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Genomic Sister-Disorders of Neurodevelopment:

an Evolutionary Approach

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Abstract

Genomic sister-disorders are defined here as diseases mediated by duplications versus deletions of the same region. Such disorders can provide unique information concerning the genomic underpinnings of human neurodevelopment because effects of diametric variation in gene copy number on cognitive and behavioral phenotypes can be inferred. We describe evidence from the literature on deletions versus duplications for the regions underlying the best-known human neurogenetic sister-disorders, including Williams syndrome, Velocardiofacial syndrome, and Smith-Magenis syndrome, as well as the X-chromosomal conditions Klinefelter and Turner syndromes. These data suggest that diametric copy-number alterations can, like diametric alterations to imprinted genes, generate contrasting phenotypes associated with autistic-spectrum and psychotic-spectrum conditions. Genomically-based perturbations to the development of the human social brain are thus apparently mediated to a notable degree by effects of variation in gene copy number. We also conducted the first analyses of positive selection for genes in the regions affected by these disorders. We found evidence consistent with adaptive evolution of protein-coding genes, or selective sweeps, for three of the four sets of sister-syndromes analyzed. These studies of selection facilitate identification of candidate genes for the phenotypes observed and lend a novel evolutionary dimension to the analysis of human cognitive architecture and neurogenetic disorders.

Keywords: gene copy-number variation, schizophrenia, autism, evolution, positive Darwinian selection

Introduction

Recent advances in genomic technology have allowed the efficient, large-scale characterization of gene copy number variation in the human genome (Emanuel and Saitta 2007; Beaudet and Belmont 2008; Korbel et al. 2008). Copy-number variants and polymorphisms, which can involve from one to dozens of genes, are increasingly being linked with human diseases (Sharp et al. 2006; McCarroll and Altschuler 2007), including neurodevelopmental conditions such as autism (Sebat et al. 2007) and schizophrenia (Cantor and Geschwind 2008; Mulle 2008), and they are currently the subject of intense interest from medical geneticists. An important role for genomic copy number variation in human evolution has also been postulated (Dumas et al. 2007), given that about one-third of over 24,000 genes analyzed have been found to exhibit copy-number variation among species of humans and other primates (Dumas et al. 2007), with humans and chimpanzees in particular differing by over 6% in their complements of genes (Demuth et al. 2006). However, the roles of selection and other processes in the evolution of such differences have only recently come under scrutiny (Nguyen et al. 2006, 2008; Cooper et al. 2007; Bonnefont et al. 2008; Korbel et al. 2008), and such evolutionary-genomic studies have yet to focus on neurogenetic conditions underlain by variation in gene copy number.

A key feature of gene copy-number variation is that it normally engenders both deletions and duplications of the same genomic region, generating individuals with one copy or three copies of the genes involved, in addition to the usual complement of two (Stankiewicz and Lupski 2002; Redon et al. 2006; Sharp et al. 2006; Beckmann et al. 2007). Such variation provides unique opportunities to analyze the phenotypic effects of variation in copy number, with naturally-occurring variants that may generate reduced, normal, and increased gene expression (or other effects), depending upon the nature of the alterations involved (e. g., Somerville et al. 2005; Meechan et al. 2007; Stranger et al. 2007; Molina et al. 2008; Buchanan and Scherer 2008). Similarly, variation in copy number for an entire chromosome is represented by Turner syndrome (45,X females) in comparison to Klinefelter syndrome (usually 47,XXY). In this case, the aneuploidies may cause variable expression of genes not subject to X inactivation, which comprise the two pseudoautosomal regions and 15-20% of other X-linked genes (Carrel and Willard 2005).

Diametric variation in gene copy number can generate what can be referred to as ‘sister’-disorders, pairs of disorders that are mediated by directly-opposite alterations to genomic regions that may result in diametric changes to gene expression or transcriptional-regulation patterns. In principle, sister-disorders might be expected to result in diametric phenotypes to the extent that genotype-phenotype mappings are relatively simple functions of gene copy number and diametric alterations to developmental-genetic pathways; for example, Bi et al.

(2007) reported hypoactivity vs hyperactivity in mice with the *RAI1* gene experimentally deleted vs duplicated.

Genomic and developmental alterations due to gene copy number variation are directly analogous to diametric, large-magnitude effects due to alterations of imprinted genes, which are usually expressed from only one chromosome but when dysregulated may exhibit either doubled or absent expression (Sha 2008). Genes subject to imprinting effects are expected from the kinship theory of imprinting to be involved in physiological and social-behavioral interactions between mothers and developing offspring (Haig 2004), and dysregulation of such systems, towards increased relative effects from either maternal or paternal genes, can mediate the development of psychotic-spectrum versus autistic-spectrum conditions respectively (Crespi and Badcock 2008). Alterations to genomic copy number and to imprinted gene expression may thus both lead, by different mechanisms, to large-scale, diametric genetic changes to neurodevelopment that may provide useful insights into the genomic architecture of psychiatric disorders involving the social brain.

The purpose of this review is to synthesize recent data and compare the major human neurogenetic sister-disorders recognized and characterized to date, to assess the extent to which they exhibit diametric phenotypes with regard to aspects of cognition and behavior. To achieve this goal, we have synthesized two main sources of information from the literature: (1) data on the phenotypes associated with the four best-known human genomic sister-disorders, and (2) data on linkages of the genes involved to psychiatric conditions. We also conducted the first tests of positive selection (adaptive evolution) for the genes salient to these syndromes, under the hypothesis that positively-selected genes or haplotypes in these regions have, historically, exhibited functional phenotypic effects on neurodevelopment, cognition and behavior that make them especially strong positional and functional candidates for the causes of variation in social-cognitive phenotypes observed across pairs of sister-disorders. Examples of genes exhibiting variants that affect cognition and psychiatric phenotypes, as well as showing evidence for recent positive selection in humans, include *FOXP2* (Enard et al. 2002), *EFHC2* (Weiss et al. 2007), and *MCPH1* (Evans et al. 2005; Lencz et al. 2007a), as well as positively-selected genes underlying schizophrenia (Crespi et al. 2007). Most generally, this paper is intended to facilitate the integration of evolutionary principles and methods into analyses of the genetic and genomic bases for human neurocognitive disorders and the architecture of non-clinical cognitive and behavioral phenotypes.

