M. J. & O'Donovan, M. C. (2006). Convergent evidence that oligodendrocyte lineage transcription factor 2 (OLIG2) and interacting genes influence susceptibility to schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 12469–12474.

Germain-Lee, E. L., Ding, C. L., Deng, Z., Crane, J. L., Saji, M., Ringel, M. D. & Levine, M. A. (2002). Paternal imprinting of Galpha(s) in the human thyroid as the basis of TSH resistance in pseudohypoparathyroidism type 1a. *Biochemical and Biophysical Research Communications* **296**, 67–72.

Germain-Lee, E. L., Schwindinger, W., Crane, J. L., Zewdu, R., Zweifel, L. S., Wand, G., Huso, D. L., Saji, M., Ringel, M. D. & Levine, M. A. (2005). A mouse model of albright hereditary osteodystrophy generated by targeted disruption of exon 1 of the Gnas gene. *Endocrinology* **146**, 4697–4709.

Gershon, E. S., Badner, J. A., Detera-Wadleigh, S. D., Ferraro, T. N. & Berrettini, W. H. (1996). Maternal inheritance and chromosome 18 allele sharing in unilineal bipolar illness pedigrees. *American Journal of Medical Genetics* **67**, 202–207.

Geschwind, D. H., Gregg, J., Boone, K., Karrim, J., Pawlikowska-Haddal, A., Rao, E., Ellison, J., Ciccodicola, A., D'Urso, M., Woods, R., Rappold, G. A., Swerdloff, R. & Nelson, S. F. (1998). Klinefelter's syndrome as a model of anomalous cerebral laterality: testing gene dosage in the X chromosome pseudoautosomal region using a DNA microarray. *Developmental Genetics* **23**, 215–229.

Geschwind, D. H. & Levitt, P. (2007). Autism spectrum disorders: developmental disconnection syndromes. *Current Opinion in Neurobiology* **17**, 103–111.

Gillberg, C. & Billstedt, E. (2000). Autism and Asperger syndrome: coexistence with other clinical disorders. *Acta Psychiatrica Scandinavica* **102**, 321–330.

Gillessen-Kaesbach, G., Robinson, W., Lohmann, D., Kaya-Westerloh, S., Passarge, E. & Horsthemke, B. (1995). Genotype-phenotype correlation in a series of 167 deletion and non-deletion patients with Prader-Willi syndrome. *Human Genetics* **96**, 638–643.

Gilmour, J., Skuse, D. & Pembrey, M. (2001). Hyperphagic short stature and Prader-Willi syndrome: a comparison of behavioural phenotypes, genotypes and indices of stress. *British Journal of Psychiatry.* **179**, 129–137.

Girirajan, S., Elsas, L. J. 2nd, Devriendt, K. & Elsea, S. H. (2005). RAI1 variations in Smith-Magenis syndrome patients without 17p11.2 deletions. *Journal of Medical Genetics.* **42**, 820–828.

Girirajan, S., Vlangos, C. N., Szomju, B. B., Edelman, E., Trevors, C. D., Dupuis, L., Nezarati, M., Bunyan, D. J. & Elsea, S. H. (2006). Genotype-phenotype correlation in Smith-Magenis syndrome: evidence that multiple genes in 17p11.2 contribute to the clinical spectrum. *Genetics in Medicine* **8**, 417–427.

Glasgow, E., Ryu, S., Yamashita, M., Zhang, B., Mutsuga, N. & Gainer, H. (2005). APeg3, a novel paternally expressed gene 3 antisense RNA transcript specifically expressed in vasopressinergic magnocellular neurons in the rat supraoptic nucleus. *Brain Research. Molecular Brain Research* **137**, 143–151.

Glatt, S. J., Everall, I. P., Kremen, W. S., Corbeil, J., Šášik, R., Khanlou, N., Han, M., Liew, C. C. & Tsuang, M. T. (2005). Comparative gene expression analysis of blood and brain provides concurrent validation of SELENBP1 up-regulation in schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 15533–15538.

Glaze, D. G. (2004). Rett syndrome: of girls and mice–lessons for regression in autism. *Mental Retardation and Developmental Disabilities Research Reviews* **10**, 154–158.

Gluckman, P. D., Hanson, M. A., Morton, S. M. & Pinal, C. S. (2005). Life-long echoes–a critical analysis of the developmental origins of adult disease model. *Biology of the Neonate* **87**, 127–139.

Goes, F. S., Zandi, P. P., Miao, K., McMahon, F. J., Steele, J., Willour, V. L., Mackinnon, D. F., Mondimore, F. M., Schweizer, B., Nurnberger, J. I., Rice, J. P., Scheftner, W., Coryell, W., Berrettini, W. H., Kelsoe, J. R., Byerley, W., Murphy, D. L., Gershon, E. S., Bipolar Disorder Phenome Group, Depaulo, J. R., McInnis, M. G. & Potash, J. B. (2007). Mood-incongruent psychotic features in bipolar disorder: familial aggregation and suggestive linkage to 2p11-q14 and 13q21-33. *American Journal of Psychiatry* **164**, 236–247.

Goldberg, T. E. & Weinberger, D. R. (2004). Genes and the parsing of cognitive processes. *Trends in Cognitive Sciences* **8**, 325–335.

Goldberger, C., Gourion, D., Leroy, S., Schürhoff, F., Bourdel, M., Leboyer, M. & Krebs, M. (2005). Population-based and family-based association study of 5'UTR polymorphism of the reelin gene and schizophrenia. *American Journal of Medical Genetics, B* **137**, 51–55.

Goldman, M. B. & Mitchell, C. P. (2004). What is the functional significance of hippocampal pathology in schizophrenia? *Schizophrenia Bulletin* **30**, 367–392.

Goldstone, A. P. (2004). Prader-Willi syndrome: advances in genetics, pathophysiology and treatment. *Trends in Endocrinology and Metabolism* **15**, 12–20.

Goldstone, A. P. (2006). The hypothalamus, hormones, and hunger: alterations in human obesity and illness. *Progress in Brain Research* **153**, 57–73.

Gomot, M., Bernard, F. A., Davis, M. H., Belmonte, M. K., Ashwin, C., Bullmore, E. T. & Baron-Cohen, S. (2006). Change detection in children with autism: an auditory event-related fMRI study. *NeuroImage* **29**, 475–484.

Gong, X., Jia, M., Ruan, Y., Shuang, M., Liu, J., Wu, S., Guo, Y., Yang, J., Ling, Y., Yang, X. & Zhang, D. (2004). Association between the FOXP2 gene and autistic disorder in Chinese population. *American Journal of Medical Genetics, B* **127**, 113–116.

Good, C. D., Lawrence, K., Thomas, N. S., Price, C. J., Ashburner, J., Friston, K. J., Frackowiak, R. S. J., Oreland, L. & Skuse, D. H. (2003). Dosage-sensitive X-linked locus influences the development of amygdala and orbitofrontal cortex, and fear recognition in humans. *Brain* **126**, 2431–2446.

Goos, L. M. & Ragsdale, G. (2008). Genomic imprinting and human psychology: Cognition, behavior and pathology.

In J. Wilkins (Ed.), *Genomic Imprinting* (pp. 71–88). New York: Springer.

Goos, L. M. & Silverman, I. (2001). The influence of genomic imprinting on brain development and behavior. *Evolution and Human Behavior* **22**, 385–407.

Gorlova, O. Y., Amos, C. I., Wang, N. W., Shete, S., Turner, S. T. & Boerwinkle, E. (2003). Genetic linkage and imprinting effects on body mass index in children and young adults. *European Journal of Human Genetics* **11**, 425–432.

Gorwood, P., Pouchot, J., Vinceneux, P., Puéchal, X., Flipo, R. M., De Bandt, M. & Adès, J. (2004). Rheumatoid arthritis and schizophrenia: a negative association at a dimensional level. *Schizophrenia Research* **66**, 21–29.

Goshu, E., Jin, H., Lovejoy, J., Marion, J. F., Michaud, J. L. & Fan, C. M. (2004). Sim2 contributes to neuroendocrine hormone gene expression in the anterior hypothalamus. *Molecular Endocrinology* **18**, 1251–1262.

Gould, T. J., Bizily, S. P., Tokarczyk, J., Kelly, M. P., Siegel, S. J., Kanes, S. J. & Abel, T. (2004). Sensorimotor gating deficits in transgenic mice expressing a constitutively active form of Gs alpha. *Neuropsychopharmacology* **29**, 494–501.

Grabowski, M., Zimprich, A., Lorenz-Depiereux, B., Kalscheuer, V., Asmus, F., Gasser, T., Meitinger, T. & Strom, T. M. (2003). The epsilon-sarcoglycan gene (SGCE), mutated in myoclonus-dystonia syndrome, is maternally imprinted. *European Journal of Human Genetics* **11**, 138–144.

Graham, J. M., Jr, Bashir, A. S., Stark, R. E., Silbert, A. & Walzer, S. (1988). Oral and written language abilities of XXY boys: implications for anticipatory guidance. *Pediatrics* **81**, 795–806.

Gratacos, M., Gonzalez, J. R., Mercader, J. M., De Cid, R., Urretavizcaya, M. & Estivill, X. (2007). Brain-derived neurotrophic factor Val66Met and psychiatric disorders: meta-analysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia. *Biological Psychiatry* **61**, 911–922.

Grayson, D. R., Chen, Y., Costa, E., Dong, E., Guidotti, A., Kundakovic, M. & Sharma, R. P. (2006). The human reelin gene: transcription factors (+), repressors (-) and the methylation switch (+/-) in schizophrenia. *Pharmacology & Therapeutics* **111**, 272–286.

Grayson, D. R., Jia, X., Chen, Y., Sharma, R. P., Mitchell, C. P., Guidotti, A. & Costa, E. (2005). Reelin promoter hypermethylation in schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 9341–9346.

Grigorenko, E. L., Wood, F. B., Meyer, M. S., Pauls, J. E., Hart, L. A. & Pauls, D. L. (2001). Linkage studies suggest a possible locus for developmental dyslexia on chromosome 1p. *American Journal of Medical Genetics* **105**, 120–129.

Grimaldi, B., Bonnin, A., Fillion, M. P., Prudhomme, N. & Fillion, G. (1999). 5-Hydroxytryptamine-moduline: a novel endogenous peptide involved in the control of anxiety. *Neuroscience* **93**, 1223–1225.

Guerini, F. R., Manca, S., Sotgiu, S., Tremolada, S., Zanzottera, M., Agliardi, C., Zanetta, L., Saresella, M., Mancuso, R., De Silvestri, A., Fois, M. L., Arru, G. & Ferrante, P. (2006). A Family Based Linkage Analysis of HLA and 5-HTTLPR Gene Polymorphisms in Sardinian Children with Autism Spectrum Disorder. *Human Immunology* **67**, 108–117.

Guidotti, A., Auta, J., Davis, J. M., Dong, E., Grayson, D. R., Veldic, M., Zhang, X. & Costa, E. (2005). GABAergic dysfunction in schizophrenia: new treatment strategies on the horizon. *Psychopharmacology* **180**, 191–205.

Guillin, O., Demily, C. & Thibaut, F. (2007). Brain-derived neurotrophic factor in schizophrenia and its relation with dopamine. *International Review of Neurobiology* **78**, 377–395.

Gurling, H. M. D., Critchley, H., Datta, S. R., McQuillin, A., Blaveri, E., Thirumalai, S., Pimm, J., Krasucki, R., Kalsi, G., Quested, D., Lawrence, J., Bass, N., Choudhury, K., Puri, V., O'Daly, O., Curtis, D., Blackwood, D., Muir, W., Malhotra, A. K., Buchanan, R. W., Good, C. D., Frackowiak, R. S. J. & Dolan, R. J. (2006). Genetic association and brain morphology studies and the chromosome 8p22 pericentriolar material 1 (PCM1) gene in susceptibility to schizophrenia. *Archives of General Psychiatry* **63**, 844–854.

Hager, R., Cheverud, J. M. & Wolf, J. B. (2008). Maternal effects as the cause of parent-of-origin effects that mimic genomic imprinting. *Genetics* (in press).

Haig, D. (1993). Genetic conflicts in human pregnancy. *Quarterly Review of Biology* **68**, 495–532.

Haig, D. (1996). Placental hormones, genetic imprinting, and maternal-fetal communication. *Journal of Evolutionary Biology* **9**, 357–357.

Haig, D. (1999). Genetic conflicts of pregnancy and childhood. In *Evolution in Health and Disease* (ed. C. Stearns), pp. 77–90. Oxford University Press, Oxford.

Haig, D. (2000*a*). Genomic imprinting, sex-biased dispersal, and social behavior. In *Evolutionary Perspectives on Human Reproductive Behavior* (eds. D LeCroy and P Moller), pp. 149–163.

Haig, D. (2000*b*). The kinship theory of genomic impriting. *Annual Review of Ecology and Systematics* **31**, 9–32.

Haig, D. (2004*a*). Evolutionary conflicts in pregnancy and calcium metabolism–a review. *Placenta* **25** Suppl A, s10–s15.

Haig, D. (2004*b*). Genomic imprinting and kinship: how good is the evidence? *Annual Review of Genetics* **38**, 553–585.

Haig, D. (2006*a*). Intragenomic politics. *Cytogenetic and Genome Research* **113**, 68–74.

Haig, D. (2006*b*). Self-imposed silence: parental antagonism and the evolution of X-chromosome inactivation. *Evolution* **60**, 440–447.

Haig, D. (2008). Huddling: brown fat, genomic imprinting and the warm inner glow. *Current Biology* **18**, r172–r174.

Haig, D. & Wharton, R. (2003). Prader-Willi syndrome and the evolution of human childhood. *American Journal of Human Biology* **15**, 320–329.

Hamshere, M. L., Bennett, P., Williams, N., Segurado, R., Cardno, A., Norton, N., Lambert, D., Williams, H., Kirov, G., Corvin, A., Holmans, P., Jones, L., Jones, I., Gill, M., O'Donovan, M. C., Owen, M. J. & Craddock, N. (2005). Genomewide linkage scan in schizoaffective disorder: significant evidence for linkage at 1q42 close to DISC1, and suggestive evidence at 22q11 and 19p13. *Archives of General Psychiatry* **62**, 1081–1088.

Hancock, A. L., Brown, K. W., Moorwood, K., Moon, H., Holmgren, C., Mardikar, S. H., Dallosso, A. R., Klenova, E., Loukinov, D., Ohlsson, R., Lobanenkov, V. V. & Malik, K. (2007). A CTCF-binding silencer regulates the imprinted genes AWT1 and WT1-AS and exhibits sequential epigenetic defects during Wilms' tumourigenesis. *Human Molecular Genetics* **16**, 343–354.

Happé, F., Ronald, A. & Plomin, R. (2006). Time to give up on a single explanation for autism. *Nature Neuroscience* **9**, 1218–1220.

Harrison, P. J. & Weinberger, D. R. (2005). Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Molecular Psychiatry* **10**, 40–68.

Hashimoto, T., Bergen, S. E., Nguyen, Q. L., Xu, B., Monteggia, L. M., Pierri, J. N., Sun, Z., Sampson, A. R. & Lewis, D. A.

(2005). Relationship of brain-derived neurotrophic factor and its receptor TrkB to altered inhibitory prefrontal circuitry in schizophrenia. *Journal of Neuroscience* **25**, 372–383.

Hashimoto, K., Iwata, Y., Nakamura, K., Tsujii, M., Tsuchiya, K. J., Sekine, Y., Suzuki, K., Minabe, Y., Takei, N., Iyo, M. & Mori, N. (2006). Reduced serum levels of brain-derived neurotrophic factor in adult male patients with autism. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **30**, 1529–1531.

Hattori, E., Liu, C., Zhu, H. & Gershon, E. S. (2005). Genetic tests of biologic systems in affective disorders. *Molecular Psychiatry* **10**, 719–740.

Hawi, Z., Gibson, S., Straub, R. E., Walsh, D., Kendler, K. S. & Gill, M. (1999). Schizophrenia and HLA: No association with PCR-SSOP typed classical loci in a large Irish familial sample. *American Journal of Medical Genetics* **88**, 422–429.

Hawi, Z., Segurado, R., Conroy, J., Sheehan, K., Lowe, N., Kirley, A., Shields, D., Fitzgerald, M., Gallagher, L. & Gill, M. (2005). Preferential transmission of paternal alleles at risk genes in attention-deficit/hyperactivity disorder. *American Journal of Human Genetics* **77**, 958–965.

Hay, G. G. & Jolley, D. J. (1974). The Capgras syndrome. *British Journal of Psychiatry* **124**, 314–315.

Hay, G. G., Jolley, D. J. & Jones, R. G. (1974). A case of the Capgras syndrome in association with pseudo-hypoparathyroidism. *Acta Psychiatrica Scandinavica* **50**, 73–77.

Hayesmoore, J. B., Bray, N. J., Owen, M. J., O'Donovan, M. C. (2008). DISC1 mRNA expression is not influenced by common Cis-acting regulatory polymorphisms or imprinting. *American Journal of Medical Genetics, B* (in press).

Heijmans, B. T., Kremer, D., Tobi, E. W., Boomsma, D. I. & Slagboom, P. E. (2007). Heritable rather than age-related environmental and stochastic factors dominate variation in DNA methylation of the human IGF2/H19 locus. *Human Molecular Genetics* **16**, 547–554.

Heilstedt, H. A., Ballif, B. C., Howard, L. A., Lewis, R. A., Stal, S., Kashork, C. D., Bacino, C. A., Shapira, S. K. & Shaffer, L. G. (2003). Physical map of 1p36, placement of breakpoints in monosomy 1p36, and clinical characterization of the syndrome. *American Journal of Human Genetics* **72**, 1200–1212.

Heim, S., Kissler, J., Elbert, T. & Rockstroh, B. (2004). Cerebral lateralization in schizophrenia and dyslexia: neuromagnetic responses to auditory stimuli. *Neuropsychologia* **42**, 692–697.

Heinrich, T. W. & Grahm, G. (2003). Hypothyroidism presenting as psychosis: myxedema madness revisited. *Primary Care Companion to the Journal of Clinical Psychiatry* **5**, 260–266.

Hellings, J. A., Hossain, S., Martin, J. K. & Baratang, R. R. (2002). Psychopathology, GABA, and the Rubinstein-Taybi syndrome: a review and case study. *American Journal of Medical Genetics* **114**, 190–195.

Hernandez, A., Martinez, M. E., Croteau, W. & St Germain, D. L. (2004). Complex organization and structure of sense and antisense transcripts expressed from the DIO3 gene imprinted locus. *Genomics* **83**, 413–424.

Hernandez, A., Martinez, M. E., Fiering, S., Galton, V. A. & St Germain, D. (2006). Type 3 deiodinase is critical for the maturation and function of the thyroid axis. *Journal of Clinical Investigation* **116**, 476–484.

Hirstein, W. & Ramachandran, V. S. (1997). Capgras syndrome: a novel probe for understanding the neural representation of the identity and familiarity of persons. *Proceedings of the Royal Society of London, Part B, Biological Sciences* **264**, 437–444.

Hogart, A., Nagarajan, R. P., Patzel, K. A., Yasui, D. H. & Lasalle, J. M. (2007). 15q11-13 GABAA receptor genes are normally biallelically expressed in brain yet are subject to epigenetic dysregulation in autism-spectrum disorders. *Human Molecular Genetics* **16**, 691–703.

Hohjoh, H., Ohashi, J., Takasu, M., Nishioka, T., Ishida, T. & Tokunaga, K. (2003). Recent divergence of the HLA-DRB1*04 allelic lineage from the DRB1*0701 lineage after the separation of the human and chimpanzee species. *Immunogenetics* **54**, 856–861.

Holden, R. J. & Pakula, I. S. (1999). The link between diabetes and schizophrenia: an immunological explanation. *Australian and New Zealand Journal of Psychiatry* **33**, 286–287.

Holland, A., Whittington, J. & Hinton, E. (2003). The paradox of Prader-Willi syndrome: a genetic model of starvation. *Lancet* **362**, 989–991.

Hong, S. B., Joo, E. Y., Tae, W. S., Lee, J., Han, S. J. & Lee, H. W. (2006). Episodic diencephalic hypoperfusion in Kleine-Levin syndrome. *Sleep* **29**, 1091–1093.

Hordijk, R., Wierenga, H., Scheffer, H., Leegte, B., Hofstra, R. M. & Stolte-Dijkstra, I. (1999). Maternal uniparental disomy for chromosome 14 in a boy with a normal karyotype. *Journal of Medical Genetics* **36**, 782–785.

Horike, S., Cai, S., Miyano, M., Cheng, J. F. & Kohwi-Shigematsu, T. (2005). Loss of silent-chromatin looping and impaired imprinting of DLX5 in Rett syndrome. *Nature Genetics* **37**, 31–40.

Horrobin, D. F. (1998*a*). Schizophrenia: the illness that made us human. *Medical Hypotheses* **50**, 269–288.

Horrobin, D. F. (1998*b*). The membrane phospholipid hypothesis as a biochemical basis for the neurodevelopmental concept of schizophrenia. *Schizophrenia Research* **30**, 193–208.

Horrobin, D. (2001). *The Madness of Adam and Eve: How Schizophrenia Shaped Humanity*. Transworld Publishers, London.

Horsthemke, B. & Buiting, K. (2008). Chapter 8: Genomic imprinting and imprinting defects in humans. *Advances in Genetics* **61**, 225–246.

Hou, J. (2003). Chromosomal 10Q26 trisomy resulting from paternal T(9;10)(PTER;Q26.1). *Journal of the Formosan Medical Association* **102**, 887–892.

Hsieh, H., Palmer, C. G. S., Harney, S., Newton, J. L., Wordsworth, P., Brown, M. A. & Sinsheimer, J. S. (2006). The v-MFG test: investigating maternal, offspring and maternal-fetal genetic incompatibility effects on disease and viability. *Genetic Epidemiology* **30**, 333–347.

Hsiung, G. R., Kaplan, B. J., Petryshen, T. L., Lu, S. & Field, L. L. (2004). A dyslexia susceptibility locus (DYX7) linked to dopamine D4 receptor (DRD4) region on chromosome 11p15.5. *American Journal of Medical Genetics, B* **125**, 112–119.

Hu, V. W., Frank, B. C., Heine, S., Lee, N. H. & Quackenbush, J. (2006). Gene expression profiling of lymphoblastoid cell lines from monozygotic twins discordant in severity of autism reveals differential regulation of neurologically relevant genes. *BMC Genomics* **7**, 118.

Hu, Y., Li, Z., Guo, L., Wang, L., Zhang, L., Cai, X., Zhao, H. & Zha, X. (2007). MAGI-2 Inhibits cell migration and proliferation via PTEN in human hepatocarcinoma cells. *Archives of Biochemistry and Biophysics* **467**, 1–9.

Infante-Rivard, C. & Weinberg, C. R. (2005). Parent-of-origin transmission of thrombophilic alleles to intrauterine growth-restricted newborns and transmission-ratio distortion in unaffected newborns. *American Journal of Epidemiology* **162**, 891–897.

Ingrosso, D., Cimmino, A., Perna, A. F., Masella, L., De Santo, N. G., De Bonis, M. L., Vacca, M., D'Esposito, M., D'Urso, M., Galletti, P. & Zappia, V. (2003). Folate treatment and unbalanced methylation and changes of allelic expression induced by hyperhomocysteinaemia in patients with uraemia. *Lancet* **361**, 1693–1699.

International Molecular Genetic Study of Autism Consortium (IMGSAC) (2001*a*). A genomewide screen for autism: strong evidence for linkage to chromosomes 2q, 7q, and 16p. *American Journal of Human Genetics* **69**, 570–581.

International Molecular Genetic Study of Autism Consortium (IMGSAC) (2001*b*). Further characterization of the autism susceptibility locus AUTS1 on chromosome 7q. *Human Molecular Genetics* **10**, 973–982.

Iossifov, I., Zheng, T., Baron, M., Gilliam, T. C. & Rzhetsky, A. (2008). Genetic-linkage mapping of complex hereditary disorders to a whole-genome molecular-interaction network. *Genome Research* (in press).

Ischia, R., Lovisetti-Scamihorn, P., Hogue-Angeletti, R., Wolkersdorfer, M., Winkler, H. & Fischer-Colbrie, R. (1997). Molecular cloning and characterization of NESP55, a novel chromogranin-like precursor of a peptide with 5-HT1B receptor antagonist activity. *Journal of Biological Chemistry* **272**, 11657–11662.

Ishikawa, H., Rattigan, A., Fundele, R. & Burgoyne, P. S. (2003). Effects of sex chromosome dosage on placental size in mice. *Biology of Reproduction* **69**, 483–488.

Isles, A. R. & Holland, A. J. (2005). Imprinted genes and mother-offspring interactions. *Early Human Development* **81**, 73–77.

Isles, A. R. & Humby, T. (2006). Modes of imprinted gene action in learning disability. *Journal of Intellectual Disability Research* **50**, 318–325.

Isles, A. R. & Wilkinson, L. S. (2000). Imprinted genes, cognition and behaviour. *Trends in Cognitive Science* **4**, 309–318.

Itaba-Matsumoto, N., Maegawa, S., Yamagata, H., Kondo, I., Oshimura, M. & Nanba, E. (2007). Imprinting status of paternally imprinted DLX5 gene in Japanese patients with Rett syndrome. *Brain & Development* **29**, 491–495.

Itokawa, M., Yamada, K., Iwayama-Shigeno, Y., Ishitsuka, Y., Detera-Wadleigh, S. & Yoshikawa, T. (2003). Genetic analysis of a functional GRIN2A promoter (GT)n repeat in bipolar disorder pedigrees in humans. *Neuroscience Letters* **345**, 53–56.

Itti, E., Gaw Gonzalo, I. T., Boone, K. B., Geschwind, D. H., Berman, N., Pawlikowska-Haddal, A., Itti, L., Mishkin, F. S. & Swerdloff, R. S. (2003). Functional neuroimaging provides evidence of anomalous cerebral laterality in adults with Klinefelter's syndrome. *Annals of Neurology* **54**, 669–673.

Itti, E., Gaw Gonzalo, I. T., Pawlikowska-Haddal, A., Boone, K. B., Mlikotic, A., Itti, L., Mishkin, F. S. & Swerdloff, R. S. (2006). The structural brain correlates of cognitive deficits in adults with Klinefelter's syndrome. *Journal of Clinical Endocrinology and Metabolism* **91**, 1423–1427.

Iwayama-Shigeno, Y., Yamada, K., Itokawa, M., Toyota, T., Meerabux, J. M. A., Minabe, Y., Mori, N., Inada, T. & Yoshikawa, T. (2005). Extended analyses support the association of a functional (GT)n polymorphism in the GRIN2A promoter with Japanese schizophrenia. *Neuroscience Letters* **378**, 102–105.

Jablensky, A., Sartorius, N., Ernberg, G., Anker, M., Korten, A., Cooper, J. E., Day, R. & Bertelsen, A. (1992). Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. Psychological Medicine. *Monograph Supplement* **20**, 1–97.

Jackson-Grusby, L., Beard, C., Possemato, R., Tudor, M., Fambrough, D., Csankovszki, G., Dausman, J., Lee, P., Wilson, C., Lander, E. & Jaenisch, R. (2001). Loss of genomic methylation causes p53-dependent apoptosis and epigenetic deregulation. *Nature Genetics* **27**, 31–39.

Jacob, S. & Moley, K. H. (2005). Gametes and embryo epigenetic reprogramming affect developmental outcome: implication for assisted reproductive technologies. *Pediatric Research* **58**, 437–446.

Jamain, S., Betancur, C., Quach, H., Philippe, A., Fellous, M., Giros, B., Gillberg, C., Leboyer, M. & Bourgeron, T. (2002). Linkage and association of the glutamate receptor 6 gene with autism. *Molecular Psychiatry* **7**, 302–310.

James, S. J., Melnyk, S., Jernigan, S., Cleves, M. A., Halsted, C. H., Wong, D. H., Cutler, P., Bock, K., Boris, M., Bradstreet, J. J., Baker, S. M. & Gaylor, D. W. (2006). Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism. *American Journal of Medical Genetics, B* **141**, 947–956.

Jedele, K. B. (2007). The overlapping spectrum of Rett and Angelman syndromes: a clinical review. *Seminars in Pediatric Neurology* **14**, 108–117.

Jentsch, J. D., Arguello, P. A. & Anzivino, L. A. (2003). Null mutation of the arginine-vasopressin gene in rats slows attentional engagement and facilitates response accuracy in a lateralized reaction time task. *Neuropsychopharmacology* **28**, 1597–1605.

Jiang, Y., Sahoo, T., Michaelis, R. C., Bercovich, D., Bressler, J., Kashork, C. D., Liu, Q., Shaffer, L. G., Schroer, R. J., Stockton, D. W., Spielman, R. S., Stevenson, R. E. & Beaudet, A. L. (2004). A mixed epigenetic/genetic model for oligogenic inheritance of autism with a limited role for UBE3A. *American Journal of Medical Genetics* **131**, 1–10.

Jin, L. Q., Wang, H. Y. & Friedman, E. (2001). Stimulated D(1) dopamine receptors couple to multiple Galpha proteins in different brain regions. *Journal of Neurochemistry* **78**, 981–990.

Johnson, W. G. (2003). Teratogenic alleles and neurodevelopmental disorders. *BioEssays* **25**, 464–477.

Johnstone, K. A., DuBose, A. J., Futtner, C. R., Elmore, M. D., Brannan, C. I. & Resnick, J. L. (2006). A human imprinting centre demonstrates conserved acquisition but diverged maintenance of imprinting in a mouse model for Angelman syndrome imprinting defects. *Human Molecular Genetics* **15**, 393–404.

Jungerius, B. J., Hoogendoorn, M. L., Bakker, S. C., Van't Slot, R., Bardoel, A. F., Ophoff, R. A., Wijmenga, C., Kahn, R. S. & Sinke, R. J. (2007). An association screen of myelin-related genes implicates the chromosome 22q11 PIK4CA gene in schizophrenia. *Molecular Psychiatry* (in press).

Kagami, M., Sekita, Y., Nishimura, G., Irie, M., Kato, F., Okada, M., Yamamori, S., Kishimoto, H., Nakayama, M., Tanaka, Y., Matsuoka, K., Takahashi, T., Noguchi, M., Tanaka, Y., Masumoto, K., Utsunomiya, T., Kouzan, H., Komatsu, Y., Ohashi, H., Kurosawa, K., Kosaki, K., Ferguson-Smith, A. C., Ishino, F. & Ogata, T. (2008). Deletions and epimutations affecting the human 14q32.2 imprinted region in individuals with paternal and maternal upd(14)-like phenotypes. *Nature Genetics.* **40**, 237–242.

Kalkman, H. O. (2006). The role of the phosphatidylinositide 3-kinase-protein kinase B pathway in schizophrenia. *Pharmacology & Therapeutics* **110**, 117–134.

Kapitány, A., Zilahi, E., Szántó, S., Szücs, G., Szabó, Z., Végvári, A., Rass, P., Sipka, S., Szegedi, G. & Szekanecz, Z. (2005). Association of Rheumatoid Arthritis with HLA-DR1

and HLA-DR4 in Hungary. *Annals of the New York Academy of Sciences* **1051**, 263–270.

Karayiorgou, M. & Gogos, J. A. (2006). Schizophrenia genetics: uncovering positional candidate genes. *European Journal of Human Genetics* **14**, 512–519.

Kato, C., Tochigi, M., Ohashi, J., Koishi, S., Kawakubo, Y., Yamamoto, K., Matsumoto, H., Hashimoto, O., Kim, S. Y., Watanabe, K., Kano, Y., Nanba, E., Kato, N. & Sasaki, T. (2008) Association study of the 15q11-q13 maternal expression domain in Japanese autistic patients. *American Journal of Medical Genetics, B* (in press).

Kato, T. (2001). Molecular genetics of bipolar disorder. *Neuroscience Research* **40**, 105–113.

Kaufmann, C. A., Suarez, B., Malaspina, D., Pepple, J., Svrakic, D., Markel, P. D., Meyer, J., Zambuto, C. T., Schmitt, K., Matise, T. C., Harkavy Friedman, J. M., Hampe, C., Lee, H., Shore, D., Wynne, D., Faraone, S. V., Tsuang, M. T. & Cloninger, C. R. (1998). NIMH Genetics Initiative Millenium Schizophrenia Consortium: linkage analysis of African-American pedigrees. *American Journal of Medical Genetics* **81**, 282–289.

Kebers, F., Janvier, S., Colin, A., Legros, J. J. & Ansseau, M. (2002). What is the interest of Klinefelter's syndrome for (child) psychiatrists? *L'Encéphale* **28**, 260–265.

Keller, M. C. & Miller, G. (2006). Resolving the paradox of common, harmful, heritable mental disorders: which evolutionarygenetic models work best? *Behavioral and Brain Sciences* **29**, 385–404.

Kelsey, G. (2007). Genomic imprinting–roles and regulation in development. *Endocrine Development* **12**, 99–112.

Kelsoe, J. R., Spence, M. A., Loetscher, E., Foguet, M., Sadovnick, A. D., Remick, R. A., Flodman, P., Khristich, J., Mroczkowski-Parker, Z., Brown, J. L., Masser, D., Ungerleider, S., Rapaport, M. H., Wishart, W. L. & Luebbert, H. (2001). A genome survey indicates a possible susceptibility locus for bipolar disorder on chromosome 22. *Proceedings of the National Academy of Sciences of the United States of America* **98**, 585–590.

Kempf, L., Hussain, N. & Potash, J. B. (2005). Mood disorder with psychotic features, schizoaffective disorder, and schizophrenia with mood features: trouble at the borders. *International Review of Psychiatry* **17**, 9–19.

Kent, L., Bowdin, S., Kirby, G. A., Cooper, W. N. & Maher, E. R. (2008). *Beckwith Weidemann syndrome: A behavioral phenotype-genotype study. American Journal of Medical Genetics, B (in press)*.

Kent, L., Green, E., Hawi, Z., Kirley, A., Dudbridge, F., Lowe, N., Raybould, R., Langley, K., Bray, N., Fitzgerald, M., Owen, M. J., O'Donovan, M. C., Gill, M., Thapar, A. & Craddock, N. (2005). Association of the paternally transmitted copy of common Valine allele of the Val66Met polymorphism of the brain-derived neurotrophic factor (BDNF) gene with susceptibility to ADHD. *Molecular Psychiatry* **10**, 939–943.

Keverne, E. B., Fundele, R., Narasimha, M., Barton, S. C. & Surani, M. A. (1996). Genomic imprinting and the differential roles of parental genomes in brain development. *Brain Research. Developmental Brain Research* **92**, 91–100.

Keverne, E. B. (1999). GABA-ergic neurons and the neurobiology of schizophrenia and other psychoses. *Brain Research Bulletin* **48**, 467–473.

Keverne, E. B. (2001). Genomic imprinting and the maternal brain. *Progress in Brain Research* **133**, 279–285.

Kilpinen, H., Ylisaukko-Oja, T., Hennah, W., Palo, O. M., Varilo, T., Vanhala, R., Nieminen-von Wendt, T., von Wendt, L., Paunio, T. & Peltonen, L. (2008). Association of DISC1 with autism and Asperger syndrome. *Molecular Psychiatry* **13**, 187–196.

Kim, J., Noskov, V. N., Lu, X., Bergmann, A., Ren, X., Warth, T., Richardson, P., Kouprina, N. & Stubbs, L. (2000). Discovery of a novel, paternally expressed ubiquitin-specific processing protease gene through comparative analysis of an imprinted region of mouse chromosome 7 and human chromosome 19q13.4. *Genome Research* **10**, 1138–1147.

Kim, J., Bergmann, A., Lucas, S., Stone, R. & Stubbs, L. (2004). Lineage-specific imprinting and evolution of the zinc-finger gene ZIM2. *Genomics* **84**, 47–58.

Kim, S. A., Kim, J. H., Park, M., Cho, I. H. & Yoo, H. J. (2007). Family-based association study between GRIK2 polymorphisms and autism spectrum disorders in the Korean trios. *Neuroscience Research* **58**, 332–335.

Kim, S. J., Brune, C. W., Kistner, E. O., Christian, S. L., Courchesne, E. H., Cox, N. J. & Cook, E. H. (2008). Transmission disequilibrium testing of the chromosome 15q11-q13 region in autism. *American Journal of Medical Genetics, B* (in press).

Kim, S. J., Gonen, D., Hanna, G. L., Leventhal, B. L., Cook, E. H., Jr (2000). Deletion polymorphism in the coding region of the human NESP55 alternative transcript of GNAS1. *Molecular and Cellular Probes* **14**, 191–194.

Kishino, T. (2006). Imprinting in neurons. *Cytogenetic and Genome Research* **113**, 209–214.

Kishore, S. & Stamm, S. (2006). The snoRNA HBII-52 regulates alternative splicing of the serotonin receptor 2C. *Science* **311**, 230–232.

Klauck, S. M., Lindsay, S., Beyer, K. S., Splitt, M., Burn, J. & Poustka, A. (2002). A mutation hot spot for nonspecific X-linked mental retardation in the MECP2 gene causes the PPM-X syndrome. *American Journal of Human Genetics* **70**, 1034–1037.

Kleefstra, T., Brunner, H. G., Amiel, J., Oudakker, A. R., Nillesen, W. M., Magee, A., Geneviève, D., Cormier-Daire, V., van Esch, H., Fryns, J. P., Hamel, B. C., Sistermans, E. A., de Vries, B. B. & van Bokhoven, H. (2006). Loss-of-function mutations in euchromatin histone methyl transferase 1 (EHMT1) cause the 9q34 subtelomeric deletion syndrome. *American Journal of Human Genetics* **79**, 370–377.

Kleefstra, T. & Hamel, B. C. J. (2005). X-linked mental retardation: further lumping, splitting and emerging phenotypes. *Clinical Genetics* **67**, 451–467.

Knapp, M. & Strauch, K. (2004). Affected-sib-pair test for linkage based on constraints for identical-by-descent distributions corresponding to disease models with imprinting. *Genetic Epidemiology* **26**, 273–285.

Kohn, Y., Danilovich, E., Filon, D., Oppenheim, A., Karni, O., Kanyas, K., Turetsky, N., Korner, M. & Lerer, B. (2004). Linkage disequlibrium in the DTNBP1 (dysbindin) gene region and on chromosome 1p36 among psychotic patients from a genetic isolate in Israel: findings from identity by descent haplotype sharing analysis. *American Journal of Medical Genetics, B* **128**, 65–70.

Kohn, Y. & Lerer, B. (2005). Excitement and confusion on chromosome 6q: the challenges of neuropsychiatric genetics in microcosm. *Molecular Psychiatry* **10**, 1062–1073.

Kotzot, D. (2004). Maternal uniparental disomy 14 dissection of the phenotype with respect to rare autosomal recessively inherited traits, trisomy mosaicism, and genomic imprinting. *Annales De Génétique* **47**, 251–260.

Kotzot, D. (2007). Growth parameters in maternal uniparental disomy 7 and 14. *European Journal of Pediactrics* **166**, 1143–1149.

Köves, K., Kausz, M., Reser, D., Illyés, G., Takács, J., Heinzlmann, A., Gyenge, E. & Horváth, K. (2004). Secretin and autism: a basic morphological study about the distribution of secretin in the nervous system. *Regulatory Peptides* **123**, 209–216.

Kozlov, S. V., Bogenpohl, J. W., Howell, M. P., Wevrick, R., Panda, S., Hogenesch, J. B., Muglia, L. J., Van Gelder, R. N., Herzog, E. D. & Stewart, C. L. (2007). The imprinted gene Magel2 regulates normal circadian output. *Nature Genetics* **39**, 1266–1272.

Kumra, S., Wiggs, E., Krasnewich, D., Meck, J., Smith, A. C., Bedwell, J., Fernandez, T., Jacobsen, L. K., Lenane, M. & Rapoport, J. L. (1998). Brief report: association of sex chromosome anomalies with childhood-onset psychotic disorders. *Journal of the American Academy of Child and Adolescent Psychiatry* **37**, 292–296.