Methods

Literature review

PubMed and Web of Science were searched using the names of specific known syndromes, and the terms ‘deletion’ and ‘duplication’ in conjunction with the

names, genomic locations, and genes associated with the syndromes analyzed. Psychiatric and behavioral phenotypes associated with these syndromes and regions were searched using syndrome names, genomic regions, and genes, in conjunction with the names of the major psychiatric conditions. We also used the schizophrenia gene database (Allen et al. 2008) and Sullivan laboratory evidence project database (Konneker et al. 2008), to collect and synthesize evidence regarding the genetic bases of psychiatric phenotypes.

Analyses of positive selection

We used two measures of positive selection for the genes involved in the neurogenetic syndromes analyzed here: the iHS statistic developed by Voight et al. (2006), which quantifies the probabilities of recent selective sweeps for given genes and regions of the genome from human HapMap data, and the branch-site likelihood ratio tests of branch-site models implemented in PAML (Zhang et al. 2005), which allows inference of adaptive protein evolution. Methods in PAML followed those in Crespi et al. (2007), and we tested for selection along the human lineage, the human-chimp stem lineage, and the lineage at the origin of primates (the ancestral primate lineage leading to Catarhinni, including Old World monkeys, lesser apes and great apes), as these lineages exhibit phenotypic changes that we consider most salient to the evolution of social cognition.

Results

The primary genetic, genomic, and phenotypic features of the syndromes analyzed here are summarized in Tables 1 and 2. We describe each pair of sister-syndromes, summarize the evidence for positive selection on the genes involved, and synthesize the available information.

Smith-Magenis and Potocki-Lupski syndromes

Smith-Magenis syndrome is caused by a microdeletion of about 3.7 Mb at 17p11.2, or by mutations in the gene *RAI1* (retinoic acid inducible 1), the gene believed to underlie most of the behavioral, neurological and craniofacial traits found in this condition (Smith et al. 2005; Bi et al. 2006; Girirajan et al. 2006; Elsea and Girirajan 2008) (Table 1). Potocki-Lupski syndrome, due to duplication of this same region, has recently been identified and described (Potocki et al. 2007) and it appears to be due predominantly to increased copy number of *RAI1* (Molina et al. 2008).

Smith-Magenis syndrome

Behavioral and cognitive characteristics that have been described for Smith-Magenis syndrome include generalized complacency and lethargy in infancy, speech delay, stereotypies that involve self-hugging and 'licking and flipping' the pages of books, hyperactivity, impulsivity, aggression, self-injury, skin picking,

mood lability, and a friendly, affectionate personality (Smith et al. 2005; Girirajan et al. 2006; Gropman et al. 2007; Shelley and Robertson 2005; Martin et al. 2006). Traits ascribed to this condition also include a high level of social attention-seeking and friendliness with strangers, high sensitivity and irritability (Sarimski 2004), decreased sensitivity to pain (Bi et el. 2006; Shelley and Robertson 2005), high sociability as infants, with appealing smiles and lack of crying, and good eye contact and sense of humor as children (Smith et al. 1998). Individuals with Smith-Magenis syndrome exhibit moderate to severe mental retardation (Sarimski 2004), with a relative strength in verbal skills, but relatively weak sequential processing abilities (Dykens et al. 1997).

The psychiatric phenotypes associated with Smith-Magenis syndrome include a case report of 'mood disorder' involving extreme mood shifts, depression and 'explosive behavior' (Bersani et al. 2007), a case report of Tourette's syndrome (Shelley et al. 2007), and three cases of Smith-Magenis syndrome due to *RAI1* point mutations that involved 'bipolar episodes' in two individuals, and 'explosive tantrums' in another. Genome-scan studies have linked the 17p11.2 region with a variety of disorders, including schizophrenia (Williams et al. 2003; Bulayeva et al. 2005, 2007), ADHD (Ogdie et al. 2003) and autism (Trikalinos et al. 2006; Ylisaukko-oja et al. 2006), and cytogenetic anomalies of this region have been associated with autism (Lauritsen et al. 1999; Vorstman et al. 2006). Variation in the number of CAG repeats in the *RAI1* gene have been linked with drug responses in schizophrenics, but these variants were not associated with schizophrenia itself (Joober et al. 1999). However, polymorphisms in the two genes immediately proximal and distal to *RAI1*, *PEMT* and *SREBF1,* have recently been linked with schizophrenia (Liu et al. 2007; Le Hellard et al. 2008).

Potocki-Lupski syndrome

Potocki-Lupski syndrome is characterized by failure to thrive in infancy, developmental delay, speech impairments including absent speech, echolalia (repetition of heard speech), verbal apraxia, mild mental retardation, autistic features, epileptiform EEG, seizures, and hyperactivity (Potocki et al. 2007; Girirajan et al. 2007). Two individuals with this syndrome were formally diagnosed with autism (Potocki et al. 2007; Moog et al. 2004), and specific autistic features that have been described include decreased eye contact, motor mannerisms, sensory hypersensitivities or preoccupations, and repetitive behavior (Potocki et al. 2007). Potocki et al. (2007) suggested that nearly all patients with this syndrome exhibited features of autism spectrum disorders.