Kundakovic, M., Chen, Y., Costa, E. & Grayson, D. R. (2007). DNA methyltransferase inhibitors coordinately induce expression of the human reelin and GAD67 genes. *Molecular Pharmacology* **71**, 644–653.

Kunugi, H., Lee, K. B. & Nanko, S. (1999). Cytogenetic findings in 250 schizophrenics: evidence confirming an excess of the X chromosome aneuploidies and pericentric inversion of chromosome 9. *Schizophrenia Research* **40**, 43–47.

Kurosawa, K., Kawame, H., Okamoto, N., Ochiai, Y., Akatsuka, A., Kobayashi, M., Shimohira, M., Mizuno, S., Wada, K., Fukushima, Y., Kawawaki, H., Yamamoto, T., Masuno, M., Imaizumi, K. & Kuroki, Y. (2005). Epilepsy and neurological findings in 11 individuals with 1p36 deletion syndrome. *Brain & Development* **27**, 378–382.

Kuwajima, T., Nishimura, I. & Yoshikawa, K. (2006). Necdin promotes GABAergic neuron differentiation in cooperation with Dlx homeodomain proteins. *Journal of Neuroscience* **26**, 5383–5392.

Kuzmin, A., Han, Z., Golding, M. C., Mann, M. R., Latham, K. E. & Varmuza, S. (2008). The PcG gene Sfmbt2 is paternally expressed in extraembryonic tissues. *Gene Expression Patterns* **8**, 107–116.

Lai, I. C., Liou, Y. J., Chen, J. Y. & Wang, Y. C. (2005). No association between the ionotropic glutamate receptor kainate 3 gene ser310ala polymorphism and schizophrenia. *Neuropsychobiology* **51**, 211–213.

Laje, G., Paddock, S., Manji, H., Rush, A. J., Wilson, A. F., Charney, D. & McMahon, F. J. (2007). Genetic markers of suicidal ideation emerging during citalopram treatment of major depression. *American Journal of Psychiatry* **164**, 1530–1538.

Lamb, J. A., Barnby, G., Bonora, E., Sykes, N., Bacchelli, E., Blasi, F., Maestrini, E., Broxholme, J., Tzenova, J., Weeks, D., Bailey, A. J. & Monaco, A. P. (2005). Analysis of IMGSAC autism susceptibility loci: evidence for sex limited and parent of origin specific effects. *Journal of Medical Genetics* **42**, 132–137.

Lambert, D., Middle, F., Hamshere, M. L., Segurado, R., Raybould, R., Corvin, A., Green, E., O'Mahony, E., Nikolov, I., Mulcahy, T., Haque, S., Bort, S., Bennett, P., Norton, N., Owen, M. J., Kirov, G., Lendon, C., Jones, L., Jones, I., Holmans, P., Gill, M. & Craddock, N. (2005). Stage 2 of the Wellcome Trust UK-Irish bipolar affective disorder sibling-pair genome screen: evidence for linkage on chromosomes 6q16-q21, 4q12-q21, 9p21, 10p14-p12 and 18q22. *Molecular Psychiatry* **10**, 831–841.

Lan, T. H., Beaty, T. H., Raymond Depaulo, J. & McInnis, M. G. (2007). Parent-of-origin effect in the segregation analysis of bipolar affective disorder families. *Psychiatric Genetics* **17**, 93–101.

Lara, D. R. (2002). Inhibitory deficit in schizophrenia is not necessarily a GABAergic deficit. *Cellular and Molecular Neurobiology* **22**, 239–247.

Lara, D. R., Dall'igna, O. P., Ghisolfi, E. S. & Brunstein, M. G. (2006). Involvement of adenosine in the neurobiology of schizophrenia and its therapeutic implications. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **30**, 617–629.

Larsson, M., Pedersen, N. L. & Stattin, H. (2007). Associations between iris characteristics and personality in adulthood. *Biological Psychology* **75**, 165–175.

LaSalle, J. M. (2007). The odyssey of MeCP2 and parental imprinting. *Epigenetics* **2**, 5–10.

LaSalle, J. M., Hogart, A. & Thatcher, K. N. (2005). Rett syndrome: a Rosetta stone for understanding the molecular pathogenesis of autism. *International Review of Neurobiology* **71**, 131–165.

Laurin, N., Ickowicz, A., Pathare, T., Malone, M., Tannock, R., Schachar, R., Kennedy, J. L. & Barr, C. L. (2006). Investigation of the G protein subunit Galpha(olf) gene (GNAL) in attention deficit/hyperactivity disorder. *Journal of Psychiatric Research* **42**, 117–124.

Lauritsen, M. B., Pedersen, C. B. & Mortensen, P. B. (2005). Effects of familial risk factors and place of birth on the risk of autism: a nationwide register-based study. *Journal of Child Psychology and Psychiatry, and Allied Disciplines* **46**, 963–971.

Lauterbach, E. C., Spears, T. E., Prewett, M. J., Price, S. T., Jackson, J. G. & Kirsh, A. D. (1994). Neuropsychiatric disorders, myoclonus, and dystonia in calcification of basal ganglia pathways. *Biological Psychiatry* **35**, 345–351.

Laval, S. H., Dann, J. C., Butler, R. J., Loftus, J., Rue, J., Leask, S. J., Bass, N., Comazzi, M., Vita, A., Nanko, S., Shaw, S., Peterson, P., Shields, G., Smith, A. B., Stewart, J., DeLisi, L. E. & Crow, T. J. (1998). Evidence for linkage to psychosis and cerebral asymmetry (relative hand skill) on the X chromosome. *American Journal of Medical Genetics* **81**, 420–427.

Laviolette, S. R. (2007). Dopamine modulation of emotional processing in cortical and subcortical neural circuits: evidence for a final common pathway in schizophrenia? *Schizophrenia Bulletin* **33**, 971–981.

Lee, A. F., Ho, D. K., Zanassi, P., Walsh, G. S., Kaplan, D. R. & Miller, F. D. (2004). Evidence that DeltaNp73 promotes neuronal survival by p53-dependent and p53-independent mechanisms. *Journal of Neuroscience* **24**, 9174–9184.

Lee, D. O. & Ousley, O. Y. (2006). Attention-deficit hyperactivity disorder symptoms in a clinic sample of children and adolescents with pervasive developmental disorders. *Journal of Child and Adolescent Psychopharmacology* **16**, 737–746.

Lee, H. K., Hsu, A. K., Sajdak, J., Qin, J., & Pavlidis, P. (2004) Coexpression analysis of human genes across many microarray data sets (bioinformatics.ubc.ca/Gemma/). *Genome Research* **14**, 1085–94.

Lee, L., Zachary, A. A., Leffell, M. S., Newschaffer, C. J., Matteson, K. J., Tyler, J. D. & Zimmerman, A. W. (2006). HLA-DR4 in families with autism. *Pediatric Neurology* **35**, 303–307.

Lee, S., Walker, C. L., Karten, B., Kuny, S. L., Tennese, A. A., O'Neill, M. A. & Wevrick, R. (2005). Essential role for the Prader-Willi syndrome protein necdin in axonal outgrowth. *Human Molecular Genetics* **14**, 627–637.

Le-Niculescu, H., Balaraman, Y., Patel, S., Tan, J., Sidhu, K., Jerome, R. E., Edenberg, H. J., Kuczenski, R., Geyer, M. A., Nurnberger, J. I. Jr., Faraone, S. V., Tsuang, M. T. & Niculescu, A. B. (2007). Towards understanding the schizophrenia code:

An expanded convergent functional genomics approach. *American Journal of Medical Genetics, B* **144**, 129–158.

Lerer, B., Segman, R. H., Hamdan, A., Kanyas, K., Karni, O., Kohn, Y., Korner, M., Lanktree, M., Kaadan, M., Turetsky, N., Yakir, A., Kerem, B. & Macciardi, F. (2003). Genome scan of Arab Israeli families maps a schizophrenia susceptibility gene to chromosome 6q23 and supports a locus at chromosome 10q24. *Molecular Psychiatry* **8**, 488–498.

Levi, A., Kohn, Y., Kanyas, K., Amann, D., Pae, C., Hamdan, A., Segman, R. H., Avidan, N., Karni, O., Korner, M., Jun, T., Beckmann, J. S., Macciardi, F. & Lerer, B. (2005). Fine mapping of a schizophrenia susceptibility locus at chromosome 6q23: increased evidence for linkage and reduced linkage interval. *European Journal of Human Genetics* **13**, 763–771.

Levitt, P., Ebert, P., Mirnics, K., Nimgaonkar, V. L. & Lewis, D. A. (2006). Making the case for a candidate vulnerability gene in schizophrenia: Convergent evidence for regulator of G-protein signaling 4 (RGS4). *Biological Psychiatry* **60**, 534–537.

Lewis, A. & Redrup, L. (2005). Genetic imprinting: conflict at the Callipyge locus. *Current Biology* **15**, r291–r294.

Lewis, C. M., Levinson, D. F., Wise, L. H., DeLisi, L. E., Straub, R. E., Hovatta, I., Williams, N. M., Schwab, S. G., Pulver, A. E., Faraone, S. V., Brzustowicz, L. M., Kaufmann, C. A., Garver, D. L., Gurling, H. M. D., Lindholm, E., Coon, H., Moises, H. W., Byerley, W., Shaw, S. H., Mesen, A., Sherrington, R., O'Neill, F. A., Walsh, D., Kendler, K. S., Ekelund, J., Paunio, T., Lönnqvist, J., Peltonen, L., O'Donovan, M. C., Owen, M. J., Wildenauer, D. B., Maier, W., Nestadt, G., Blouin, J., Antonarakis, S. E., Mowry, B. J., Silverman, J. M., Crowe, R. R., Cloninger, C. R., Tsuang, M. T., Malaspina, D., Harkavy-Friedman, J. M., Svrakic, D. M., Bassett, A. S., Holcomb, J., Kalsi, G., McQuillin, A., Brynjolfson, J., Sigmundsson, T., Petursson, H., Jazin, E., Zoëga, T. & Helgason, T. (2003). Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia. *American Journal of Human Genetics* **73**, 34–48.

Lewis, S. J., Zammit, S., Gunnell, D. & Smith, G. D. (2005). A meta-analysis of the MTHFR C677T polymorphism and schizophrenia risk. *American Journal of Medical Genetics, B* **135**, 2–4.

Li, H., Yamagata, T., Mori, M. & Momoi, M. Y. (2005). Absence of causative mutations and presence of autism-related allele in FOXP2 in Japanese autistic patients. *Brain & Development* **27**, 207–210.

Li, H., Li, Y., Shao, J., Li, R., Qin, Y., Xie, C. & Zhao, Z. (2008). The association analysis of RELN and GRM8 genes with autistic spectrum disorder in Chinese Han population. *American Journal of Medical Genetics, B* **147**, 194–200.

Li, L., Keverne, E. B., Aparicio, S. A., Ishino, F., Barton, S. C. & Surani, M. A. (1999). Regulation of maternal behavior and offspring growth by paternally expressed Peg3. *Science* **284**, 330–333.

Li, T., Underhill, J., Liu, X. H., Sham, P. C., Donaldson, P., Murray, R. M., Wright, P. & Collier, D. A. (2001). Transmission disequilibrium analysis of HLA class II DRB1, DQA1, DQB1 and DPB1 polymorphisms in schizophrenia using family trios from a Han Chinese population. *Schizophrenia Research* **49**, 73–78.

Lin, P., McInnis, M. G., Potash, J. B., Willour, V. L., Mackinnon, D. F., Miao, K., Depaulo, J. R. & Zandi, P. P. (2005). Assessment of the effect of age at onset on linkage to bipolar disorder: evidence on chromosomes 18p and 21q. *American Journal of Human Genetics* **77**, 545–555.

Lindsay, R. S., Kobes, S., Knowler, W. C., Bennett, P. H. & Hanson, R. L. (2001). Genome-wide linkage analysis assessing parent-of-origin effects in the inheritance of type 2 diabetes and BMI in Pima Indians. *Diabetes* **50**, 2850–2857.

Lindsay, S., Splitt, M., Edney, S., Berney, T. P., Knight, S. J., Davies, K. E., O'Brien, O., Gale, M. & Burn, J. (1996). PPM-X: a new X-linked mental retardation syndrome with psychosis, pyramidal signs, and macroorchidism maps to Xq28. *American Journal of Human Genetics* **58**, 1120–1126.

Lindsell, C. E., Boulter, J., DiSibio, G., Gossler, A. & Weinmaster, G. (1996). Expression patterns of Jagged, Delta1, Notch1, Notch2, and Notch3 genes identify ligand-receptor pairs that may function in neural development. *Molecular and Cellular Neuroscience.* **8**, 14–27.

Ling, J. Q., Li, T., Hu, J. F., Vu, T. H., Chen, H. L., Qiu, X. W., Cherry, A. M. & Hoffman, A. R. (2006). CTCF mediates interchromosomal colocalization between Igf2/H19 and Wsb1/Nf1. *Science* **312**, 269–272.

Linglart, A., Gensure, R. C., Olney, R. C., Jüppner, H. & Bastepe, M. (2005). A novel STX16 deletion in autosomal dominant pseudohypoparathyroidism type Ib redefines the boundaries of a cis-acting imprinting control element of GNAS. *American Journal of Human Genetics* **76**, 804–814.

Lipska, B. K., Mitkus, S. N., Mathew, S. V., Fatula, R., Hyde, T. M., Weinberger, D. R. & Kleinman, J. E. (2006). Functional genomics in postmortem human brain: abnormalities in a DISC1 molecular pathway in schizophrenia. *Dialogues in Clinical Neuroscience* **8**, 353–357.

Liu, H., Heath, S. C., Sobin, C., Roos, J. L., Galke, B. L., Blundell, M. L., Lenane, M., Robertson, B., Wijsman, E. M., Rapoport, J. L., Gogos, J. A. & Karayiorgou, M. (2002). Genetic variation at the 22q11 PRODH2/DGCR6 locus presents an unusual pattern and increases susceptibility to schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America* **99**, 3717–3722.

Liu, J., Chen, M., Deng, C., Bourc'his, D., Nealon, J. G., Erlichman, B., Bestor, T. H. & Weinstein, L. S. (2005). Identification of the control region for tissue-specific imprinting of the stimulatory G protein alpha-subunit. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 5513–5518.

Liu, J., Nyholt, D. R., Magnussen, P., Parano, E., Pavone, P., Geschwind, D., Lord, C., Iversen, P., Hoh, J., Ott, J. & Gilliam, T. C. (2001). A genomewide screen for autism susceptibility loci. *American Journal of Human Genetics* **69**, 327–340.

Liu, J., Yu, S., Litman, D., Chen, W. & Weinstein, L. S. (2000). Identification of a methylation imprint mark within the mouse Gnas locus. *Molecular and Cellular Biology* **20**, 5808–5817.

Liu, W., Pappas, G. D. & Carter, C. S. (2005). Oxytocin receptors in brain cortical regions are reduced in haploinsufficient (+/−) reeler mice. *Neurological Research* **27**, 339–345.

Loat, C., Curran, S., Lewis, C., Abrahams, B., Duvall, J., Geschwind, D., Bolton, P. & Craig, I. (2008). Methyl - CpG - binding protein (MECP2) polymorphisms and vulnerability to autism. *Genes, Brain and Behavior.* (in press).

Lohoff, F. W., Sander, T., Ferraro, T. N., Dahl, J. P., Gallinat, J. & Berrettini, W. H. (2005). Confirmation of association between the Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene and bipolar I disorder. *American Journal of Medical Genetics, B* **139**, 51–53.

Luedi, P. P., Dietrich, F. S., Weidman, J. R., Bosko, J. M., Jirtle, R. L. & Hartemink, A. J. (2007). Computational and

experimental identification of novel human imprinted genes. *Genome Research* **17**, 1723–1730.

Luedi, P. P., Hartemink, A. J. & Jirtle, R. L. (2005). Genome-wide prediction of imprinted murine genes. *Genome Research* **15**, 875–884.

Lukusa, T. & Fryns, J. P. (2000). Pure distal monosomy 10q26 in a patient displaying clinical features of Prader-Willi syndrome during infancy and distinct behavioural phenotype in adolescence. *Genetic Counseling.* **11**, 119–126.

Lung, F., Tzeng, D. & Shu, B. (2002). Ethnic heterogeneity in allele variation in the DRD4 gene in schizophrenia. *Schizophrenia Research* **57**, 239–245.

MacDonald, H. R. & Wevrick, R. (1997). The necdin gene is deleted in Prader-Willi syndrome and is imprinted in human and mouse. *Human Molecular Genetics* **6**, 1873–1878.

Macgregor, S., Visscher, P. M., Knott, S. A., Thomson, P., Porteous, D. J., Millar, J. K., Devon, R. S., Blackwood, D. & Muir, W. J. (2004). A genome scan and follow-up study identify a bipolar disorder susceptibility locus on chromosome 1q42. *Molecular Psychiatry* **9**, 1083–1090.

Maegawa, S., Itaba, N., Otsuka, S., Kamitani, H., Watanabe, T., Tahimic, C. G. T., Nanba, E. & Oshimura, M. (2004). Coordinate downregulation of a novel imprinted transcript ITUP1 with PEG3 in glioma cell lines. *DNA Research* **11**, 37–49.

Makedonski, K., Abuhatzira, L., Kaufman, Y., Razin, A. & Shemer, R. (2005). MeCP2 deficiency in Rett syndrome causes epigenetic aberrations at the PWS/AS imprinting center that affects UBE3A expression. *Human Molecular Genetics* **14**, 1049–1058.

Malaspina, D. (2001). Paternal factors and schizophrenia risk: de novo mutations and imprinting. *Schizophrenia Bulletin* **27**, 379–393.

Malaspina, D., Reichenberg, A., Weiser, M., Fennig, S., Davidson, M., Harlap, S., Wolitzky, R., Rabinowitz, J., Susser, E. & Knobler, H. Y. (2005). Paternal age and intelligence: implications for age-related genomic changes in male germ cells. *Psychiatric Genetics* **15**, 117–125.

Mann, J. & Foreman, D. M. (1996). Homo-erotomania for a delusional parent: erotomania with Capgras and Fregoli syndromes in a young male with learning difficulties. *Journal of Intellectual Disability Research* **40**, 275–278.

Mansouri, M. R., Marklund, L., Gustavsson, P., Davey, E., Carlsson, B., Larsson, C., White, I., Gustavson, K. H. & Dahl, N. (2005). Loss of ZDHHC15 expression in a woman with a balanced translocation t(X;15)(q13.3;cen) and severe mental retardation. *European Journal of Human Genetics* **13**, 970–977.

Manzoni, M. F., Pramparo, T., Stroppolo, A., Chiaino, F., Bosi, E., Zuffardi, O. & Carrozzo, R. (2000). A patient with maternal chromosome 14 UPD presenting with a mild phenotype and MODY. *Clinical Genetics* **57**, 406–408.

Marneros, A. & Akiskal, H. S. (2006) eds. *The Overlap of Affective and Schizophrenic Spectra*. Cambridge University Press, New York.

Marui, T., Hashimoto, O., Nanba, E., Kato, C., Tochigi, M., Umekage, T., Ishijima, M., Kohda, K., Kato, N. & Sasaki, T. (2004). Association between the neurofibromatosis-1 (NF1) locus and autism in the Japanese population. *American Journal of Medical Genetics, B* **131**, 43–47.

Marui, T., Koishi, S., Funatogawa, I., Yamamoto, K., Matsumoto, H., Hashimoto, O., Nanba, E., Kato, C., Ishijima, M., Watanabe, K., Kasai, K., Kato, N. & Sasaki, T. (2005). No association of FOXP2 and PTPRZ1 on 7q31 with autism from the Japanese population. *Neuroscience Research* **53**, 91–94.

Mason, O., Startup, M., Halpin, S., Schall, U., Conrad, A. & Carr, V. (2004). Risk factors for transition to first episode psychosis among individuals with 'at-risk mental states'. *Schizophrenia Research* **71**, 227–237.

Mata, I., Gilvarry, C. M., Jones, P. B., Lewis, S. W., Murray, R. M. & Sham, P. C. (2003). Schizotypal personality traits in nonpsychotic relatives are associated with positive symptoms in psychotic probands. *Schizophrenia Bulletin* **29**, 273–283.

Matsuoka, T., Sumiyoshi, T., Tanaka, K., Tsunoda, M., Uehara, T., Itoh, H. & Kurachi, M. (2005). NC-1900, an arginine-vasopressin analogue, ameliorates social behavior deficits and hyperlocomotion in MK-801-treated rats: therapeutic implications for schizophrenia. *Brain Research* **1053**, 131–136.

Maynard, N. D., Chen, J., Stuart, R. K., Fan, J. B. & Ren, B. (2008). Genome-wide mapping of allele-specific protein-DNA interactions in human cells. *Nature Methods* **5**, 307–309.

Maziade, M., Roy, M., Chagnon, Y. C., Cliche, D., Fournier, J., Montgrain, N., Dion, C., Lavallée, J., Garneau, Y., Gingras, N., Nicole, L., Pirès, A., Ponton, A., Potvin, A., Wallot, H. & Mérette, C. (2005). Shared and specific susceptibility loci for schizophrenia and bipolar disorder: a dense genome scan in Eastern Quebec families. *Molecular Psychiatry* **10**, 486–499.

Mbarek, O., Marouillat, S., Martineau, J., Barthélémy, C., Müh, J. P. & Andres, C. (1999). Association study of the NF1 gene and autistic disorder. *American Journal of Medical Genetics* **88**, 729–732.

McAvoy, S., Ganapathiraju, S. C., Ducharme-Smith, A. L., Pritchett, J. R., Kosari, F., Perez, D. S., Zhu, Y., James, C. D. & Smith, D. I. (2007). Non-random inactivation of large common fragile site genes in different cancers. *Cytogenetic and Genome Research* **118**, 260–269.

McDermott, M., Molloy, M., Cashin, P., McMahon, M., Spencer, S., Jennings, S., Sneyd, A., Greally, J., Silman, A. & Ollier, W. (1986). A multicase family study of rheumatoid arthritis in south west Ireland. *Disease Markers* **4**, 103–111.

McGuffin, P., Knight, J., Breen, G., Brewster, S., Boyd, P. R., Craddock, N., Gill, M., Korszun, A., Maier, W., Middleton, L., Mors, O., Owen, M. J., Perry, J., Preisig, M., Reich, T., Rice, J., Rietschel, M., Jones, L., Sham, P. & Farmer, A. E. (2005). Whole genome linkage scan of recurrent depressive disorder from the depression network study. *Human Molecular Genetics* **14**, 3337–3345.

McInnes, L. A., Escamilla, M. A., Service, S. K., Reus, V. I., Leon, P., Silva, S., Rojas, E., Spesny, M., Baharloo, S., Blankenship, K., Peterson, A., Tyler, D., Shimayoshi, N., Tobey, C., Batki, S., Vinogradov, S., Meza, L., Gallegos, A., Fournier, E., Smith, L. B., Barondes, S. H., Sandkuijl, L. A. & Freimer, N. B. (1996). A complete genome screen for genes predisposing to severe bipolar disorder in two Costa Rican pedigrees. *Proceedings of the National Academy of Sciences of the United States of America* **93**, 13060–13065.

McInnis, M. G., Dick, D. M., Willour, V. L., Avramopoulos, D., MacKinnon, D. F., Simpson, S. G., Potash, J. B., Edenberg, H. J., Bowman, E. S., McMahon, F. J., Smiley, C., Chellis, J. L., Huo, Y., Diggs, T., Meyer, E. T., Miller, M., Matteini, A. T., Rau, N. L., DePaulo, J. R., Gershon, E. S., Badner, J. A., Rice, J. P., Goate, A. M., Detera-Wadleigh, S. D., Nurnberger, J. I., Reich, T., Zandi, P. P. & Foroud, T. M. (2003*a*). Genome-wide scan and conditional analysis in bipolar disorder: evidence for genomic interaction in the National Institute of Mental Health genetics initiative bipolar pedigrees. *Biological Psychiatry* **54**, 1265–1273.

McInnis, M. G., Lan, T., Willour, V. L., McMahon, F. J., Simpson, S. G., Addington, A. M., MacKinnon, D. F., Potash,

J. B., Mahoney, A. T., Chellis, J., Huo, Y., Swift-Scanlan, T., Chen, H., Koskela, R., Stine, O. C., Jamison, K. R., Holmans, P., Folstein, S. E., Ranade, K., Friddle, C., Botstein, D., Marr, T., Beaty, T. H., Zandi, P. & DePaulo, J. R. (2003*b*). Genome-wide scan of bipolar disorder in 65 pedigrees: supportive evidence for linkage at 8q24, 18q22, 4q32, 2p12, and 13q12. *Molecular Psychiatry* **8**, 288–298.

McMahon, F. J., Simpson, S. G., McInnis, M. G., Badner, J. A., MacKinnon, D. F. & DePaulo, J. R. (2001). Linkage of bipolar disorder to chromosome 18q and the validity of bipolar II disorder. *Archives of General Psychiatry* **58**, 1025–1031.

McMinn, J., Wei, M., Schupf, N., Cusmai, J., Johnson, E. B., Smith, A. C., Weksberg, R., Thaker, H. M. & Tycko, B. (2006). Unbalanced placental expression of imprinted genes in human intrauterine growth restriction. *Placenta* **27**, 540–549.

McQueen, M. B., Devlin, B., Faraone, S. V., Nimgaonkar, V. L., Sklar, P., Smoller, J. W., Abou Jamra, R., Albus, M., Bacanu, S. A., Baron, M., Barrett, T. B., Berrettini, W., Blacker, D., Byerley, W., Cichon, S., Coryell, W., Craddock, N., Daly, M. J., Depaulo, J. R., Edenberg, H. J., Foroud, T., Gill, M., Gilliam, T. C., Hamshere, M., Jones, I., Jones, L., Juo, S. H., Kelsoe, J. R., Lambert, D., Lange, C., Lerer, B., Liu, J., Maier, W., Mackinnon, J. D., McInnis, M. G., McMahon, F. J., Murphy, D. L., Nothen, M. M., Nurnberger, J. I., Pato, C. N., Pato, M. T., Potash, J. B., Propping, P., Pulver, A. E., Rice, J. P., Rietschel, M., Scheftner, W., Schumacher, J., Segurado, R., Van Steen, K., Xie, W., Zandi, P. P. & Laird, N. M. (2005). Combined analysis from eleven linkage studies of bipolar disorder provides strong evidence of susceptibility loci on chromosomes 6q and 8q. *American Journal of Human Genetics* **77**, 582–595.

Meador-Woodruff, J. H., Davis, K. L. & Haroutunian, V. (2001). Abnormal kainate receptor expression in prefrontal cortex in schizophrenia. *Neuropsychopharmacology* **24**, 545–552.

Medina, M., Marinescu, R. C., Overhauser, J. & Kosik, K. S. (2000). Hemizygosity of delta-catenin (CTNND2) is associated with severe mental retardation in Cri-du-Chat syndrome. *Genomics* **63**, 157–164.

Meyer, G., Cabrera Socorro, A., Perez Garcia, C. G., Martinez Millan, L., Walker, N. & Caput, D. (2004). Developmental roles of p73 in Cajal-Retzius cells and cortical patterning. *Journal of Neuroscience* **24**, 9878–9887.

Meyer, G., Perez-Garcia, C. G., Abraham, H. & Caput, D. (2002). Expression of p73 and Reelin in the developing human cortex. *Journal of Neuroscience* **22**, 4973–4986.

Michaud, J. L., Boucher, F., Melnyk, A., Gauthier, F., Goshu, E., Lévy, E., Mitchell, G. A., Himms-Hagen, J. & Fan, C. M. (2001). Sim1 haploinsufficiency causes hyperphagia, obesity and reduction of the paraventricular nucleus of the hypothalamus. *Human Molecular Genetics* **10**, 1465–1473.

Middeldorp, C. M., Hottenga, J. J., Slagboom, P. E., Sullivan, P. F., De Geus, E. J., Posthuma, D., Willemsen, G. & Boomsma, D. I. (2008). Linkage on chromosome 14 in a genome-wide linkage study of a broad anxiety phenotype. *Molecular Psychiatry* **13**, 84–89.

Middleton, F. A., Pato, M. T., Gentile, K. L., Morley, C. P., Zhao, X., Eisener, A. F., Brown, A., Petryshen, T. L., Kirby, A. N., Medeiros, H., Carvalho, C., Macedo, A., Dourado, A., Coelho, I., Valente, J., Soares, M. J., Ferreira, C. P., Lei, M., Azevedo, M. H., Kennedy, J. L., Daly, M. J., Sklar, P. & Pato, C. N. (2004). Genomewide linkage analysis of bipolar disorder by use of a high-density single-nucleotide-polymorphism (SNP) genotyping assay: a comparison with microsatellite marker assays and finding of significant linkage to chromosome 6q22. *American Journal of Human Genetics* **74**, 886–897.

Minoretti, P., Politi, P., Coen, E., Di Vito, C., Bertona, M., Bianchi, M. & Emanuele, E. (2006). The T393C polymorphism of the GNAS1 gene is associated with deficit schizophrenia in an Italian population sample. *Neuroscience Letters* **397**, 159–163.

Miyashita, A., Arai, H., Asada, T., Imagawa, M., Matsubara, E., Shoji, M., Higuchi, S., Urakami, K., Kakita, A., Takahashi, H., Toyabe, S., Akazawa, K., Kanazawa, I., Ihara, Y. & Kuwano, R.; Japanese Genetic Study Consortium for Alzheimer's Disease. (2007). Genetic association of CTNNA3 with late-onset Alzheimer's disease in females. *Human Molecular Genetics* **16**, 2854–2869.

Miyazaki, K., Narita, N. & Narita, M. (2005). Maternal administration of thalidomide or valproic acid causes abnormal serotonergic neurons in the offspring: implication for pathogenesis of autism. *International Journal of Developmental Neuroscience* **23**, 287–297.

Mizukami, K., Koizumi, J., Shiraishi, H. & Nagase, S. (1989). A clinical case of Klinefelter's syndrome with various psychiatric symptoms. *Japanese Journal of Psychiatry and Neurology* **43**, 639–644.

Mo, Z. & Zecevic, N. (2007). Is Pax6 critical for neurogenesis in the human fetal brain? *Cerebral Cortex* **18**, 1455–1465.

Moberg, P. J., Arnold, S. E., Doty, R. L., Gur, R. E., Balderston, C. C., Roalf, D. R., Gur, R. C., Kohler, C. G., Kanes, S. J., Siegel, S. J. & Turetsky, B. I. (2006). Olfactory functioning in schizophrenia: relationship to clinical, neuropsychological, and volumetric MRI measures. *Journal of Clinical and Experimental Neuropsychology* **28**, 1444–1461.

Moises, H. W., Yang, L., Kristbjarnarson, H., Wiese, C., Byerley, W., Macciardi, F., Arolt, V., Blackwood, D., Liu, X. & Sjögren, B. (1995). An international two-stage genome-wide search for schizophrenia susceptibility genes. *Nature Genetics* **11**, 321–324.

Molloy, C. A., Morrow, A. L., Meinzen-Derr, J., Schleifer, K., Dienger, K., Manning-Courtney, P., Altaye, M. & Wills-Karp, M. (2006). Elevated cytokine levels in children with autism spectrum disorder. *Journal of Neuroimmunology* **172**, 198–205.

Moon, H. J., Yim, S., Lee, W. K., Jeon, Y., Kim, Y. H., Ko, Y. J., Lee, K., Lee, K., Han, S. & Rha, H. K. (2006). Identification of DNA copy-number aberrations by array-comparative genomic hybridization in patients with schizophrenia. *Biochemical and Biophysical Research Communications* **344**, 531–539.

Moore, T. R. (1997). Fetal growth in diabetic pregnancy. *Clinical Obstetrics and Gynecology* **40**, 771–786.

Morison, I. M., Ramsay, J. P. & Spencer, H. G. (2005). A census of mammalian imprinting. *Trends in Genetics* **21**, 457–465.

Mors, O., Mortensen, P. B. & Ewald, H. (2001). No evidence of increased risk for schizophrenia or bipolar affective disorder in persons with aneuploidies of the sex chromosomes. *Psychological Medicine* **31**, 425–430.

Mraz, K. D., Green, J., Dumont-Mathieu, T., Makin, S. & Fein, D. (2007). Correlates of head circumference growth in infants later diagnosed with autism spectrum disorders. *Journal of Child Neurology* **22**, 700–713.

Muglia, P., Petronis, A., Mundo, E., Lander, S., Cate, T. & Kennedy, J. L. (2002). Dopamine D4 receptor and tyrosine hydroxylase genes in bipolar disorder: evidence for a role of DRD4. *Molecular Psychiatry* **7**, 860–866.

Muglia, P., Vicente, A. M., Verga, M., King, N., Macciardi, F. & Kennedy, J. L. (2003). Association between the BDNF gene and schizophrenia. *Molecular Psychiatry* **8**, 146–147.

Mukherjee, O., Meera, P., Ghosh, S., Kubendran, S., Kiran, K., Manjunath, K. R., Subhash, M. N., Benegal, V., Brahmachari, S. K., Majumder, P. P. & Jain, S. (2006). Evidence of linkage and association on 18p11.2 for psychosis. *American Journal of Medical Genetics, B* **141**, 868–873.

Mulle, J. G., Fallin, M. D., Lasseter, V. K., McGrath, J. A., Wolyniec, P. S. & Pulver, A. E. (2007). Dense SNP association study for bipolar I disorder on chromosome 18p11 suggests two loci with excess paternal transmission. *Molecular Psychiatry* **12**, 367–375.

Muntjewerff, J. W., Hoogendoorn, M. L., Kahn, R. S., Sinke, R. J., Den Heijer, M., Kluijtmans, L. A. & Blom, H. J. (2005). Hyperhomocysteinemia, methylenetetrahydrofolate reductase 677TT genotype, and the risk for schizophrenia: a Dutch population based case-control study. *American Journal of Medical Genetics, B* **135**, 69–72.

Murrell, A., Heeson, S., Cooper, W. N., Douglas, E., Apostolidou, S., Moore, G. E., Maher, E. R. & Reik, W. (2004). An association between variants in the IGF2 gene and Beckwith-Wiedemann syndrome: interaction between genotype and epigenotype. *Human Molecular Genetics* **13**, 247–255.

Muscatelli, F., Abrous, D. N., Massacrier, A., Boccaccio, I., Le Moal, M., Cau, P. & Cremer, H. (2000). Disruption of the mouse Necdin gene results in hypothalamic and behavioral alterations reminiscent of the human Prader-Willi syndrome. *Human Molecular Genetics* **9**, 3101–3110.

Mustanski, B. S., Dupree, M. G., Nievergelt, C. M., Bocklandt, S., Schork, N. J. & Hamer, D. H. (2005). A genomewide scan of male sexual orientation. *Human Genetics* **116**, 272–278.

Naeye, R. L. (1981). Maternal blood pressure and fetal growth. *American Journal of Obstetrics & Gynecology* **141**, 780–787.

Nagarajan, R. P., Hogart, A. R., Gwye, Y., Martin, M. R. & LaSalle, J. M. (2006). Reduced MeCP2 expression is frequent in autism frontal cortex and correlates with aberrant MECP2 promoter methylation. *Epigenetics* **1**, e1–e11.

Narr, K. L., Bilder, R. M., Luders, E., Thompson, P. M., Woods, R. P., Robinson, D., Szeszko, P. R., Dimtcheva, T., Gurbani, M. & Toga, A. W. (2007). Asymmetries of cortical shape: Effects of handedness, sex and schizophrenia. *NeuroImage* **34**, 939–948.

Naumova, A. K., Greenwood, C. M. & Morgan, K. (2001). Imprinting and deviation from Mendelian transmission ratios. *Genome* **44**, 311–320.

Naus, S., Richter, M., Wildeboer, D., Moss, M., Schachner, M. & Bartsch, J. W. (2004). Ectodomain shedding of the neural recognition molecule CHL1 by the metalloprotease-disintegrin ADAM8 promotes neurite outgrowth and suppresses neuronal cell death. *Journal of Biological Chemistry.* **279**, 16083–16090.

Neul, J. L. & Zoghbi, H. Y. (2004). Rett syndrome: a prototypical neurodevelopmental disorder. *Neuroscientist* **10**, 118–128.

Neves-Pereira, M., Cheung, J. K., Pasdar, A., Zhang, F., Breen, G., Yates, P., Sinclair, M., Crombie, C., Walker, N. & St Clair, D. M. (2005). BDNF gene is a risk factor for schizophrenia in a Scottish population. *Molecular Psychiatry* **10**, 208–212.

Newbury, D. F., Bonora, E., Lamb, J. A., Fisher, S. E., Lai, C. S. L., Baird, G., Jannoun, L., Slonims, V., Stott, C. M., Merricks, M. J., Bolton, P. F., Bailey, A. J. & Monaco, A. P. (2002). FOXP2 is not a major susceptibility gene for autism or specific language impairment. *American Journal of Human Genetics* **70**, 1318–1327.

Newman, T. M., Macomber, D., Naples, A. J., Babitz, T., Volkmar, F., Grigorenko, E. L. (2007). Hyperlexia in children with autism spectrum disorders. *Journal of Autism and Developmental Disorders* **37**, 760–774.

Newton, J. L., Harney, S. M., Timms, A. E., Sims, A. M., Rockett, K., Darke, C., Wordsworth, B. P., Kwiatkowski, D. & Brown, M. A. (2004). Dissection of class III major histocompatibility complex haplotypes associated with rheumatoid arthritis. *Arthritis and Rheumatism* **50**, 2122–2129.

Ni, X., Trakalo, J., Valente, J., Azevedo, M. H., Pato, M. T., Pato, C. N. & Kennedy, J. L. (2005). Human p53 tumor suppressor gene (TP53) and schizophrenia: case-control and family studies. *Neuroscience Letters* **388**, 173–178.

Nicholls, R. D. (2000). The impact of genomic imprinting for neurobehavioral and developmental disorders. *Journal of Clinical Investigation* **105**, 413–418.

Nicholls, R. D. & Knepper, J. L. (2001). Genome organization, function, and imprinting in Prader-Willi and Angelman syndromes. *Annual Review of Genomics and Human Genetics* **2**, 153–175.

Niehaus, D. J., Koen, L., Laurent, C., Muller, J., Deleuze, J. F., Mallet, J., Seller, C., Jordaan, E. & Emsley, R. (2005). Positive and negative symptoms in affected sib pairs with schizophrenia: implications for genetic studies in an African Xhosa sample. *Schizophrenia Research* **79**, 239–249.

Nikaido, I., Saito, C., Wakamoto, A., Tomaru, Y., Arakawa, T., Hayashizaki, Y. & Okazaki, Y. (2004). EICO (Expression-based Imprint Candidate Organizer): finding disease-related imprinted genes. *Nucleic Acids Research* **32**, d548–d551.

Nishimura, K., Nakamura, K., Anitha, A., Yamada, K., Tsujii, M., Iwayama, Y., Hattori, E., Toyota, T., Takei, N., Miyachi, T., Iwata, Y., Suzuki, K., Matsuzaki, H., Kawai, M., Sekine, Y., Tsuchiya, K., Sugihara, G., Suda, S., Ouchi, Y., Sugiyama, T., Yoshikawa, T. & Mori, N. (2007). Genetic analyses of the brain-derived neurotrophic factor (BDNF) gene in autism. *Biochemichal and Biophysical Research Communications* **356**, 200–206.

Noh, J. S., Sharma, R. P., Veldic, M., Salvacion, A. A., Jia, X., Chen, Y., Costa, E., Guidotti, A. & Grayson, D. R. (2005). DNA methyltransferase 1 regulates reelin mRNA expression in mouse primary cortical cultures. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 1749–1754.

Nomura, T., Kimura, M., Horii, T., Morita, S., Soejima, H., Kudo, S. & Hatada, I. (2008). MeCP2-dependent repression of an imprinted miR-184 released by depolarization. *Human Molecular Genetics* **17**, 1192–1199.