Evidence of positive selection

Using PAML, the *RAI1* gene was inferred as subject to positive selection for the primate origin lineage (Table 3), but not in the human or human-chimp lineages, nor in the human HapMap data.

Synthesis

Smith-Magenis and Potocki-Lupski syndromes are clear genomic sister-disorders that appear to exhibit diametric phenotypes with regard to sociability and verbal abilities. Although Potocki-Lupski syndrome is strongly associated with autism, the behavioral phenotype and psychiatric correlates of Smith-Magenis syndrome have yet to be analyzed systematically, although they appear to involve high levels of sociability and a high incidence of dysregulated mood. The presence of positive selection for the *RAI1* gene in the primate origin lineage is notable given that only 7 of 120 randomly-chosen 'control' genes involved in neurological functions have shown evidence of selection on this lineage (Crespi et al. 2007)

Velocardiofacial syndrome and duplications of the VCFS region

Velocardiofacial syndrome involves congenital malformation of the heart, face and limbs, usually due to a 3Mb deletion at 22q11.2 that contains over 30 genes (Feinstein et al. 2002; Maynard et al. 2002; Gothelf 2007; Kobrynski and Sullivan 2007; Gothelf et al. 2008; Prasad et al. 2008). A syndrome mediated by duplication of this region has recently been recognized, and is being better-characterized as more cases accumulate (Table 2).

Velocardiofacial syndrome

Velocardiofacial syndrome involves mild mental retardation, impaired language development, motor skills, and verbal working memory, and especially-limited abilities in reading comprehension, visual-spatial tasks and mathematics, in contrast to relatively well-preserved verbal skills (Bearden et al. 2001; Niklasson et al. 2001; Simon et al. 2005a, 2005b; Zinkstok and van Amelsvoort 2005; Lajiness-O'Neill et al. 2006). The behavioral phenotype of VCFS patients in childhood and early adolescence involves withdrawal, shyness, impulsiveness, inattentiveness (Dykens et al. 2000), emotional lability, angry outbursts, and high scores on scales of schizotypy (Baker and Skuse 2005), and anxiety, depression, social withdrawal and psychotic episodes (mainly auditory hallucinations) (Debbané et al. 2006). In adolescence and adulthood, about 30% of VCFS patients are diagnosed with schizophrenia, of a form with a relatively high incidence of positive symptoms (Murphy 2002; Vogels et al. 2002). This syndrome thus represents the most common genetic alteration known to mediate risk of schizophrenia (Bassett and Chow 2008), and one of the most penetrant causes of schizophrenia. VCFS also demonstrates notable similarities to schizophrenia in overall neurocognitive profile (Chow et al. 2006; Lewandowski et al. 2007), and brain structure in VCFS appears similar to that found in schizophrenia in some respects (Gothelf et al. 2007a,b, 2008). Gothelf (2007) describes the wider psychopathological profile of VCFS patients, as involving high rates of schizophrenia and schizoaffective disorder, bipolar disorder, depression, dysthymia, phobias, OCD, generalized anxiety disorder, panic disorder, ADHD, PDD-NOS, and psychotic symptoms.

Velocardiofacial syndrome has also been associated with autism spectrum conditions (e. g., Antshel et al. 2007; Kates et al. 2007), but such diagnoses appear to be based on superficial psychological similarities of autism or PDD-NOS with schizotypy and negative symptoms of schizophrenia that are not underlain by biological evidence (Eliez 2007; Feinstein and Singh 2007; Crespi and Badcock 2008; Sugihara et al. 2008).

Many of the physical features of VCFS are apparently mediated by haploinsufficiency of the *TBX1* gene (Zweier et al. 2007; Paylor et al. 2006), and several genes in the deletion region, notably *COMT, DGCR2, GNB1L, ProDH2*, *UFD1L* have been implicated in liability to schizophrenia among individuals without VCFS syndrome (Liu et al. 2002; Antshel et al. 2005; Wonodi et al. 2005; Gothelf et al. 2005; Shifman et al. 2006; Allen et al. 2008; Prasad et al. 2008; Williams et al. 2008). Given that over 30 genes are commonly deleted in this syndrome, the physical and psychiatric phenotypes appear to be mediated by reduced expression of multiple genes, whose relative importance for different phenotypes remains to be elucidated (Meechan et al. 2007).

VCFS-region duplications

About 30 cases of duplications of the VCFS region have thus far been reported (Mukaddes and Herguner 2007). These duplications are associated with phenotypes that include some combination of hyperactivity, attention deficits, learning disability, speech delays, impulsivity, seizures, and aggressive behavior (Mukaddes and Herguner 2007; Hassed et al. 2004a; Portnoï et al. 2005; Yobb et al. 2005; Alberti et al. 2007). This condition appears milder, more variable, and less distinctive than VCFS (de La Rochebrochard et al. 2006; Courtens et al. 2008; Ou et al. 2008], and it has not been ascertained independently of other conditions, although the duplication was found in 2 of 275 females referred for fragile X testing (Yobb et al. 2005).

Mukkades and Herguner (2007) presented a case report of severe autism associated with this duplication, with minimal speech, stereotypic behavior, and lack of eye contact, joint attention or play; the father of this patient exhibited the same duplication, and was described as introverted, obsessive and learning disabled. Hassed et al. (2004b) diagnosed a case of Asperger syndrome in an individual with this region duplicated, and Marshall et al. (2008) and Christian et al. (2008) each reported two cases of autistic individuals with the duplication. Although schizophrenia risk is increased ~30 fold in 22q11.2 deletion cases, a recent study reported no cases of 22q11.2 duplications in a sample of 190 patients with schizophrenia (Brunet et al. 2008).

Evidence of positive selection

Maximum-likelihood analyses detected four genes (of 29 analyzed) in the 3Mb typically-deleted VCFS region as subject to positive selection in the primate-origin lineage (Table 3). This proportion of genes inferred as selected (13.8%) is higher

than the proportion selected (5.8%) on this lineage among 120 'control' neurological-function genes (Crespi et al. 2007) but not significantly so ($\chi^2 = 2.16$, P = 0.14). One gene, *UFD1L*, showed evidence of selection along the human lineage. Of the six total genes inferred as selected with maximum likelihood, four of them (*CLDN5*, *COMT*, *GNB1L*, and *UFD1L*) have been associated with schizophrenia in one or more study (Allen et al. 2008; Williams et al. 2008).

Genes showing HapMap evidence of selection (P < 0.05 in one or more of the three populations) in recent human ancestry include *DGCR6* and a block of contiguous genes spanning *HIRA, MRPL40, UFD1L, CDC45L*, and *CLDN5*, with the former four of these genes showing evidence of selection for all three populations, which is very rare for HapMap-based selection studies (Voight et al. 2006).

Synthesis

VCFS is strongly associated with schizophrenia and related disorders, and the genetic and neuroanatomical correlates of these conditions. The phenotypes associated with VCFS-duplication syndrome are only now emerging, and robust evaluation of the behavioral and psychiatric features in this syndrome requires standardized study of a substantial number of cases. However, the association of autism with VCFS-region duplications in multiple studies is striking, and should motivate analyses that further evaluate the presence of autism-associated biological traits (such as macrocephaly and seizures) and well as cognitive profiles and formal DSM criteria.

Three lines of evidence: (1) the notable proportion of VCFS-region genes inferred as subject to positive selection for the primate-origin lineage, (2) the HapMap selection signal across a block of four genes in three populations, and (3) the finding that one schizophrenia-associated gene, *UFD1L*, shows evidence of positive selection for the human lineage from both HapMap and PAML analyses, suggest that some of the genes underlying the phenotypic effects of VCFS have undergone primate-specific and human-specific adaptive evolution with functional relevance to the etiologies of schizophrenia and autism.

Williams syndrome and Williams-syndrome region duplications

Williams syndrome is typically caused by deletion of a region of 7q11.23 that includes 25-30 genes (Tassabehji 2003), although analyses of atypical deletions have shown that a small subset of these genes is sufficient to elicit the main phenotypic traits involved. This deletion is mediated by low-copy-repeats that flank this region (Antonell et al. 2005), which also cause duplications that have recently been identified and characterized with regard to their phenotypic effects (Kirchhoff et al. 2007; Berg et al. 2007; Depienne et al. 2007).

Williams syndrome

Williams syndrome is characterized by a suite of behavioral and cognitive features that include hypersociality and inappropriate social engagement of strangers, fascination with faces and enhanced gazing into faces, hyperverbal speech with a relative strength in vocabulary and social-emotional language, increased empathy and acute attentiveness to the emotional states of others, and increased attention-seeking and affectionate behavior (Feinstein and Singh 2007; Pober and Dykens 1996; Doyle et al. 2004; Fidler et al. 2007; Porter et al. 2007; Martens et al. 2008).

Expressive language has been considered to be a notable relative strength in Williams syndrome, although the degree to which aspects of this trait are selectively enhanced, relative to IQ-matched controls, remains unclear (Meyer-Lindenberg et al. 2006; Brock 2007). However, verbal skills are clearly much better than visual-spatial abilities, which are selectively and strongly deficient (Porter and Coltheart 2005; Tager-Flusberg and Sullivan 2000; Reiss et al. 2004; Vicari et al. 2004). The overall cognitive profile of Williams syndrome has been described as similar to that found in VCFS, especially with regard to visual-spatial deficits but relatively spared verbal skills (Bearden et al. 2002).

Williams syndrome is also characterized by a set of behavioral and cognitive phenotypes related to psychiatric disorders, although few studies have addressed the issue of formal diagnoses of such disorders. Thus, Pober and Dykens (1996) noted high levels of anxiety, worry, preoccupation, crying and fearfulness, as well as depressive symptoms, in Williams syndrome individuals, and Dykens (2003), and Leyfer et al. (2006) and Meyer-Lindenberg et al. (2006) describe substantially-elevated rates of anxiety and phobias. In a study of 4-18 years olds, about 50% of individuals met DSM criteria for specific phobia (Leyfer et al. 2006) and frequencies of diagnosis were also high for ADHD (65%) and Generalized Anxiety Disorder (12%).

The presence of autism spectrum disorders in Williams syndrome is controversial (Lincoln et al. 2007; Riby and Hancock 2008). There have been several case reports of autism diagnoses in individuals with this syndrome (Herguner and Mukaddes 2006; Klein-Tasman et al. 2007), and both conditions can involve impaired pragmatics of language, unusual interests, impaired development of pointing and gesturing, and difficulties in forming and maintaining social relationships (Fidler et al. 2007; Klein-Tasman et al. 2007; Laws and Bishop 2004). However, theory of mind skills have been reported as comparable to matched controls in Williams syndrome, and levels of empathy appear to be elevated above controls (Tager-Flusberg and Sullivan 2000; Sullivan and Tager-Flusberg 1999). These findings, and such traits as fascination with faces and selective attention to social stimuli in Williams syndrome (Jones et al. 2000; Mervis et al. 2003), and the relative strengths in visual-spatial skills reported for autistics (Caron et al. 2004, 2006), have motivated the hypothesis that Williams syndrome and autism represent neurocognitive opposites (Peterson and Panksepp 2004). These views can be reconciled by considering the usual

Williams syndrome neurocognitive profile as involving a mosaic of behavioral traits, some of which are not uncommon on the autism spectrum while others are strikingly non-autistic (Lincoln et al. 2007).