Norton, N., Williams, H. J. & Owen, M. J. (2006). An update on the genetics of schizophrenia. *Current Opinion in Psychiatry* **19**, 158–164.

Nöthen, M. M., Cichon, S., Rohleder, H., Hemmer, S., Franzek, E., Fritze, J., Albus, M., Borrmann-Hassenbach, M., Kreiner, R., Weigelt, B., Minges, J., Lichtermann, D., Maier, W., Craddock, N., Fimmers, R., Höller, T., Baur, M. P., Rietschel, M. & Propping, P. (1999). Evaluation of linkage of bipolar affective disorder to chromosome 18 in a sample of 57 German families. *Molecular Psychiatry* **4**, 76–84.

Nowicki, S. T., Tassone, F., Ono, M. Y., Ferranti, J., Croquette, M. F., Goodlin-Jones, B. & Hagerman, R. J. (2007). The Prader-Willi phenotype of Fragile X syndrome. *Journal of Developmental and Behavioral Pediatrics.* **28**, 133–138.

Nurmi, E. L., Amin, T., Olson, L. M., Jacobs, M. M., McCauley, J. L., Lam, A. Y., Organ, E. L., Folstein, S. E., Haines, J. L. & Sutcliffe, J. S. (2003). Dense linkage disequilibrium mapping in the 15q11-q13 maternal expression domain yields evidence for association in autism. *Molecular Psychiatry* **8**, 624–634.

O'Brien, E. K., Zhang, X., Nishimura, C., Tomblin, J. B. & Murray, J. C. (2003). Association of specific language impairment (SLI) to the region of 7q31. *American Journal of Human Genetics* **72**, 1536–1543.

Ogden, C. A., Rich, M. E., Schork, N. J., Paulus, M. P., Geyer, M. A., Lohr, J. B., Kuczenski, R. & Niculescu, A. B. (2004). Candidate genes, pathways and mechanisms for bipolar (manic-depressive) and related disorders: an expanded convergent functional genomics approach. *Molecular Psychiatry* **9**, 1007–1029.

Ogdie, M. N., Macphie, I. L., Minassian, S. L., Yang, M., Fisher, S. E., Francks, C., Cantor, R. M., McCracken, J. T., McGough, J. J., Nelson, S. F., Monaco, A. P. & Smalley, S. L. (2003). A genomewide scan for attention-deficit/hyperactivity disorder in an extended sample: suggestive linkage on 17p11. *American Journal of Human Genetics* **72**, 1268–1279.

Okada, T., Hashimoto, R., Numakawa, T., Iijima, Y., Kosuga, A., Tatsumi, M., Kamijima, K., Kato, T. & Kunugi, H. (2006). A complex polymorphic region in the brain-derived neurotrophic factor (BDNF) gene confers susceptibility to bipolar disorder and affects transcriptional activity. *Molecular Psychiatry* **11**, 695–703.

Okita, C., Meguro, M., Hoshiya, H., Haruta, M., Sakamoto, Y. & Oshimura, M. (2003). A new imprinted cluster on the human chromosome 7q21-q31, identified by human-mouse monochromosomal hybrids. *Genomics* **81**, 556–559.

Ollier, W., Silman, A., Gosnell, N., Currey, H., Awad, J., Doyle, P., McCloskey, D., Alonso, A., Hossain, M. A. & Festenstein, H. (1986). Hla and rheumatoid arthritis: an analysis of multicase families. *Disease Markers* **4**, 85–98.

Ottoni, G., Lucchese, I., Martins, F., Grillo, R., Bogo, M. & Lara, D. (2005). Association between 2592C > T ins polymorphism of adenosine A2A receptor gene and schizophrenia. *Schizophrenia Bulletin* **31**, 274–274.

Oudejans, C. B., Mulders, J., Lachmeijer, A. M., Van Dijk, M., Könst, A. A., Westerman, B. A., Van Wijk, I. J., Leegwater, P. A., Kato, H. D., Matsuda, T., Wake, N., Dekker, G. A., Pals, G., Ten Kate, L. P. & Blankenstein, M. A. (2004). The parent-of-origin effect of 10q22 in pre-eclamptic females coincides with two regions clustered for genes with down-regulated expression in androgenetic placentas. *Molecular Human Reproduction* **10**, 589–598.

Oyebode, F. & Sargeant, R. (1996). Delusional misidentification syndromes: a descriptive study. *Psychopathology* **29**, 209–214.

Pae, C. U., Serretti, A., Mandelli, L., Yu, H. S., Patkar, A. A., Lee, C. U., Lee, S. J., Jun, T. Y., Lee, C., Paik, I. H. & Kim, J. J. (2006). Effect of 5-haplotype of dysbindin gene (DTNBP1) polymorphisms for the susceptibility to bipolar I disorder. *American Journal of Medical Genetics, B* **144**, 701–703.

Palmer, A. A., Breen, L. L., Flodman, P., Conti, L. H., Spence, M. A. & Printz, M. P. (2003). Identification of quantitative trait loci for prepulse inhibition in rats. *Psychopharmacology* **165**, 270–279.

Palomino, A., Vallejo-Illarramendi, A., González-Pinto, A., Aldama, A., González-Gómez, C., Mosquera, F., González-García, G. & Matute, C. (2006). Decreased levels of plasma BDNF in first-episode schizophrenia and bipolar disorder patients. *Schizophrenia Research* **86**, 321–322.

Park, N., Juo, S. H., Cheng, R., Liu, J., Loth, J. E., Lilliston, B., Nee, J., Grunn, A., Kanyas, K., Lerer, B., Endicott, J., Gilliam, T. C. & Baron, M. (2004). Linkage analysis of psychosis in bipolar pedigrees suggests novel putative loci for bipolar disorder and shared susceptibility with schizophrenia. *Molecular Psychiatry* **9**, 1091–1099.

Pato, C. N., Pato, M. T., Kirby, A., Petryshen, T. L., Medeiros, H., Carvalho, C., Macedo, A., Dourado, A., Coelho, I., Valente, J., Soares, M. J., Ferreira, C. P., Lei, M., Verner, A., Hudson, T. J., Morley, C. P., Kennedy, J. L., Azevedo, M. H., Daly, M. J. & Sklar, P. (2004). Genome-wide scan in Portuguese Island families implicates multiple loci in bipolar disorder: fine mapping adds support on chromosomes 6 and 11. *American Journal of Medical Genetics, B* **127**, 30–34.

Patwardhan, A. J., Brown, W. E., Bender, B. G., Linden, M. G., Eliez, S. & Reiss, A. L. (2002). Reduced size of the amygdala in individuals with 47,XXY and 47,XXX karyotypes. *American Journal of Medical Genetics* **114**, 93–98.

Paunio, T., Tuulio-Henriksson, A., Hiekkalinna, T., Perola, M., Varilo, T., Partonen, T., Cannon, T. D., Lönnqvist, J. & Peltonen, L. (2004). Search for cognitive trait components of schizophrenia reveals a locus for verbal learning and memory on 4q and for visual working memory on 2q. *Human Molecular Genetics* **13**, 1693–1702.

Peet, M. (2004). Nutrition and schizophrenia: beyond omega-3 fatty acids. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* **70**, 417–422.

Peralta, V. & Cuesta, M. J. (2005). The underlying structure of diagnostic systems of schizophrenia: a comprehensive poly-diagnostic approach. *Schizophrenia Research* **79**, 217–229.

Persico, A. M., D'Agruma, L., Maiorano, N., Totaro, A., Militerni, R., Bravaccio, C., Wassink, T. H., Schneider, C., Melmed, R., Trillo, S., Montecchi, F., Palermo, M., Pascucci, T., Puglisi-Allegra, S., Reichelt, K. L., Conciatori, M., Marino, R., Quattrocchi, C. C., Baldi, A., Zelante, L., Gasparini, P. & Keller, F. (2001). Reelin gene alleles and haplotypes as a factor predisposing to autistic disorder. *Molecular Psychiatry* **6**, 150–159.

Pescucci, C., Meloni, I. & Renieri, A. (2005). Is Rett syndrome a loss-of-imprinting disorder? *Nature Genetics* **37**, 10–11.

Peters, J., Holmes, R., Monk, D., Beechey, C. V., Moore, G. E. & Williamson, C. M. (2006). Imprinting control within the compact Gnas locus. *Cytogenetic and Genome Research* **113**, 194–201.

Peters, S. U., Beaudet, A. L., Madduri, N. & Bacino, C. A. (2004). Autism in Angelman syndrome: implications for autism research. *Clinical Genetics* **66**, 530–536.

Petronis, A., Popendikyte, V., Kan, P. & Sasaki, T. (2002). Major psychosis and chromosome 22: genetics meets epigenetics. *CNS Spectrums* **7**, 209–214.

Petry, C. J., Ong, K. K. & Dunger, D. B. (2007). Does the fetal genotype affect maternal physiology during pregnancy? *Trends in Molecular Medicine* **13**, 414–421.

Philippe, A., Martinez, M., Guilloud-Bataille, M., Gillberg, C., Råstam, M., Sponheim, E., Coleman, M., Zappella, M., Aschauer, H., Van Maldergem, L., Penet, C., Feingold, J., Brice, A. & Leboyer, M. (1999). Genome-wide scan for autism susceptibility genes. Paris Autism Research International Sibpair Study. *Human Molecular Genetics* **8**, 805–812.

Pickard, B., Dean, W., Engemann, S., Bergmann, K., Fuermann, M., Jung, M., Reis, A., Allen, N., Reik, W. & Walter, J. (2001). Epigenetic targeting in the mouse zygote marks DNA for later methylation: a mechanism for maternal effects in development. *Mechanisms of Development* **103**, 35–47.

Pickard, B. S., Malloy, M. P., Christoforou, A., Thomson, P. A., Evans, K. L., Morris, S. W., Hampson, M., Porteous, D. J., Blackwood, D. H. R. & Muir, W. J. (2006). Cytogenetic and genetic evidence supports a role for the kainate-type glutamate receptor gene, GRIK4, in schizophrenia and bipolar disorder. *Molecular Psychiatry* **11**, 847–857.

Picker, J. D. & Coyle, J. T. (2005). Do maternal folate and homocysteine levels play a role in neurodevelopmental processes

that increase risk for schizophrenia? *Harvard Review of Psychiatry* **13**, 197–205.

Pinabel, F., Gorwood, P. & Ades, J. (1997). The impact of oestradiol on ages at onset in schizophrenia reevaluated through Klinefelter syndrome. *Schizophrenia Research* **23**, 269–270.

Piras, G., El Kharroubi, A., Kozlov, S., Escalante-Alcalde, D., Hernandez, L., Copeland, N. G., Gilbert, D. J., Jenkins, N. A. & Stewart, C. L. (2000). Zac1 (Lot1), a potential tumor suppressor gene, and the gene for epsilon-sarcoglycan are maternally imprinted genes: identification by a subtractive screen of novel uniparental fibroblast lines. *Molecular and Cellular Biology* **20**, 3308–3315.

Pirker, S., Schwarzer, C., Wieselthaler, A., Sieghart, W. & Sperk, G. (2000). GABA(A) receptors: immunocytochemical distribution of 13 subunits in the adult rat brain. *Neuroscience* **101**, 815–850.

Plagge, A., Gordon, E., Dean, W., Boiani, R., Cinti, S., Peters, J. & Kelsey, G. (2004). The imprinted signaling protein XL alpha s is required for postnatal adaptation to feeding. *Nature Genetics* **36**, 818–826.

Plagge, A., Isles, A. R., Gordon, E., Humby, T., Dean, W., Gritsch, S., Fischer-Colbrie, R., Wilkinson, L. S. & Kelsey, G. (2005). Imprinted Nesp55 influences behavioral reactivity to novel environments. *Molecular and Cellular Biology* **25**, 3019–3026.

Plante, I., Davidovic, L., Ouellet, D. L., Gobeil, L. A., Tremblay, S., Khandjian, E. W. & Provost, P. (2006). Dicer-derived microRNAs are utilized by the Fragile X mental retardation protein for assembly on target RNAs. *Journal of Biomedicine and Biotechnology* **2006**, 64347.

Pooley, E. C., Fairburn, C. G., Cooper, Z., Sodhi, M. S., Cowen, P. J. & Harrison, P. J. (2004). A 5-HT2C receptor promoter polymorphism (HTR2C - 759C/T) is associated with obesity in women, and with resistance to weight loss in heterozygotes. *American Journal of Medical Genetics, B* **126**, 124–127.

Porter, R. H., Eastwood, S. L. & Harrison, P. J. (1997). Distribution of kainate receptor subunit mRNAs in human hippocampus, neocortex and cerebellum, and bilateral reduction of hippocampal GluR6 and KA2 transcripts in schizophrenia. *Brain Research* **751**, 217–231.

Potocki, L., Bi, W., Treadwell-Deering, D., Carvalho, C. M., Eifert, A., Friedman, E. M., Glaze, D., Krull, K., Lee, J. A., Lewis, R. A., Mendoza-Londono, R., Robbins-Furman, P., Shaw, C., Shi, X., Weissenberger, G., Withers, M., Yatsenko, S. A., Zackai, E. H., Stankiewicz, P. & Lupski, J. R. (2007). Characterization of Potocki-Lupski syndrome (dup(17)(p11.2p11.2)) and delineation of a dosage-sensitive critical interval that can convey an autism phenotype. *American Journal of Human Genetics* **80**, 633–649.

Preskorn, S. H. & Reveley, A. (1978). Pseudohypoparathyroidism and Capgras syndrome. *British Journal of Psychiatry* **133**, 34–37.

Prior, T. I., Chue, P. S. & Tibbo, P. (2000). Investigation of Turner syndrome in schizophrenia. *American Journal of Medical Genetics* **96**, 373–378.

Qian, L., Zhao, J., Shi, Y., Zhao, X., Feng, G., Xu, F., Zhu, S. & He, L. (2007). Brain-derived neurotrophic factor and risk of schizophrenia: an association study and meta-analysis. *Biochemical and Biophysical Research Communications* **353**, 738–743.

Ramadan, S., Terrinoni, A., Catani, M. V., Sayan, A. E., Knight, R. A., Mueller, M., Krammer, P. H., Melino, G. & Candi, E. (2005). p73 induces apoptosis by different mechanisms. *Biochemical and Biophysical Research Communications* **331**, 713–717.

Rampersaud, E., Morris, R. W., Weinberg, C. R., Speer, M. C. & Martin, E. R. (2007). Power calculations for likelihood ratio tests for offspring genotype risks, maternal effects, and parent-of-origin (POO) effects in the presence of missing parental genotypes when unaffected siblings are available. *Genetic Epidemiology* **31**, 18–30.

Rapoport, J. L., Addington, A. M., Frangou, S. & Psych, M. R. (2005). The neurodevelopmental model of schizophrenia: update 2005. *Molecular Psychiatry* **10**, 434–449.

Ravyn, V. & Bostwick, J. R. (2006). Functional coupling of the Gaolf variant XLGaolf with the human adenosine A2A receptor. *Journal of Receptor and Signal Transduction Research* **26**, 241–258.

Raymond, C. K., Kas, A., Paddock, M., Qiu, R., Zhou, Y., Subramanian, S., Chang, J., Palmieri, A., Haugen, E., Kaul, R. & Olson, M. V. (2005). Ancient haplotypes of the HLA class II region. *Genome Research* **15**, 1250–1257.

Redcay, E. & Courchesne, E. (2005). When is the brain enlarged in autism? A meta-analysis of all brain size reports. *Biological Psychiatry* **58**, 1–9.

Reichenberg, A., Gross, R., Weiser, M., Bresnahan, M., Silverman, J., Harlap, S., Rabinowitz, J., Shulman, C., Malaspina, D., Lubin, G., Knobler, H. Y., Davidson, M. & Susser, E. (2006). Advancing paternal age and autism. *Archives of General Psychiatry* **63**, 1026–1032.

Reik, W., Maher, E. R., Morrison, P. J., Harding, A. E. & Simpson, S. A. (1993). Age at onset in Huntington's disease and methylation at D4S95. *Journal of Medical Genetics* **30**, 185–188.

Reik, W. & Walter, J. (2001). Genomic imprinting: parental influence on the genome. *Nature Reviews Genetics* **2**, 21–32.

Riedel, H. (2004). Grb10 exceeding the boundaries of a common signaling adapter. *Frontiers in Bioscience* **9**, 603–618.

Riedel, M., Spellmann, I., Schwarz, M. J., Strassnig, M., Sikorski, C., Moller, H. J. & Muller, N. (2007). Decreased T cellular immune response in schizophrenic patients. *Journal of Psychiatric Research* **41**, 3–7.

Riley, B. & Kendler, K. S. (2006). Molecular genetic studies of schizophrenia. *European Journal of Human Genetics* **14**, 669–680.

Rinehart, N. J., Bradshaw, J. L., Brereton, A. V. & Tonge, B. J. (2002). Lateralization in individuals with high-functioning autism and Asperger's disorder: a frontostriatal model. *Journal of Autism and Developmental Disorders* **32**, 321–331.

Roberts, R. C. (2007). Schizophrenia in translation: disrupted in schizophrenia (DISC1): integrating clinical and basic findings. *Schizophrenia Bulletin* **33**, 11–15.

Rogers, S. J. (2004). Developmental regression in autism spectrum disorders. *Mental Retardation and Developmental Disabilities Research Reviews* **10**, 139–143.

Rojas, P., Joodmardi, E., Hong, Y., Perlmann, T. & Ogren, S. O. (2007). Adult mice with reduced Nurr1 expression: an animal model for schizophrenia. *Molecular Psychiatry* **12**, 756–766.

Rosa, A., Cuesta, M. J., Fatjó-Vilas, M., Peralta, V., Zarzuela, A. & Fañanás, L. (2006). The Val66Met polymorphism of the brain-derived neurotrophic factor gene is associated with risk for psychosis: evidence from a family-based association study. *American Journal of Medical Genetics, B* **141**, 135–138.

Rosenberg, A. & Kagan, J. (1987). Iris pigmentation and behavioral inhibition. *Developmental Psychobiology* **20**, 377–392.

Rosenberg, A. A. & Kagan, J. (1989). Physical and physiological correlates of behavioral inhibition. *Developmental Psychobiology* **22**, 753–770.

Ross, J. L., Roeltgen, D. P., Stefanatos, G., Benecke, R., Zeger, M. P., Kushner, H., Ramos, P., Elder, F. F. & Zinn, A. R. (2008). Cognitive and motor development during childhood in

boys with Klinefelter syndrome. *American Journal of Medical Genetics* **146**, 708–719.

Rossi, A. & Daneluzzo, E. (2002). Schizotypal dimensions in normals and schizophrenic patients: a comparison with other clinical samples. *Schizophrenia Research* **54**, 67–75.

Roudier, J. (2006). HLA-DRB1 genes and extraarticular rheumatoid arthritis. *Arthritis Research & Therapy* **8**, 103.

Rovet, J. (2004). Turner syndrome: a review of genetic and hormonal influences on neuropsychological functioning. *Child Neuropsychology* **10**, 262–279.

Royo, H., Bortolin, M. L., Seitz, H. & Cavaillé, J. (2006). Small non-coding RNAs and genomic imprinting. *Cytogenetic and Genome Research* **113**, 99–108.

Royo, H. & Cavaillé, J. (2008). Non-coding RNAs in imprinted gene clusters. *Biology of the Cell* **100**, 149–166.

Ruf, N., Dünzinger, U., Brinckmann, A., Haaf, T., Nürnberg, P. & Zechner, U. (2006). Expression profiling of uniparental mouse embryos is inefficient in identifying novel imprinted genes. *Genomics* **87**, 509–519.

Runte, M., Varon, R., Horn, D., Horsthemke, B. & Buiting, K. (2005). Exclusion of the C/D box snoRNA gene cluster HBII-52 from a major role in Prader-Willi syndrome. *Human Genetics* **116**, 228–230.

Sacco, R., Militerni, R., Frolli, A., Bravaccio, C., Gritti, A., Elia, M., Curatolo, P., Manzi, B., Trillo, S., Lenti, C., Saccani, M., Schneider, C., Melmed, R., Reichelt, K. L., Pascucci, T., Puglisi-Allegra, S. & Persico, A. M. (2007). Clinical, morphological, and biochemical correlates of head circumference in autism. *Biological Psychiatry* **62**, 1038–1047.