Neuroanatomical contrasts between idiopathic autism and Williams syndrome that may be relevant to neurocognition include overall brain size smaller in Williams syndrome (Chiang et al. 2007) but larger on average in autism (e. g., Sacco et al. 2007), disproportionate reductions in white matter in Williams syndrome (Reiss et al. 2000) but increases in autism (Herbert et al. 2004), and a cerebellar vermis that is larger in Williams syndrome (Schmitt et al. 2001) but smaller in autism (Kaufmann et al. 2003). Additional biological evidence salient to autism and other psychiatric disorders in Williams syndrome is the presence, in the region that directly flanks the typical deletion and may show reduced gene expression as an apparent result (Merla et al. 2006), of the *AUTS2* gene, which exhibits mutations and a breakpoint associated with mental retardation and autism (Kalscheuer et al. 2007), and an SNP, D7S1816, strongly linked to lithium-responsive bipolar disorder in a genome scan (Turecki et al. 2001). This latter finding is of notable interest given that social impulsiveness and disinhibition, mediated in part by orbitofrontal cortex abnormalities, represent a prominent phenotype in both bipolar disorder and Williams syndrome (Altshuler et al. 2005; Meyer-Lindenberg et al. 2005; Porter et al. 2007). One gene in the Williams-syndrome region, *STX1A*, exhibits genetic variants that have been associated with schizophrenia (Wong et al. 2004); moreover, elevated expression of the *STX1A* gene, as well as a positive genetic association, have been reported for autism (Nakamura et al. 2008).

Genes in the Williams syndrome region that appear to be associated with core aspects of its neurocognitive profile, based on genotype-phenotype associations of variable-size deletions, mouse mutants for specific genes, and knowledge of gene function, include *CYLN2, Gtf2I, Gtf2IRD1*, and *LIMK1* (Hoogenraad et al. 2004; Gray et al. 2006; Edelmann et al. 2007; Young et al. 2008). Taken together, these studies suggest that several genes are involved, and affect different cognitive features of Williams syndrome: reduced copy-number of *Gft2RD1* has been implicated in decreased fear and increased social behavior in a mouse model (Young et al. 2008), *LIMK1* hemizygous mice exhibit impairments in spatial abilities (Meng et al. 2002), and both *CYLN2* and *LIMK1* hemizygous mice exhibit impaired learning (Hoogenraad et al. 2004).

Williams syndrome-region duplications

Berg et al. (2007) reviewed the phenotypic features of the 10 individuals reported thus far with duplications of the Williams syndrome region, who were ascertained by developmental delays. Weight, growth and length were highly variable, but three of seven individuals measured were at or above 90% percentile in head circumference; three of 10 individuals also exhibited seizures. All 10 cases involved severe to moderate speech delay and mental retardation, but visual-

spatial abilities were reported as spared in the five individuals evaluated for this phenotype (Berg et al. 2007). Four of seven individuals with behavioral information available showed stereotyped or repetitive behavior, and two of four individuals administered the ADOS met or exceeded the cutoff for ASD or autism. In previous case studies, Kirchhoff et al. (2007) reported a case of 'suspected Asperger syndrome', and Depienne et al. (2007) reported a case of autism identified from screening 206 patients with autism spectrum disorders for this duplication. Among cases described to date, Orellana et al. (2008) noted striking variability in phenotype, including good social skills in several individuals, but severe language delay as a highly consistent symptom.

Evidence of positive selection

None of the seven genes analyzed spanning *GTF2*I to *LIMK1* demonstrated statistical significance in maximum-likelihood analyses, although *RFC2* showed borderline non-significance ($0.05 < P < 0.06$) for the primate-origin lineage (Table 3). None of the genes showed gene-wide evidence of selection in the HapMap analyses. Haploinsufficiency of *RFC2* causes impaired *ATR*-mediated DNA damage response in Williams-syndrome cell lines, indicating that this gene may be responsible in part for the microcephaly and developmental delays found in Williams syndrome (O'Driscoll et al. 2007).

Synthesis

Somerville et al. (2005) and Berg et al. (2007) noted that the contrasting effects of deletions versus duplications for the Williams syndrome region provide evidence for strong effects of quantitative gene dosage variation on human language, sociality, and visual-spatial abilities. Expressive language in particular appears to be relatively-spared (compared to other cognitive functions) in Williams syndrome deletions, but it is strikingly-impaired in individuals with duplications for this region. The genetic basis of these contrasting phenotypes remains unclear, but to the extent that the variation in gene expression of *GTF2IRD1* modulates the observed effects on social-behavioral phenotypes in humans as well as mice (Young et al. 2008), it represents a strong functional candidate as a gene whose over-expression can cause autism and associated deficits in the development of language. Our inference of possible selection on the *RFC2* gene also suggests that this gene, thus far neglected in studies of Williams syndrome, may play a role in the evolution of primate neurodevelopment, brain size evolution, and in the etiology of this syndrome.

X chromosome aneuploidies

The most common human disorders involving sex chromosome are Turner syndrome (usually 45,X, or a mosaic of 45,X and 46,XX) in females (Good et al. 2003; Rovet 2004), and Klinefelter syndrome (usually 47,XXY) in males (Simpson

et al. 2003) (Table 1). Phenotypic effects of copy number variation for genes on the X chromosome are also mediated by whether genes are X-inactivated: genes in both pseudoautosomal regions of the X, and about 15-20% of other genes on this chromosome, are not X-inactivated (Carrel and Willard 2005), and should thus exhibit variable expression levels between 45,X, 46,XX, 46,XY, and 47,XXY individuals.

Turner syndrome (45,X)

The neurocognitive profile of adults with Turner syndrome is characterized by three main features: (1) normal or enhanced verbal skills, especially with regard to reading level, accuracy and comprehension, including a relatively-high incidence of hyperlexia, (2) notable impairments of visual-spatial skills as assayed, for example, via tests of mental rotation, block design, object assembly and mathematical ability, and (3) impaired social skills (Money 1993; Temple and Carney 1996; Nijhuis-van der Sanden et al. 2003; Lawrence et al. 2003; Molko et al. 2004; Temple 2006; Kesler 2007).

In addition to the traits described above, the behavioral profile of Turner syndrome females also involves high rates of impulsivity, hyperactivity and inattentiveness (Russell et al. 2006), and social anxiety (Kesler 2007). Turner syndrome females also commonly exhibit a set of behavioral and neurocognitive phenotypes including poor peer relationships, joint attention deficits, and reduced ability to interpret social cues (Donnelly et al. 2000), gaze aversion (Lawrence et al. 2003) and impaired recognition of fear (Weiss et al. 2007; Lawrence et al. 2003). This syndrome has also been reported to involve a significantly lower incidence of schizophrenia and bipolar disorder (considered together) (Mors et al. 2001) and a greatly-increased risk of autism (Skuse 2000, 2005; Skuse et al. 1997).

Klinefelter syndrome (47,XXY)

Klinefelter syndrome is associated with infantile hypotonia, hypogonadism, cryptorchidism, low birth weight, reduced length, and small head size, but increased adult height (Ratcliffe et al. 1990, 1994; Varrela 1984; Brandes and Mesrobian 2005; Ross et al. 2005; Giedd et al. 2007). The neurocognitive profile of Klinefelter syndrome is characterized by selective impairment of verbal abilities, especially in language processing, reading, and working verbal memory, with visual-spatial abilities relatively spared (Simpson et al. 2003; Graham et al. 1988; Geschwind et al. 2000; Boone et al. 2001; Fales et al. 2003; Itti et al. 2003, 2006; DeLisi et al. 2005). Money (1993) described this profile as the neurocognitive opposite of that found in Turner syndrome, with the core deficit in Klinefelter syndrome attributable to impaired “mental processing of sequence and synchrony in the temporal dimension, including the temporal dimension of language” and Boone et al. (2001) suggested that such verbal, left-hemisphere deficits are related to slow early brain development.

Psychiatric conditions associated with Klinefelter syndome include anxiety, depression, bipolar disorder, schizoaffective disorder and schizophrenia (DeLisi et al. 1994, 2005; Mizukami et al. 1989; Everman and Stoudemire 1994; van Rijn et al. 2005, 2006; Boks et al. 2007). Several studies have demonstrated that schizophrenia in particular shows a high prevalence in Klinefelter syndrome, with a four-fold to ten-fold increase (DeLisi et al. 1994, 2005; van Rijn et al. 2006). By contrast, Mors et al. (2001) reported similar rates of schizophrenia and bipolar disorder in Klinefelter syndrome compared to controls, and they attributed the results of DeLisi et al. (1994) to unspecified sampling biases. DeLisi et al. (2005) also noted that the neurocognitive profiles are similar in Klinefelter syndrome and idiopathic (cause-unknown) schizophrenia, and Van Rijn et al. (2006) showed that Klinefelter individuals scored significantly high than controls on scales of schizotypy. Klinefelter syndrome also involves an uneven profile of hyperfunctional emotional experience and reactivity, but impaired ability to identify and verbalize emotions, which resembles the pattern seen in schizophrenics (van Rijn 2005, 2006).

Genetic basis of sex-chromosome aneuploidy phenotypes

The Turner syndrome neurocognitive phenotype of visual-spatial deficits with preserved or enhanced verbal skills has been mapped to Xp22.3, in pseudoautosomal region 1 (PAR1) (Zinn et al. 2007; Ross et al. 2006). A strong positional and functional candidate for a gene in this region underlying at least one aspect of the Turner syndrome neurocognitive phenotype, and the contrasting pattern in Klinefelter syndrome of verbal deficits but spared visual-spatial abilities, has been identified by Vawter et al. (2007). These authors compared gene expression in 47,XXY vs 46,XY individuals, and found that the gene *GTPBP6*, in PAR1 at Xp22.33, exhibited significantly higher expression in 47,XXY males, and that within Klinefelter patients, higher expression of this gene was associated with significantly reduced verbal skills.

The altered rates of schizophrenia and autism in individuals with sex chromosome aneuploidies implicate effects of non-inactivated X-linked genes, or XY homologous genes, in these disorders. This hypothesis is supported by recent linkage of two loci in PAR1 (and the Turner syndrome neurocognitive region) with these neurodevelopmental disorders: the *CSF2RA-IL3RA* locus shows allelic variants associated with schizophrenia (Lencz et al. 2007b; Sun et al. 2008), and the *ASMT* gene bears variants associated with autism (Melke et al. 2008).

Evidence of positive selection

We used maximum likelihood analyses to test for positive selection on 20 genes in pseudoautosomal region I, as this region has been implicated in the phenotypic effects of Turner and Klinefelter syndromes. Positive selection was inferred for four genes, *ASMTL, GTPBP6, IL3RA*, and *P2RY8*, all on the primate-origin lineage (Table 3). This proportion of genes inferred as selected (20%) is

significantly higher than the proportion selected (5.8%) on this lineage among 120 'control' neurological-function genes (Crespi et al. 2007) (χ^2 = 5.03, P = 0.025).