Sahoo, T., Del Gaudio, D., German, J. R., Shinawi, M., Peters, S. U., Person, R. E., Garnica, A., Cheung, S. W. & Beaudet, A. L. (2008) Prader-Willi phenotype caused by paternal deficiency for the HBII-85 C/D box small nucleolar RNA cluster. *Nature Genetics* **40**, 719–721.

Salem, J. E. & Kring, A. M. (1998). The role of gender differences in the reduction of etiologic heterogeneity in schizophrenia. *Clinical Psychology Review* **18**, 795–819.

Samaco, R. C., Hogart, A. & LaSalle, J. M. (2005). Epigenetic overlap in autism-spectrum neurodevelopmental disorders: MECP2 deficiency causes reduced expression of UBE3A and GABRB3. *Human Molecular Genetics* **14**, 483–492.

Samaco, R. C., Nagarajan, R. P., Braunschweig, D. & LaSalle, J. M. (2004). Multiple pathways regulate MeCP2 expression in normal brain development and exhibit defects in autism-spectrum disorders. *Human Molecular Genetics* **13**, 629–639.

Sandovici, I., Leppert, M., Hawk, P. R., Suarez, A., Linares, Y. & Sapienza, C. (2003). Familial aggregation of abnormal methylation of parental alleles at the IGF2/H19 and IGF2R differentially methylated regions. *Human Molecular Genetics* **12**, 1569–1578.

Sanjuán, J., Tolosa, A., González, J. C., Aguilar, E. J., Pérez-Tur, J., Nájera, C., Moltó, M. D. & De Frutos, R. (2006). Association between FOXP2 polymorphisms and schizophrenia with auditory hallucinations. *Psychiatric Genetics* **16**, 67–72.

Santangelo, S. L. & Tsatsanis, K. (2005). What is known about autism: genes, brain, and behavior. *American Journal of Pharmacogenomics* **5**, 71–92.

Sazci, A., Ergul, E., Kucukali, I., Kara, I. & Kaya, G. (2005). Association of the C677T and A1298C polymorphisms of methylenetetrahydrofolate reductase gene with schizophrenia: association is significant in men but not in women. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **29**, 1113–1123.

Schanen, N. C. (2006). Epigenetics of autism spectrum disorders. *Human Molecular Genetics* **15** Suppl. 2, r138–r150.

Schellenberg, G. D., Dawson, G., Sung, Y. J., Estes, A., Munson, J., Rosenthal, E., Rothstein, J., Flodman, P., Smith, M., Coon, H., Leong, L., Yu, C., Stodgell, C., Rodier, P. M., Spence, M. A., Minshew, N., McMahon, W. M. & Wijsman, E. M. (2006). Evidence for multiple loci from a genome scan of autism kindreds. *Molecular Psychiatry* **11**, 1049–1060.

Schiffer, H. H. & Heinemann, S. F. (2007). Association of the human kainate receptor GluR7 gene (GRIK3) with recurrent major depressive disorder. *American Journal of Medical Genetics, B* **144**, 20–26.

Schiffer, H. H., Swanson, G. T., Masliah, E. & Heinemann, S. F. (2000). Unequal expression of allelic kainate receptor GluR7 mRNAs in human brains. *Journal of Neuroscience* **20**, 9025–9033.

Schimmelmann, B. G., Friedel, S., Dempfle, A., Warnke, A., Lesch, K. P., Walitza, S., Renner, T. J., Romanos, M., Herpertz-Dahlmann, B., Linder, M., Schafer, H., Seitz, C., Palmason, H., Freitag, C., Meyer, J., Konrad, K., Hinney, A. & Hebebrand, J. (2007). No evidence for preferential transmission of common valine allele of the Val66Met polymorphism of the brain-derived neurotrophic factor gene (BDNF) in ADHD. *Journal of Neural Transmission* **144**, 523–526.

Schmahmann, J. D., Weilburg, J. B. & Sherman, J. C. (2007). The neuropsychiatry of the cerebellum - insights from the clinic. *Cerebellum* **6**, 254–267.

Schüle, B., Li, H. H., Fisch-Kohl, C., Purmann, C. & Francke, U. (2007). DLX5 and DLX6 expression is biallelic and not modulated by MeCP2 deficiency. *American Journal of Human Genetics* **81**, 492–506.

Schulze, T. G., Buervenich, S., Badner, J. A., Steele, C. J. M., Detera-Wadleigh, S. D., Dick, D., Foroud, T., Cox, N. J., MacKinnon, D. F., Potash, J. B., Berrettini, W. H., Byerley, W., Coryell, W., DePaulo, J. R., Jr, Gershon, E. S., Kelsoe, J. R., McInnis, M. G., Murphy, D. L., Reich, T., Scheftner, W., Nurnberger, J. I., Jr & McMahon, F. J. (2004). Loci on chromosomes 6q and 6p interact to increase susceptibility to bipolar affective disorder in the national institute of mental health genetics initiative pedigrees. *Biological Psychiatry* **56**, 18–23.

Schulze, T. G., Chen, Y., Badner, J. A., McInnis, M. G., DePaulo, J. R., Jr & McMahon, F. J. (2003). Additional, physically ordered markers increase linkage signal for bipolar disorder on chromosome 18q22. *Biological Psychiatry* **53**, 239–243.

Schumacher, J., Kaneva, R., Jamra, R. A., Diaz, G. O., Ohlraun, S., Milanova, V., Lee, Y. A., Rivas, F., Mayoral, F., Fuerst, R., Flaquer, A., Windemuth, C., Gay, E., Sanz, S., González, M. J., Gil, S., Cabaleiro, F., Del Rio, F., Perez, F., Haro, J., Kostov, C., Chorbov, V., Nikolova-Hill, A., Stoyanova, V., Onchev, G., Kremensky, I., Strauch, K., Schulze, T. G., Nürnberg, P., Gaebel, W., Klimke, A., Auburger, G., Wienker, T. F., Kalaydjieva, L., Propping, P., Cichon, S., Jablensky, A., Rietschel, M. & Nöthen, M. M. (2005). Genomewide scan and fine-mapping linkage studies in four European samples with bipolar affective disorder suggest a new susceptibility locus on chromosome 1p35-p36 and provides further evidence of loci on chromosome 4q31 and 6q24. *American Journal of Human Genetics* **77**, 1102–1111.

Schürhoff, F., Laguerre, A., Szöke, A., Méary, A. & Leboyer, M. (2005). Schizotypal dimensions: continuity between schizophrenia and bipolar disorders. *Schizophrenia Research* **80**, 235–242.

Schwab, S. G., Becker, T., Knapp, M., Albus, M., Borrmann-Hassenbach, M., Maier, W. & Wildenauer, D. B. (2006).

Evidence for sex-specific transmission of DNA sequence variants in the dysbindin gene to offspring affected with schizophrenia. *Schizophrenia Research* **81**, s8–s9.

Schwab, S. G., Hallmayer, J., Albus, M., Lerer, B., Hanses, C., Kanyas, K., Segman, R., Borrman, M., Dreikorn, B., Lichtermann, D., Rietschel, M., Trixler, M., Maier, W. & Wildenauer, D. B. (1998*a*). Further evidence for a susceptibility locus on chromosome 10p14-p11 in 72 families with schizophrenia by nonparametric linkage analysis. *American Journal of Medical Genetics* **81**, 302–307.

Schwab, S. G., Hallmayer, J., Lerer, B., Albus, M., Borrmann, M., Hönig, S., Strauss, M., Segman, R., Lichtermann, D., Knapp, M., Trixler, M., Maier, W. & Wildenauer, D. B. (1998*b*). Support for a chromosome 18p locus conferring susceptibility to functional psychoses in families with schizophrenia, by association and linkage analysis. *American Journal of Human Genetics* **63**, 1139–1152.

Schwarz, M. J., Chiang, S., Müller, N. & Ackenheil, M. (2001). T-helper-1 and T-helper-2 responses in psychiatric disorders. *Brain, Behavior, and Immunity* **15**, 340–370.

Schwarz, M. J., Krönig, H., Riedel, M., Dehning, S., Douhet, A., Spellmann, I., Ackenheil, M., Möller, H. J. & Müller, N. (2006). IL-2 and IL-4 polymorphisms as candidate genes in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience* **256**, 72–76.

Seeman, P., Weinshenker, D., Quirion, R., Srivastava, L. K., Bhardwaj, S. K., Grandy, D. K., Premont, R. T., Sotnikova, T. D., Boksa, P., El-Ghundi, M., O'dowd, B. F., George, S. R., Perreault, M. L., Männistö, P. T., Robinson, S., Palmiter, R. D. & Tallerico, T. (2005). Dopamine supersensitivity correlates with D2High states, implying many paths to psychosis. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 3513–3518.

Segurado, R., Detera-Wadleigh, S. D., Levinson, D. F., Lewis, C. M., Gill, M., Nurnberger, J. I., Jr, Craddock, N., DePaulo, J. R., Baron, M., Gershon, E. S., Ekholm, J., Cichon, S., Turecki, G., Claes, S., Kelsoe, J. R., Schofield, P. R., Badenhop, R. F., Morissette, J., Coon, H., Blackwood, D., McInnes, L. A., Foroud, T., Edenberg, H. J., Reich, T., Rice, J. P., Goate, A., McInnis, M. G., McMahon, F. J., Badner, J. A., Goldin, L. R., Bennett, P., Willour, V. L., Zandi, P. P., Liu, J., Gilliam, C., Juo, S., Berrettini, W. H., Yoshikawa, T., Peltonen, L., Lönnqvist, J., Nöthen, M. M., Schumacher, J., Windemuth, C., Rietschel, M., Propping, P., Maier, W., Alda, M., Grof, P., Rouleau, G. A., Del-Favero, J., Van Broeckhoven, C., Mendlewicz, J., Adolfsson, R., Spence, M. A., Luebbert, H., Adams, L. J., Donald, J. A., Mitchell, P. B., Barden, N., Shink, E., Byerley, W., Muir, W., Visscher, P. M., Macgregor, S., Gurling, H., Kalsi, G., McQuillin, A., Escamilla, M. A., Reus, V. I., Leon, P., Freimer, N. B., Ewald, H., Kruse, T. A., Mors, O., Radhakrishna, U., Blouin, J., Antonarakis, S. E. & Akarsu, N. (2003). Genome scan meta-analysis of schizophrenia and bipolar disorder, part III: Bipolar disorder. *American Journal of Human Genetics* **73**, 49–62.

Seitz, H., Royo, H., Bortolin, M. L., Lin, S. P., Ferguson-Smith, A. C. & Cavaillé, J. (2004*a*). A large imprinted microRNA gene cluster at the mouse Dlk1-Gtl2 domain. *Genome Research* **14**, 1741–1748.

Seitz, H., Royo, H., Lin, S. P., Youngson, N., Ferguson-Smith, A. C. & Cavaillé, J. (2004*b*). Imprinted small RNA genes. *Biological Chemistry* **385**, 905–911.

Serajee, F. J., Nabi, R., Zhong, H. & Mahbubul Huq, A. H. M. (2003). Association of INPP1, PIK3CG, and TSC2 gene variants with autistic disorder: implications for phosphatidylinositol signalling in autism. *Journal of Medical Genetics* **40**, e119–e119.

Serajee, F. J., Zhong, H. & Mahbubul Huq, A. H. (2006). Association of reelin gene polymorphisms with autism. *Genomics* **87**, 75–83.

Shaltiel, G., Maeng, S., Malkesman, O., Pearson, B., Schloesser, R. J., Tragon, T., Rogawski, M., Gasior, M., Luckenbaugh, D., Chen, G. & Manji, H. K. (2008). Evidence for the involvement of the kainate receptor subunit GluR6 (GRIK2) in mediating behavioral displays related to behavioral symptoms of mania. *Molecular Psychiatry* (in press).

Shapleske, J., Rossell, S. L., Woodruff, P. W. & David, A. S. (1999). The planum temporale: a systematic, quantitative review of its structural, functional and clinical significance. *Brain Research Reviews* **29**, 26–49.

Sheffler, D. J., Kroeze, W. K., Garcia, B. G., Deutch, A. Y., Hufeisen, S. J., Leahy, P., Brüning, J. C. & Roth, B. L. (2006). p90 ribosomal S6 kinase 2 exerts a tonic brake on G protein-coupled receptor signaling. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 4717–4722.

Shete, S. & Zhou, X. (2005). Parametric approach to genomic imprinting analysis with applications to Angelman's syndrome. *Human Heredity* **59**, 26–33.

Shibata, H., Aramaki, T., Sakai, M., Ninomiya, H., Tashiro, N., Iwata, N., Ozaki, N. & Fukumaki, Y. (2006). Association study of polymorphisms in the GluR7, KA1 and KA2 kainate receptor genes (GRIK3, GRIK4, GRIK5) with schizophrenia. *Psychiatry Research* **141**, 39–51.

Shibayama, A., Cook, E. H. Jr, Feng, J., Glanzmann, C., Yan, J., Craddock, N., Jones, I. R., Goldman, D., Heston, L. L. & Sommer, S. S. (2004). MECP2 structural and 3'-UTR variants in schizophrenia, autism and other psychiatric diseases: a possible association with autism. *American Journal of Medical Genetics, B* **128**, 50–53.

Shields, D. C., Kirke, P. N., Mills, J. L., Ramsbottom, D., Molloy, A. M., Burke, H., Weir, D. G., Scott, J. M. & Whitehead, A. S. (1999). The "thermolabile" variant of methylenetetrahydrofolate reductase and neural tube defects: An evaluation of genetic risk and the relative importance of the genotypes of the embryo and the mother. *American Journal of Human Genetics* **64**, 1045–1055.

Shifman, S., Johannesson, M., Bronstein, M., Chen, S. X., Collier, D. A., Craddock, N. J., Kendler, K. S., Li, T., O'Donovan, M., O'Neill, F. A., Owen, M. J., Walsh, D., Weinberger, D. R., Sun, C., Flint, J. & Darvasi, A. (2008). Genome-wide association identifies a common variant in the Reelin gene that increases the risk of schizophrenia only in women. *PLoS Genetics* **4**, e28.

Shimoda, M., Morita, S., Obata, Y., Sotomaru, Y., Kono, T. & Hatada, I. (2002). Imprinting of a small nucleolar RNA gene on mouse chromosome 12. *Genomics* **79**, 483–486.

Shuang, M., Liu, J., Jia, M. X., Yang, J. Z., Wu, S. P., Gong, X. H., Ling, Y. S., Ruan, Y., Yang, X. L. & Zhang, D. (2004). Family-based association study between autism and glutamate receptor 6 gene in Chinese Han trios. *American Journal of Medical Genetics, B* **131**, 48–50.

Simpson, J. L., de la Cruz, F., Swerdloff, R. S., Samango-Sprouse, C., Skakkebaek, N. E., Graham, J. M., Jr, Hassold, T., Aylstock, M., Meyer-Bahlburg, H. F., Willard, H. F., Hall, J. G., Salameh, W., Boone, K., Staessen, C., Geschwind,

D., Giedd, J., Dobs, A. S., Rogol, A., Brinton, B. & Paulsen, C. A. (2003). Klinefelter syndrome: expanding the phenotype and identifying new research directions. *Genetics in Medicine* **5**, 460–468.

Sipos, A., Rasmussen, F., Harrison, G., Tynelius, P., Lewis, G., Leon, D. A. & Gunnell, D. (2004). Paternal age and schizophrenia: a population based cohort study. *BMJ* **329**, 1070–1070.

Skaar, D. A., Shao, Y., Haines, J. L., Stenger, J. E., Jaworski, J., Martin, E. R., DeLong, G. R., Moore, J. H., McCauley, J. L., Sutcliffe, J. S., Ashley-Koch, A. E., Cuccaro, M. L., Folstein, S. E., Gilbert, J. R. & Pericak-Vance, M. A. (2005). Analysis of the RELN gene as a genetic risk factor for autism. *Molecular Psychiatry* **10**, 563–571.

Sklar, P., Gabriel, S. B., McInnis, M. G., Bennett, P., Lim, Y., Tsan, G., Schaffner, S., Kirov, G., Jones, I., Owen, M., Craddock, N., DePaulo, J. R. & Lander, E. S. (2002). Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. Brain-derived neutrophic factor. *Molecular Psychiatry* **7**, 579–593.

Skuse, D. H. (2000). Imprinting, the X-chromosome, and the male brain: explaining sex differences in the liability to autism. *Pediatric Research* **47**, 9–16.

Skuse, D. H. (2005). X-linked genes and mental functioning. *Human Molecular Genetics* **14** Spec No 1, r27–r32.

Skuse, D. H., James, R. S., Bishop, D. V., Coppin, B., Dalton, P., Aamodt-Leeper, G., Bacarese-Hamilton, M., Creswell, C., McGurk, R. & Jacobs, P. A. (1997). Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. *Nature* **387**, 705–708.

SLI Consortium (2002). A genomewide scan identifies two novel loci involved in specific language impairment. *American Journal of Human Genetics* **70**, 384–398.

Smalley, S. L., Kustanovich, V., Minassian, S. L., Stone, J. L., Ogdie, M. N., McGough, J. J., McCracken, J. T., MacPhie, I. L., Francks, C., Fisher, S. E., Cantor, R. M., Monaco, A. P. & Nelson, S. F. (2002). Genetic linkage of attention-deficit/hyperactivity disorder on chromosome 16p13, in a region implicated in autism. *American Journal of Human Genetics* **71**, 959–963.

Smalley, S. L., Loo, S. K., Yang, M. H. & Cantor, R. M. (2005). Toward localizing genes underlying cerebral asymmetry and mental health. *American Journal of Medical Genetics, B* **135**, 79–84.

Smith, F. M., Garfield, A. S. & Ward, A. (2006). Regulation of growth and metabolism by imprinted genes. *Cytogenetic and Genome Research* **113**, 279–291.

Smith, S. D., Pennington, B. F., Boada, R. & Shriberg, L. D. (2005). Linkage of speech sound disorder to reading disability loci. *Journal of Child Psychology and Psychiatry, and Allied Disciplines* **46**, 1057–1066.

Smits, G. & Kelsey, G. (2006). Imprinting weaves its web. *Developmental Cell.* **11**, 598–599.

Sokolov, B. P. (1998). Expression of NMDAR1, GluR1, GluR7, and KA1 glutamate receptor mRNAs is decreased in frontal cortex of "neuroleptic-free" schizophrenics: evidence on reversible up-regulation by typical neuroleptics. *Journal of Neurochemistry* **71**, 2454–2464.

Soni, S., Whittington, J., Holland, A. J., Webb, T., Maina, E., Boer, H. & Clarke, D. (2007). The course and outcome of psychiatric illness in people with Prader-Willi syndrome: implications for management and treatment. *Journal of Intellectual Disability Research* **51**, 32–42.

Soni, S., Whittington, J., Holland, A. J., Webb, T., Maina, E. N., Boer, H. & Clarke, D. (2008). The phenomenology and diagnosis of psychiatric illness in people with Prader-Willi syndrome. *Psychological Medicine* **4**, 1–10.

Sporn, A. L., Addington, A. M., Gornick, M., Kwon, L., Gogtay, N., Clasen, L. S., Greenstein, D., Ordonez, A. E., Bobb, A. J., Lenane, M. C., Gochman, P. A., Straub, R. E. & Rapoport, J. L. (2004). ATP10C and UBE3A genes in childhood onset schizophrenia. *Biological Psychiatry* **55**, s171.

Stefansson, H., Sigurdsson, E., Steinthorsdottir, V., Bjornsdottir, S., Sigmundsson, T., Ghosh, S., Brynjolfsson, J., Gunnarsdottir, S., Ivarsson, O., Chou, T. T., Hjaltason, O., Birgisdottir, B., Jonsson, H., Gudnadottir, V. G., Gudmundsdottir, E., Bjornsson, A., Ingvarsson, B., Ingason, A., Sigfusson, S., Hardardottir, H., Harvey, R. P., Lai, D., Zhou, M., Brunner, D., Mutel, V., Gonzalo, A., Lemke, G., Sainz, J., Johannesson, G., Andresson, T., Gudbjartsson, D., Manolescu, A., Frigge, M. L., Gurney, M. E., Kong, A., Gulcher, J. R., Petursson, H. & Stefansson, K. (2002). Neuregulin 1 and susceptibility to schizophrenia. *American Journal of Human Genetics* **71**, 877–892.