Synthesis

Turner syndrome and Klinefelter syndrome demonstrate a clear diametric contrast with regard to verbal and visual-spatial skills, with Turner syndrome characterized by good verbal skills but greatly-impaired visual-spatial abilities and Klinefelter syndrome individuals impaired verbally but with visual-spatial abilities spared (Money 1993; DeLisi et al. 2005). These syndromes also involve notably-different associations with psychiatric disorders, as Turner syndrome individuals exhibit an elevated incidence of autism and autistic traits, but Klinefelter syndrome involves increased rates of schizophrenia and related disorders. The localization of genetic effects on verbal skills, visual-spatial skills, and some psychiatric disorders to non-inactivated X-linked genes suggest that altered dosages of such genes underlie the contrasting neurocognitive phenotypes of Turner and Klinefelter syndromes. These findings have important implications for the evolution of sexual dimorphism as well as the developmental and neurological bases of neurogenetic syndromes, since non-inactivated X-linked genes are expected to differ in dosage between males and females (Craig et al. 2004; Davies and Wilkinson 2006; Crespi 2008a).

The inference of positive selection on PAR1-region genes that influence verbal ability (*GTPBP6*, Vawter et al. 2007) and schizophrenia risk (*IL3RA*, Lencz et al. 2007b; Sun et al. 2008) are striking, especially given that *IL3RA* is the only PAR1 gene thus far implicated in schizophrenia. The function of the *ASMTL* gene remains unclear, but part of this gene is highly homologous with the autism-associated gene *ASMT* (Ried et al. 1998; Melke et al. 2008).

Discussion

Genomic sister-disorders provide unique opportunities to assess the roles of gene copy number variation in human development and disease. For the set of neurogenetic sister-disorders analyzed here, the clearest overall pattern is that one of the pairs has been commonly associated with autism spectrum conditions (Table 2), a finding that concurs with the results of recent studies showing that a notable proportion of cases of autism can be ascribed to effects of copy-number variants (Sebat et al. 2007; Christian et al. 2008; Marshall et al. 2008; Mefford et al. 2008; Miller et al. 2008). By contrast, the sister-disorders of the autism-associated conditions noted in Table 2 appear to involve a suite of phenotypic traits that are characteristic of what has been termed the schizophrenia spectrum or psychotic spectrum, which is exemplified by the set of psychological and psychiatric conditions described for Velocardiofacial syndrome by Gothelf (2007, Table 2), as well as for Klinefelter syndrome (DeLisi et al. 2005; Mizukami et al. 1989; Everman and Stoudemire 1994; van Rijn et al. 2005, 2006; Boks et al. 2007); these conditions include schizophrenia, schizoaffective disorder, bipolar

disorder, unipolar depression, schizotypy, phobias, generalized anxiety disorder, panic disorders, and psychotic symptoms. The former five conditions have been demonstrated to exhibit strong patterns of overlap with regard to their genetic underpinnings (Craddock and Forty 2006; Potash 2006; Van Den Bogaert et al. 2006; Blackwood et al. 2007; Fanous et al. 2007), and rates of comorbidity of anxiety and phobias with schizophrenia, schizoaffective disorder, and bipolar disorder are on the order of 40-60% (Cosoff and Hafner 1998; Huppert and Smith 2005; Zutshi et al. 2006). As for autism, the etiology of schizophrenia is mediated, to a notable degree, by copy number variation across a considerable number of genomic regions (Cantor and Geschwind 2008; Mulle 2008).

The inference that pairs of neurogenetic sister-disorders tend to involve autistic-spectrum versus psychotic-spectrum phenotypes implies that human cognitive architecture may be structured along a continuum of social brain development from hypo-development in autism, to so-called normality, to hyper-development in psychosis, which is revealed most clearly by diametric perturbations to genes affecting development and evolution of the social brain (Crespi and Badcock 2008). Evidence of such a pattern has also been reported for perturbations that involve genomic imprinting, which are expected under the kinship theory of imprinting (Haig 2004) to involve social interactions and social brain development (Crespi and Badcock 2008; Crespi 2008b). The pattern for copy-number effects described here suggests that not only relatively well-known neurogenetic sister-disorders, but also disorders due to smaller-scale and less well-characterized copy number polymorphisms or variants, may mediate similarly-contrasting cognitive and psychiatric phenotypes. More generally, primate and human evolution has presumably involved the selective accumulation of alleles mediating development of an increasingly complex and sophisticated social brain, which in humans may be perturbed towards either hypo-development in autistic-spectrum conditions, or hyper-development in psychotic-spectrum conditions, where language, causal thinking, social emotionality, and self-consciousness are specifically dysregulated (Burns 2004; Crow 2008; Crespi and Badcock 2008).

The primary caveat regarding our interpretation of these data on neurogenetic sister-disorders is that some genomic alterations, such as VCFS duplications and Williams-syndrome region duplications, involve variable phenotypes that have yet to be characterized thoroughly in terms of behavioral phenotypes (Feinstein and Singh 2007), or categorized in relation to formal psychiatric conditions. Moreover, the behavioral phenotypes of Smith-Magenis syndrome and Williams syndrome involve high levels of sociability, which contrast with notable levels of autistic spectrum phenotypes in their respective duplications but require further study to evaluate in terms of psychotic spectrum conditions such as phobias and mood lability. Further analyses of neurogenetic sister-disorders might usefully focus on dissecting genotype-phenotype correlations in such cases, also taking account of potentially-causative variability in patterns of

gene expression (e. g., Meechan et al. 2007). An important consideration for such studies is the presence of superficial psychological similarities between autism and some manifestations of schizophrenia (such as childhood premorbid phenotypes and negative symptoms) that are not underlain by clearly-shared biological causes and may thus obfuscate interpretation of phenotypes in terms of psychiatric conditions (Feinstein and Singh 2007; Crespi 2008b; Crespi and Badcock 2008; Gothelf et al. 2008; Sugihara et al. 2008; see also Kates et al. 2007). Such similarities are especially problematic in studies of pediatric populations (e. g., Mefford et al. 2008; Weiss et al. 2008), given that children premorbid for schizophrenia spectrum conditions commonly exhibit deficits in social phenotypes (e. g., McClellan et al. 2003) that can lead to incorrect diagnoses of autism.