Stewart, D. R. & Kleefstra, T. (2007). The chromosome 9q subtelomere deletion syndrome. *American Journal of Medical Genetics, C* **145**, 383–392.

Stine, O. C., Xu, J., Koskela, R., McMahon, F. J., Gschwend, M., Friddle, C., Clark, C. D., McInnis, M. G., Simpson, S. G., Breschel, T. S., Vishio, E., Riskin, K., Feilotter, H., Chen, E., Shen, S., Folstein, S., Meyers, D. A., Botstein, D., Marr, T. G. & DePaulo, J. R. (1995). Evidence for linkage of bipolar disorder to chromosome 18 with a parent-of-origin effect. *American Journal of Human Genetics* **57**, 1384–1394.

Stopkova, P., Saito, T., Papolos, D. F., Vevera, J., Paclt, I., Zukov, I., Bersson, Y. B., Margolis, B. A., Strous, R. D. & Lachman, H. M. (2004). Identification of PIK3C3 promoter variant associated with bipolar disorder and schizophrenia. *Biological Psychiatry* **55**, 981–988.

Straub, R. E., MacLean, C. J., Ma, Y., Webb, B. T., Myakishev, M. V., Harris-Kerr, C., Wormley, B., Sadek, H., Kadambi, B., O'Neill, F. A., Walsh, D. & Kendler, K. S. (2002). Genome-wide scans of three independent sets of 90 Irish multiplex schizophrenia families and follow-up of selected regions in all families provides evidence for multiple susceptibility genes. *Molecular Psychiatry* **7**, 542–559.

Strauch, K., Fimmers, R., Windemuth, C., Hahn, A., Wienker, T. F. & Baur, M. P. (1999). Linkage analysis with adequate modeling of a parent-of-origin effect. *Genetic Epidemiology* **17** Suppl. 1, s331–s336.

Strawn, J. R., Ekhator, N. N., D'Souza, B. B. & Geracioti, T. D., Jr (2004). Pituitary-thyroid state correlates with central dopaminergic and serotonergic activity in healthy humans. *Neuropsychobiology* **49**, 84–87.

Strichman-Almashanu, L. Z., Lee, R. S., Onyango, P. O., Perlman, E., Flam, F., Frieman, M. B. & Feinberg, A. P. (2002). A genome-wide screen for normally methylated human CpG islands that can identify novel imprinted genes. *Genome Research* **12**, 543–554.

Suarez, B. K., Duan, J., Sanders, A. R., Hinrichs, A. L., Jin, C. H., Hou, C., Buccola, N. G., Hale, N., Weilbaecher, A. N., Nertney, D. A., Olincy, A., Green, S., Schaffer, A. W., Smith, C. J., Hannah, D. E., Rice, J. P., Cox, N. J., Martinez, M., Mowry, B. J., Amin, F., Silverman, J. M., Black, D. W., Byerley, W. F., Crowe, R. R., Freedman, R., Cloninger, C. R., Levinson, D. F. & Gejman, P. V. (2006). Genomewide Linkage Scan of 409 European-Ancestry and African American Families with Schizophrenia: Suggestive Evidence of Linkage at 8p23.3-p21.2

and 11p13.1-q14.1 in the Combined Sample. *American Journal of Human Genetics* **78**, 315–333.

Sullivan, P. F., Kendler, K. S. & Neale, M. C. (2003). Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Archives of General Psychiatry* **60**, 1187–1192.

Sutton, V. R. & Shaffer, L. G. (2000). Search for imprinted regions on chromosome 14: comparison of maternal and paternal UPD cases with cases of chromosome 14 deletion. *American Journal of Medical Genetics* **93**, 381–387.

Sweeten, T. L., Bowyer, S. L., Posey, D. J., Halberstadt, G. M. & McDougle, C. J. (2003). Increased prevalence of familial autoimmunity in probands with pervasive developmental disorders. *Pediatrics* **112**, e420.

Szatmari, P., Paterson, A. D., Zwaigenbaum, L., Roberts, W., Brian, J., Liu, X., Vincent, J. B., Skaug, J. L., Thompson, A. P., Senman, L., Feuk, L., Qian, C., Bryson, S. E., Jones, M. B., Marshall, C. R., Scherer, S. W., Vieland, V. J., Bartlett, C., Mangin, L. V., Goedken, R., Segre, A., Pericak-Vance, M. A., Cuccaro, M. L., Gilbert, J. R., Wright, H. H., Abramson, R. K., Betancur, C., Bourgeron, T., Gillberg, C., Leboyer, M., Buxbaum, J. D., Davis, K. L., Hollander, E., Silverman, J. M., Hallmayer, J., Lotspeich, L., Sutcliffe, J. S., Haines, J. L., Folstein, S. E., Piven, J., Wassink, T. H., Sheffield, V., Geschwind, D. H., Bucan, M., Brown, W. T., Cantor, R. M., Constantino, J. N., Gilliam, T. C., Herbert, M., Lajonchere, C., Ledbetter, D. H., Lese-Martin, C., Miller, J., Nelson, S., Samango-Sprouse, C. A., Spence, S., State, M., Tanzi, R. E., Coon, H., Dawson, G., Devlin, B., Estes, A., Flodman, P., Klei, L., McMahon, W. M., Minshew, N., Munson, J., Korvatska, E., Rodier, P. M., Schellenberg, G. D., Smith, M., Spence, M. A., Stodgell, C., Tepper, P. G., Wijsman, E. M., Yu, C., Rogé, B., Mantoulan, C., Wittemeyer, K., Poustka, A., Felder, B., Klauck, S. M., Schuster, C., Poustka, F., Bölte, S., Feineis-Matthews, S., Herbrecht, E., Schmötzer, G., Tsiantis, J., Papanikolaou, K., Maestrini, E., Bacchelli, E., Blasi, F., Carone, S., Toma, C., Van Engeland, H., de Jonge, M., Kemner, C., Koop, F., Langemeijer, M., Hijimans, C., Staal, W. G., Baird, G., Bolton, P. F., Rutter, M. L., Weisblatt, E., Green, J., Aldred, C., Wilkinson, J., Pickles, A., Le Couteur, A., Berney, T., McConachie, H., Bailey, A. J., Francis, K., Honeyman, G., Hutchinson, A., Parr, J. R., Wallace, S., Monaco, A. P., Barnby, G., Kobayashi, K., Lamb, J. A., Sousa, I., Sykes, N., Cook, E. H., Guter, S. J., Leventhal, B. L., Salt, J., Lord, C., Corsello, C., Hus, V., Weeks, D. E., Volkmar, F., Tauber, M., Fombonne, E. & Shih, A. (2007). Mapping autism risk loci using genetic linkage and chromosomal rearrangements. *Nature Genetics* **39**, 319–328.

Tager-Flusberg, H. & Joseph, R. M. (2003). Identifying neurocognitive phenotypes in autism. *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences* **358**, 303–314.

Takaki, H., Kikuta, R., Shibata, H., Ninomiya, H., Tashiro, N. & Fukumaki, Y. (2004). Positive associations of polymorphisms in the metabotropic glutamate receptor type 8 gene (GRM8) with schizophrenia. *American Journal of Medical Genetics, B* **128**, 6–14.

Takayanagi, Y., Kasahara, Y., Onaka, T., Takahashi, N., Kawada, T. & Nishimori, K. (2008). Oxytocin receptor-deficient mice developed late-onset obesity. *Neuroreport.* **19**, 951–955.

Talkowski, M. E., Kirov, G., Bamne, M., Georgieva, L., Torres, G., Mansour, H., Chowdari, K. V., Milanova, V., Wood, J., McClain, L., Prasad, K., Shirts, B., Zhang, J., O'Donovan, M. C., Owen, M. J., Devlin, B. & Nimgaonkar, V. L. (2008). A network of dopaminergic gene variations implicated as risk factors for schizophrenia. *Human Molecular Genetics* **17**, 747–758.

Talkowski, M. E., Seltman, H., Bassett, A. S., Brzustowicz, L. M., Chen, X., Chowdari, K. V., Collier, D. A., Cordeiro, Q., Corvin, A. P., Deshpande, S. N., Egan, M. F., Gill, M., Kendler, K. S., Kirov, G., Heston, L. L., Levitt, P., Lewis, D. A., Li, T., Mirnics, K., Morris, D. W., Norton, N., O'donovan, M. C., Owen, M. J., Richard, C., Semwal, P., Sobell, J. L., St Clair, D., Straub, R. E., Thelma, B. K., Vallada, H., Weinberger, D. R., Williams, N. M., Wood, J., Zhang, F., Devlin, B. & Nimgaonkar, V. L. (2006). Evaluation of a susceptibility gene for schizophrenia: genotype based meta-analysis of RGS4 polymorphisms from thirteen independent samples. *Biological Psychiatry* **60**, 152–162.

Tamminga, C. A. & Holcomb, H. H. (2005). Phenotype of schizophrenia: a review and formulation. *Molecular Psychiatry* **10**, 27–39.

Tang, J., Chen, X., Xu, X., Wu, R., Zhao, J., Hu, Z. & Xia, K. (2006). Significant linkage and association between a functional (GT)n polymorphism in promoter of the N-methyl-D-aspartate receptor subunit gene (GRIN2A) and schizophrenia. *Neuroscience Letters* **409**, 80–82.

Taoka, H., Hamamura, T., Endo, S., Miki, M., Lee, Y., Miyata, S., Toma, K., Ishihara, T., Sagara, H., Gomita, Y. & Kuroda, S. (2006). G(olf) protein levels in rat striatum are increased by chronic antidepressant administration and decreased by olfactory bulbectomy. *Life Sciences* **79**, 462–468.

Temple, I. K., Shrubb, V., Lever, M., Bullman, H. & Mackay, D. J. (2007). Isolated imprinting mutation of the DLK1/GTL2 locus associated with a clinical presentation of maternal uniparental disomy of chromosome 14. *Journal of Medical Genetics* **44**, 637–640.

Tiemann-Boege, I., Navidi, W., Grewal, R., Cohn, D., Eskenazi, B., Wyrobek, A. J. & Arnheim, N. (2002). The observed human sperm mutation frequency cannot explain the achondroplasia paternal age effect. *Proceedings of the National Academy of Sciences of the United States of America* **99**, 14952–14957.

Tierling, S., Dalbert, S., Schoppenhorst, S., Tsai, C., Oliger, S., Ferguson-Smith, A. C., Paulsen, M. & Walter, J. (2006). High-resolution map and imprinting analysis of the Gtl2-Dnchc1 domain on mouse chromosome 12. *Genomics* **87**, 225–235.

Toda, Y., Mori, K., Hashimoto, T., Miyazaki, M., Nozaki, S., Watanabe, Y., Kuroda, Y. & Kagami, S. (2006). Administration of secretin for autism alters dopamine metabolism in the central nervous system. *Brain & Development* **28**, 99–103.

Torres, A. R., Maciulis, A., Stubbs, E. G., Cutler, A. & Odell, D. (2002). The transmission disequilibrium test suggests that HLA-DR4 and DR13 are linked to autism spectrum disorder. *Human Immunology* **63**, 311–316.

Torres, A. R., Sweeten, T. L., Cutler, A., Bedke, B. J., Fillmore, M., Stubbs, E. G. & Odell, D. (2006). The Association and Linkage of the HLA-A2 Class I Allele with Autism. *Human Immunology* **67**, 346–351.

Torrey, E. F. & Yolken, R. H. (2001). The schizophrenia-rheumatoid arthritis connection: infectious, immune, or both? *Brain, Behavior, and Immunity* **15**, 401–410.

Trikalinos, T. A., Karvouni, A., Zintzaras, E., Ylisaukko-oja, T., Peltonen, L., Järvelä, I. & Ioannidis, J. P. (2006). A heterogeneity-based genome search meta-analysis for autism-spectrum disorders. *Molecular Psychiatry* **11**, 29–36.

Trillingsgaard, A. & ØStergaard, J. R. (2004). Autism in Angelman syndrome: an exploration of comorbidity. *Autism* **8**, 163–174.

Tsai, S. J. (2005). Is autism caused by early hyperactivity of brain-derived neurotrophic factor? *Medical Hypotheses* **65**, 79–82.

Tseng, Y. H., Butte, A. J., Kokkotou, E., Yechoor, V. K., Taniguchi, C. M., Kriauciunas, K. M., Cypess, A. M., Niinobe, M., Yoshikawa, K., Patti, M. E. & Kahn, C. R. (2005). Prediction of preadipocyte differentiation by gene expression reveals role of insulin receptor substrates and necdin. *Nature Cell Biology* **7**, 601–611.

Tucker, K. L. (2001). Methylated cytosine and the brain: a new base for neuroscience. *Neuron* **30**, 649–652.

Turecki, G., Grof, P., Cavazzoni, P., Duffy, A., Grof, E., Martin, R., Joober, R., Rouleau, G. A. & Alda, M. (1999). Lithium responsive bipolar disorder, unilineality, and chromosome 18: A linkage study. *American Journal of Medical Genetics* **88**, 411–415.

Turic, D., Langley, K., Mills, S., Stephens, M., Lawson, D., Govan, C., Williams, N., Van Den Bree, M., Craddock, N., Kent, L., Owen, M., O'Donovan, M. & Thapar, A. (2004). Follow-up of genetic linkage findings on chromosome 16p13: evidence of association of N-methyl-D aspartate glutamate receptor 2A gene polymorphism with ADHD. *Molecular Psychiatry* **9**, 169–173.

Tycko, B. (2006). Imprinted genes in placental growth and obstetric disorders. *Cytogenetic and Genome Research* **113**, 271–278.

Tycko, B. & Morison, I. M. (2002). Physiological functions of imprinted genes. *Journal of Cellular Physiology* **192**, 245–258.

Tzenova, J., Kaplan, B. J., Petryshen, T. L. & Field, L. L. (2004). Confirmation of a dyslexia susceptibility locus on chromosome 1p34-p36 in a set of 100 Canadian families. *American Journal of Medical Genetics, B* **127**, 117–124.

Valente, T., Junyent, F. & Auladell, C. (2005). Zac1 is expressed in progenitor/stem cells of the neuroectoderm and mesoderm during embryogenesis: differential phenotype of the Zac1-expressing cells during development. *Developmental Dynamics* **233**, 667–679.

Van Agtmael, T., Forrest, S. M., Del-Favero, J., Van Broeckhoven, C. & Williamson, R. (2003). Parametric and nonparametric genome scan analyses for human handedness. *European Journal of Human Genetics* **11**, 779–783.

Van Daalen, E., Swinkels, S. H., Dietz, C., van Engeland, H. & Buitelaar, J. K. (2007). Body length and head growth in the first year of life in autism. *Pediatric Neurology* **37**, 324–330.

van Os, J., Verdoux, H., Maurice-Tison, S., Gay, B., Liraud, F., Salamon, R. & Bourgeois, M. (1999). Self-reported psychosis-like symptoms and the continuum of psychosis. *Social Psychiatry and Psychiatric Epidemiology* **34**, 459–463.

van Rijn, S., Aleman, A., Swaab, H. & Kahn, R. S. (2005). Neurobiology of emotion and high risk for schizophrenia: role of the amygdala and the X-chromosome. *Neuroscience and Biobehavioral Reviews* **29**, 385–397.

van Rijn, S., Aleman, A., Swaab, H. & Kahn, R. (2006*a*). Klinefelter's syndrome (karyotype 47,XXY) and schizophrenia-spectrum pathology. *British Journal of Psychiatry* **189**, 459–460.

van Rijn, S., Swaab, H., Aleman, A. & Kahn, R. S. (2006*b*). X Chromosomal effects on social cognitive processing and emotion regulation: A study with Klinefelter men (47,XXY). *Schizophrenia Research* **84**, 194–203.

Varela, M. C., Simões-Sato, A. Y., Kim, C. A., Bertola, D. R., De Castro, C. I. & Koiffmann, C. P. (2006). A new case of interstitial 6q16.2 deletion in a patient with Prader-Willi-like phenotype and investigation of SIM1 gene deletion in 87 patients with syndromic obesity. *European Journal of Medical Genetics* **49**, 298–305.

Varrault, A., Gueydan, C., Delalbre, A., Bellmann, A., Houssami, S., Aknin, C., Severac, D., Chotard, L., Kahli, M., Le Digarcher, A., Pavlidis, P. & Journot, L. (2006). Zac1 regulates an imprinted gene network critically involved in the control of embryonic growth. *Developmental Cell* **11**, 711–722.

Vawter, M. P., Harvey, P. D. & DeLisi, L. E. (2007). Dysregulation of X-linked gene expression in Klinefelter's syndrome and association with verbal cognition. *American Journal of Medical Genetics, B* **144**, 728–734.

Veenstra-Vanderweele, J., Christian, S. L. & Cook, E. H., Jr (2004). Autism as a paradigmatic complex genetic disorder. *Annual Review of Genomics and Human Genetics* **5**, 379–405.

Veldic, M., Guidotti, A., Maloku, E., Davis, J. M. & Costa, E. (2005). In psychosis, cortical interneurons overexpress DNA-methyltransferase 1. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 2152–2157.

Verhoeven, W. M., Tuinier, S. & Curfs, L. M. (2003). Prader-Willi syndrome: the psychopathological phenotype in uniparental disomy. *Journal of Medical Genetics* **40**, e112.

Vogels, A., De Hert, M., Descheemaeker, M. J., Govers, V., Devriendt, K., Legius, E., Prinzie, P. & Fryns, J. P. (2004). Psychotic disorders in Prader-Willi syndrome. *American Journal of Medical Genetics* **127**, 238–243.

Vogels, A., Matthijs, G., Legius, E., Devriendt, K. & Fryns, J. P. (2003). Chromosome 15 maternal uniparental disomy and psychosis in Prader-Willi syndrome. *Journal of Medical Genetics* **40**, 72–73.

Voight, B. F., Kudaravalli, S., Wen, X. & Pritchard, J. K. (2006). A map of recent positive selection in the human genome. *PLoS Biology* **4**, e72–e72.

Volpicelli, F., Caiazzo, M., Greco, D., Consales, C., Leone, L., Perrone-Capano, C., Colucci D'Amato, L. & di Porzio, U. (2007). Bdnf gene is a downstream target of Nurr1 transcription factor in rat midbrain neurons in vitro. *Journal of Neurochemistry* **102**, 441–453.

von Salomé, J., Gyllensten, U. & Bergström, T. F. (2007). Full-length sequence analysis of the HLA-DRB1 locus suggests a recent origin of alleles. *Immunogenetics* **59**, 261–271.

Vuoristo, J. T., Berrettini, W. H., Overhauser, J., Prockop, D. J., Ferraro, T. N. & Ala-Kokko, L. (2000). Sequence and genomic organization of the human G-protein Golfalpha gene (GNAL) on chromosome 18p11, a susceptibility region for bipolar disorder and schizophrenia. *Molecular Psychiatry* **5**, 495–501.

Wade, P. A. (2004). Dynamic regulation of DNA methylation coupled transcriptional repression: BDNF regulation by MeCP2. *Bioessays* **26**, 217–220.

Wagschal, A. & Feil, R. (2006). Genomic imprinting in the placenta. *Cytogenetic and Genome Research* **113**, 90–98.

Walsh, T., McClellan, J. M., McCarthy, S. E., Addington, A. M., Pierce, S. B., Cooper, G. M., Nord, A. S., Kusenda, M., Malhotra, D., Bhandari, A., Stray, S. M., Rippey, C. F., Roccanova, P., Makarov, V., Lakshmi, B., Findling, R. L., Sikich, L., Stromberg, T., Merriman, B., Gogtay, N., Butler, P., Eckstrand, K., Noory, L., Gochman, P., Long, R., Chen, Z., Davis, S., Baker, C., Eichler, E. E., Meltzer, P. S., Nelson, S. F., Singleton, A. B., Lee, M. K., Rapoport, J. L., King, M. C. & Sebat, J. (2008). Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science* **320**, 539–543.

Walss-Bass, C., Montero, A. P., Armas, R., Dassori, A., Contreras, S. A., Liu, W., Medina, R., Levinson, D., Pereira, M., Atmella, I., NeSmith, L., Leach, R., Almasy, L.,

Raventos, H. & Escamilla, M. A. (2006). Linkage disequilibrium analyses in the Costa Rican population suggests discrete gene loci for schizophrenia at 8p23.1 and 8q13.3. *Psychiatric Genetics* **16**, 159–168.

Wang, B., Lin, D., Li, C. & Tucker, P. (2003). Multiple domains define the expression and regulatory properties of Foxp1 forkhead transcriptional repressors. *Journal of Biological Chemistry* **278**, 24259–24268.

Warren, R. P., Odell, J. D., Warren, W. L., Burger, R. A., Maciulis, A., Daniels, W. W. & Torres, A. R. (1996). Strong association of the third hypervariable region of HLA-DR beta 1 with autism. *Journal of Neuroimmunology* **67**, 97–102.

Warren, R. P., Singh, V. K., Cole, P., Odell, J. D., Pingree, C. B., Warren, W. L., DeWitt, C. W. & McCullough, M. (1992). Possible association of the extended MHC haplotype B44-SC30-DR4 with autism. *Immunogenetics* **36**, 203–207.

Warwick, M. M., Doody, G. A., Lawrie, S. M., Kestelman, J. N., Best, J. J. & Johnstone, E. C. (1999). Volumetric magnetic resonance imaging study of the brain in subjects with sex chromosome aneuploidies. *Journal of Neurology, Neurosurgery, and Psychiatry* **66**, 628–632.

Warwick, M. M., Lawrie, S. M., Beveridge, A. & Johnstone, E. C. (2003). Abnormal cerebral asymmetry and schizophrenia in a subject with Klinefelter's syndrome (XXY). *Biological Psychiatry* **53**, 627–629.

Wassink, T. H., Piven, J., Vieland, V. J., Jenkins, L., Frantz, R., Bartlett, C. W., Goedken, R., Childress, D., Spence, M. A., Smith, M. & Sheffield, V. C. (2005). Evaluation of the chromosome 2q37.3 gene CENTG2 as an autism susceptibility gene. *American Journal of Medical Genetics, B* **136**, 36–44.

Wassink, T. H., Piven, J., Vieland, V. J., Pietila, J., Goedken, R. J., Folstein, S. E. & Sheffield, V. C. (2002). Evaluation of FOXP2 as an autism susceptibility gene. *American Journal of Medical Genetics* **114**, 566–569.

Weaver, A. H. (2005). Reciprocal evolution of the cerebellum and neocortex in fossil humans. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 3576–3580.

Weaving, L. S., Ellaway, C. J., Gécz, J. & Christodoulou, J. (2005). Rett syndrome: clinical review and genetic update. *Journal of Medical Genetics* **42**, 1–7.

Webb, S. J., Nalty, T., Munson, J., Brock, C., Abbott, R. & Dawson, G. (2007). Rate of head circumference growth as a function of autism diagnosis and history of autistic regression. *Journal of Child Neurology* **22**, 1182–1190.

Webb, T., Maina, E. N., Soni, S., Whittington, J., Boer, H., Clarke, D. & Holland, A. (2008). In search of the psychosis gene in people with Prader-Willi syndrome. *American Journal of Medical Genetics* **146**, 843–853.

Weickert, C. S., Hyde, T. M., Lipska, B. K., Herman, M. M., Weinberger, D. R. & Kleinman, J. E. (2003). Reduced brain-derived neurotrophic factor in prefrontal cortex of patients with schizophrenia. *Molecular Psychiatry* **8**, 592–610.

Weickert, C. S., Ligons, D. L., Romanczyk, T., Ungaro, G., Hyde, T. M., Herman, M. M., Weinberger, D. R. & Kleinman, J. E. (2005). Reductions in neurotrophin receptor mRNAs in the prefrontal cortex of patients with schizophrenia. *Molecular Psychiatry* **10**, 637–650.

Weinstein, L. S. (2001). The role of tissue-specific imprinting as a source of phenotypic heterogeneity in human disease. *Biological Psychiatry* **50**, 927–931.

Weinstein, L. S., Liu, J., Sakamoto, A., Xie, T. & Chen, M. (2004). Minireview: GNAS: normal and abnormal functions. *Endocrinology* **145**, 5459–5464.

Weinstein, L. S., Xie, T., Zhang, Q. H. & Chen, M. (2007). Studies of the regulation and function of the Gs alpha gene Gnas using gene targeting technology. *Pharmacology and Therapeutics* **115**, 271–291.

Weinstein, L. S., Yu, S., Warner, D. R. & Liu, J. (2001). Endocrine manifestations of stimulatory G protein alpha-subunit mutations and the role of genomic imprinting. *Endocrine Reviews* **22**, 675–705.

Whiting, B. A. & Barton, R. A. (2003). The evolution of the cortico-cerebellar complex in primates: anatomical connections predict patterns of correlated evolution. *Journal of Human Evolution* **44**, 3–10.

Whittington, J. & Holland, T. (2004). *Prader-Willi Syndrome: Development and Manifestations*. Cambridge University Press, Cambridge.

Wijsman, E. M., Rosenthal, E. A., Hall, D., Blundell, M. L., Sobin, C., Heath, S. C., Williams, R., Brownstein, M. J., Gogos, J. A. & Karayiorgou, M. (2003). Genome-wide scan in a large complex pedigree with predominantly male schizophrenics from the island of Kosrae: evidence for linkage to chromosome 2q. *Molecular Psychiatry* **8**, 695–705.

Wilkins, J. F. (2005). Genomic imprinting and methylation: epigenetic canalization and conflict. *Trends in Genetics* **21**, 356–365.

Wilkins, J. F. & Haig, D. (2001). Genomic imprinting of two antagonistic loci. *Proceedings of the Royal Society of London, Series B, Biological Sciences* **268**, 1861–1867.

Wilkins, J. F. & Haig, D. (2002). Parental modifiers, antisense transcripts and loss of imprinting. *Proceedings of the Royal Society of London, Series B, Biological Sciences* **269**, 1841–1846.

Wilkinson, L. S., Davies, W. & Isles, A. R. (2007). Genomic imprinting effects on brain development and function. *Nature Reviews Neuroscience* **8**, 832–843.

Williams, C. A., Lossie, A. & Driscoll, D. (2001). Angelman syndrome: mimicking conditions and phenotypes. *American Journal of Medical Genetics* **101**, 59–64.

Williams, N. A., Close, J. P., Giouzeli, M. & Crow, T. J. (2006). Accelerated evolution of Protocadherin11X/Y: a candidate gene-pair for cerebral asymmetry and language. *American Journal of Medical Genetics, B* **141**, 623–633.

Williams, N. M., Norton, N., Williams, H., Ekholm, B., Hamshere, M. L., Lindblom, Y., Chowdari, K. V., Cardno, A. G., Zammit, S., Jones, L. A., Murphy, K. C., Sanders, R. D., McCarthy, G., Gray, M. Y., Jones, G., Holmans, P., Nimgaonkar, V., Adolfson, R., Osby, U., Terenius, L., Sedvall, G., O'Donovan, M. C. & Owen, M. J. (2003). A systematic genomewide linkage study in 353 sib pairs with schizophrenia. *American Journal of Human Genetics* **73**, 1355–1367.

Willour, V. L., Zandi, P. P., Badner, J. A., Steele, J., Miao, K., Lopez, V., MacKinnon, D. F., Mondimore, F. M., Schweizer, B., McInnis, M. G., Miller, E. B., Depaulo, J. R., Gershon, E. S., McMahon, F. J. & Potash, J. B. (2007). Attempted suicide in bipolar disorder pedigrees: evidence for linkage to 2p12. *Biological Psychiatry* **61**, 725–727.

Wilson, G. M., Flibotte, S., Chopra, V., Melnyk, B. L., Honer, W. G. & Holt, R. A. (2006). DNA copy-number analysis in bipolar disorder and schizophrenia reveals aberrations in genes involved in glutamate signaling. *Human Molecular Genetics* **15**, 743–749.

Wimpory, D., Nicholas, B. & Nash, S. (2002). Social timing, clock genes and autism: a new hypothesis. *Journal of Intellectual Disability Research* **46**, 352–358.

Windpassinger, C., Kroisel, P. M., Wagner, K. & Petek, E. (2002). The human gamma-aminobutyric acid A receptor delta (GABRD) gene: molecular characterisation and tissue-specific expression. *Gene* **292**, 25–31.

Windsor, L., Puschendorf, M., Allcock, R., Scott, A., Sayer, D., Kucharzak, R., Gut, I., McCann, V., Davis, E., Witt, C., Christiansen, F. & Price, P. (2005). Does a central MHC gene in linkage disequilibrium with HLA-DRB1*0401 affect susceptibility to type 1 diabetes? *Genes and Immunity* **6**, 298–304.

Wirth, J., Back, E., Hüttenhofer, A., Nothwang, H. G., Lich, C., Gross, S., Menzel, C., Schinzel, A., Kioschis, P., Tommerup, N., Ropers, H. H., Horsthemke, B. & Buiting, K. (2001). A translocation breakpoint cluster disrupts the newly defined 3' end of the SNURF-SNRPN transcription unit on chromosome 15. *Human Molecular Genetics* **10**, 201–210.

Wood, A. J., Roberts, R. G., Monk, D., Moore, G. E., Schulz, R. & Oakey, R. J. (2007). A Screen for retrotransposed imprinted genes reveals an association between X chromosome homology and maternal germ-line methylation. *PLoS Genetics* **3**, e20.

Wood, J. G., Joyce, P. R., Miller, A. L., Mulder, R. T. & Kennedy, M. A. (2002). A polymorphism in the dopamine beta-hydroxylase gene is associated with "paranoid ideation" in patients with major depression. *Biological Psychiatry* **51**, 365–369.

Worley, K. A., Rundus, V. R., Lee, E. B., Hannig, V. L., Hedges, L. K., Tsuchiya, K. & Phillips, J. A. (2001). Maternal uniparental disomy 14 presenting as language delay. *American Journal of Human Genetics* **69**, 309–309.

Wright, P., Donaldson, P. T., Underhill, J. A., Choudhuri, K., Doherty, D. G. & Murray, R. M. (1996b). Genetic association of the HLA DRB1 gene locus on chromosome 6p21.3 with schizophrenia. *American Journal of Psychiatry* **153**, 1530–1533.

Wright, P., Dawson, E., Donaldson, P. T., Underhill, J. A., Sham, P. C., Zhao, J., Gill, M., Nanko, S., Owen, M. J., McGuffin, P. & Murray, R. M. (1998). A transmission/disequilibrium study of the DRB1*04 gene locus on chromosome 6p21.3 with schizophrenia. *Schizophrenia Research* **32**, 75–80.

Wright, P., Nimgaonkar, V. L., Donaldson, P. T. & Murray, R. M. (2001). Schizophrenia and HLA: a review. *Schizophrenia Research* **47**, 1–12.

Wright, P., Sham, P. C., Gilvarry, C. M., Jones, P. B., Cannon, M., Sharma, T. & Murray, R. M. (1996a). Autoimmune diseases in the pedigrees of schizophrenic and control subjects. *Schizophrenia Research* **20**, 261–267.

Wu, S., Jia, M., Ruan, Y., Liu, J., Guo, Y., Shuang, M., Gong, X., Zhang, Y., Yang, X. & Zhang, D. (2005). Positive association of the oxytocin receptor gene (OXTR) with autism in the Chinese Han population. *Biological Psychiatry* **58**, 74–77.

Wu, Y. Q., Heilstedt, H. A., Bedell, J. A., May, K. M., Starkey, D. E., McPherson, J. D., Shapira, S. K. & Shaffer, L. G. (1999). Molecular refinement of the 1p36 deletion syndrome reveals size diversity and a preponderance of maternally derived deletions. *Human Molecular Genetics* **8**, 313–321.

Wyszynski, D. F. & Panhuysen, C. I. (1999). Parental sex effect in families with alcoholism. *Genetic Epidemiology* **17** Suppl. 1, s409–s413.

Xing, G., Zhang, L., Russell, S. & Post, R. (2006). Reduction of dopamine-related transcription factors Nurr1 and NGFI-B in the prefrontal cortex in schizophrenia and bipolar disorders. *Schizophrenia Research* **84**, 36–56.

Xing, Q., Wu, S., Lin, Z., Li, H., Yang, J., Feng, G., Wang, M., Yang, W. & He, L. (2003). Association analysis of polymorphisms in the upstream region of the human dopamine D4 receptor gene in schizophrenia. *Schizophrenia Research* **65**, 9–14.

Xu, M., St Clair, D., Ott, J., Feng, G. & He, L. (2007). Brain-derived neurotrophic factor gene C-270T and Val66Met functional polymorphisms and risk of schizophrenia: A moderate-scale population-based study and meta-analysis. *Schizophrenia Research* **91**, 6–13.

Yamada, K., Iwayama-Shigeno, Y., Yoshida, Y., Toyota, T., Itokawa, M., Hattori, E., Shimizu, H. & Yoshikawa, T. (2004*a*). Family-based association study of schizophrenia with 444 markers and analysis of a new susceptibility locus mapped to 11q13.3. *American Journal of Medical Genetics, B* **127**, 11–19.

Yamada, K., Nakamura, K., Minabe, Y., Iwayama-Shigeno, Y., Takao, H., Toyota, T., Hattori, E., Takei, N., Sekine, Y., Suzuki, K., Iwata, Y., Miyoshi, K., Honda, A., Baba, K., Katayama, T., Tohyama, M., Mori, N. & Yoshikawa, T. (2004*b*). Association analysis of FEZ1 variants with schizophrenia in Japanese cohorts. *Biological Psychiatry* **56**, 683–690.

Yamaguchi, A., Taniguchi, M., Hori, O., Ogawa, S., Tojo, N., Matsuoka, N., Miyake, S., Kasai, K., Sugimoto, H., Tamatani, M., Yamashita, T. & Tohyama, M. (2002). Peg3/Pw1 is involved in p53-mediated cell death pathway in brain ischemia/hypoxia. *Journal of Biological Chemistry* **277**, 623–629.

Yan, W. L., Guan, X. Y., Green, E. D., Nicolson, R., Yap, T. K., Zhang, J., Jacobsen, L. K., Krasnewich, D. M., Kumra, S., Lenane, M. C., Gochman, P., Damschroder-Williams, P. J., Esterling, L. E., Long, R. T., Martin, B. M., Sidransky, E., Rapoport, J. L. & Ginns, E. I. (2000). Childhood-onset schizophrenia/autistic disorder and t(1;7) reciprocal translocation: identification of a BAC contig spanning the translocation breakpoint at 7q21. *American Journal of Medical Genetics* **96**, 749–753.

Yang, A., Walker, N., Bronson, R., Kaghad, M., Oosterwegel, M., Bonnin, J., Vagner, C., Bonnet, H., Dikkes, P., Sharpe, A., McKeon, F. & Caput, D. (2000). p73-deficient mice have neurological, pheromonal and inflammatory defects but lack spontaneous tumours. *Nature* **404**, 99–103.

Yirmiya, N., Rosenberg, C., Levi, S., Salomon, S., Shulman, C., Nemanov, L., Dina, C. & Ebstein, R. P. (2006). Association between the arginine vasopressin 1a receptor (AVPR1a) gene and autism in a family-based study: mediation by socialization skills. *Molecular Psychiatry* **11**, 488–494.

Ylisaukko-oja, T., Alarcón, M., Cantor, R. M., Auranen, M., Vanhala, R., Kempas, E., von Wendt, L., Järvelä, I., Geschwind, D. H. & Peltonen, L. (2006). Search for autism loci by combined analysis of Autism Genetic Resource Exchange and Finnish families. *Annals of Neurology* **59**, 145–155.

Yntema, H. G., van den Helm, B., Kissing, J., van Duijnhoven, G., Poppelaars, F., Chelly, J., Moraine, C., Fryns, J. P., Hamel, B. C., Heilbronner, H., Pander, H. J., Brunner, H. G., Ropers, H. H., Cremers, F. P. & van Bokhoven, H. (1999). A novel ribosomal S6-kinase (RSK4; RPS6KA6) is commonly deleted in patients with complex X-linked mental retardation. *Genomics* **62**, 332–343.

Yong, P. J., Marion, S. A., Barrett, I. J., Kalousek, D. K. & Robinson, W. P. (2002). Evidence for imprinting on chromosome 16: the effect of uniparental disomy on the outcome of mosaic trisomy 16 pregnancies. *American Journal of Medical Genetics* **112**, 123–132.

Zandi, P. P., Willour, V. L., Huo, Y., Chellis, J., Potash, J. B., MacKinnon, D. F., Simpson, S. G., McMahon, F. J., Gershon,

E., Reich, T., Foroud, T., Nurnberger, J., Jr, DePaulo, J. R., Jr & McInnis, M. G. (2003). Genome scan of a second wave of NIMH genetics initiative bipolar pedigrees: chromosomes 2, 11, 13, 14, and X. *American Journal of Medical Genetics, B* **119**, 69–76.

Zerres, K. & Rudnik-Schöneborn, S. (1995). On genetic heterogeneity, anticipation, and imprinting in polycystic kidney diseases. *Nephrology Dialysis Transplantation* **10**, 7–9.

Zhang, H., Liu, X., Zhang, C., Mundo, E., Macciardi, F., Grayson, D. R., Guidotti, A. R. & Holden, J. J. A. (2002). Reelin gene alleles and susceptibility to autism spectrum disorders. *Molecular Psychiatry* **7**, 1012–1017.

Zhao, Z., Tavoosidana, G., Sjölinder, M., Göndör, A., Mariano, P., Wang, S., Kanduri, C., Lezcano, M., Sandhu, K. S., Singh, U., Pant, V., Tiwari, V., Kurukuti, S. & Ohlsson, R. (2006). Circular chromosome conformation capture (4C) uncovers extensive networks of epigenetically regulated intra- and interchromosomal interactions. *Nature Genetics* **38**, 1341–1347.

Zill, P., Engel, R., Baghai, T. C., Zwanzger, P., Schüle, C., Minov, C., Behrens, S., Rupprecht, R., Möller, H. J. & Bondy, B. (2002). Analysis of polymorphisms in the olfactory G-protein Golf in major depression. *Psychiatric Genetics* **12**, 17–22.

Zill, P., Malitas, P. N., Bondy, B., Engel, R., Boufidou, F., Behrens, S., Alevizos, B. E., Nikolaou, C. K. & Christodoulou, G. N. (2003). Analysis of polymorphisms in the alpha-subunit of the olfactory G-protein G(olf) in lithium-treated bipolar patients. *Psychiatric Genetics* **13**, 65–69.

Zintzaras, E. (2006). C677T and A1298C methylenetetrahydrofolate reductase gene polymorphisms in schizophrenia, bipolar disorder and depression: a meta-analysis of genetic association studies. *Psychiatric Genetics* **16**, 105–115.

Zobel, A., Jessen, F., von Widdern, O., Schuhmacher, A., Höfels, S., Metten, M., Rietschel, M., Scheef, L., Block, W., Becker, T., Schild, H. H., Maier, W. & Schwab, S. G. (2008). Unipolar depression and hippocampal volume: Impact of DNA sequence variants of the glucocorticoid receptor gene. *American Journal of Medical Genetics, B* (in press).

Zogel, C., Bohringer, S., Gross, S., Varon, R., Buiting, K. & Horsthemke, B. (2006). Identification of cis- and trans-acting factors possibly modifying the risk of epimutations on chromosome 15. *European Journal of Human Genetics* **14**, 752–758.

Zoghbi, H. Y. (2005). MeCP2 dysfunction in humans and mice. *Journal of Child Neurology* **20**, 736–740.

Zubenko, G. S., Maher, B., Hughes, H. B. 3rd, Zubenko, W. N., Stiffler, J. S., Kaplan, B. B. & Marazita, M. L. (2003). Genome-wide linkage survey for genetic loci that influence the development of depressive disorders in families with recurrent, early-onset, major depression. *American Journal of Medical Genetics B* **123**, 1–18.