To the extent that individuals with diametric genomic alterations exhibit diametric phenotypes, the genes mediating these phenotypes can be identified and characterized using a variety of methods including analyses of atypical deletions and single-gene mutations, mouse mutants, association studies relating variation in specific genes to salient traits, and studies of gene function and expression levels (e. g. Girirajan et al. 2008). In this study, we have analyzed how the salient genes have evolved along the lineages leading to humans and other primates, and detected signals of positive selection on a notable number of the genes that are duplicated or deleted in neurogenetic sister-disorders. Based on combined information from studies of genetics, development, mouse models, and positive selection, several genes, including *GTPBP6, IL3RA, RAI1*, and *UFD1L*, can be highlighted as especially-strong candidates for single genes whose altered expression may mediate the development of autistic and psychotic spectrum conditions, and social cognition more generally. To the extent that genes such as these have been subject to selection in the context of lower or higher levels of expression during primate evolution (e. g. Khaitovich et al. 2006), their altered expression may thus be especially likely, compared to other genes, to cause maladaptive effects on neurodevelopment that affect social-behavioral phenotypes. This hypothesis is amenable to further study via analyses of the molecular and phenotypic effects of haplotypes or amino acids inferred as selected. Our finding that positive selection was especially-prominent along the primate-origin lineage suggests that molecular-evolutionary changes underlying important features of complex social cognition were established well before separation of the human lineage. This hypothesis is consistent with complex patterns of genomic copy-number change in primates for PAR1 (Helena Mangs and Morris 2007), the VCFS region (Shaikh et al. 2000; Babcock et al. 2007), and the Williams-syndrome region (Antonell et al. 2005), and with findings from comparative primatology (e. g., Zuberbühler 2006), but it requires more-detailed comparative-genomic analyses.

Most generally, our study shows how evolutionary perspectives and tools can provide novel insights into the genetic bases of human neurodevelopment and

cognitive architecture, and complement studies based in psychiatry, neuroscience, and molecular and disease genetics. In particular, studies of positive selection can highlight genes or genomic regions with potential functional effects on medically-relevant phenotypes, and models of cognitive architecture, derived from inferences regarding the evolution of human sociality, can structure the interpretation of psychiatric phenotypes and the search for their proximate causes. Such insights from evolutionary biology are based on integration of two large research areas, the evolution of humans and the etiology of human neurogenetic conditions, that have thus far developed in considerable isolation.

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TABLE 1. Genomic sister-disorders of human growth, development, cognition and behavior, with descriptions of their genetic bases

Syndrome name or description	Primary genomic alteration and genes implicated
Smith-Magenis	Hemizygous deletion of region at 17p11.2 including *RAI1* gene; *RAI1* mutations (Gropman et al. 2007)
Potocki-Lupski	Duplication of Smith-Magenis region (Potocki et al. 2007)
VCFS region deletion	Deletion of ~30 genes at 22q11.2, effects from *COMT, DGCR2, GNB1L, TBX1, UFD1L*, other genes (Gothelf 2007; Meechan et al. 2007)
VCFS region duplication	Duplication of 22q11.2 region (Mukaddes and Herguner 2007)
Williams-syndrome region deletion	Hemizygous deletion of over 25 genes at 7q11.23; effects from *CYLN2, GTF2I, GTF2IRD1, LIMK1*, other genes (Tassabehji 2003; Gray et al. 2006; Edelmann et al. 2007; Young et al. 2008)
Williams-syndrome region duplication	Duplication of 7q11.23 region (Berg et al. 2007)

Syndrome name or description	Primary genomic alteration and genes implicated
Klinefelter	One or more excess X chromosomes; Increased expression of PAR1, PAR2 genes & other non X-inactivated genes (DeLisi et al. 2005; Vawter et al. 2007)
Turner	All or part of X chromosome lost (Sybert and McCauley 2004); haploinsufficiency of PAR1, PAR2 genes & other non X-inactivated genes (Lynn and Davies 2007); neurocognitive phenotype maps to Xp22.3 (Zinn et al. 2007)

Table 2. Genomic sister-disorders categorized into two groups, each of which shares a suite of partially-overlapping phenotypic traits. 'Psychotic-spectrum' syndromes involve an increased incidence of psychotic-spectrum psychatric conditions (mainly schizophrenia, schizoaffective disorder, bipolar disorder, depression, anxiety, and phobias), and 'autistic-spectrum' syndromes involve autistic traits, autism and Asperger syndrome.

Psychotic-spectrum syndromes	Autistic-spectrum syndromes
Smith-Magenis -High levels of sociability (Sarimski 2004; Smith et al. 1998) -Relative strength in verbal skills (Dykens et al. 1997) -Case reports of 'bipolar episodes' (Girirajan et al. 2006) -Case report of mood disorder (Bersani et al. 2007)	Potocki-Lupski -High rates of autism and autistic behavior (Moog et al. 2004; Potocki et al. 2007)
Velocardiofacial -Better verbal than visual-spatial skills (Bearden et al. 2001; Lajiness-O'Neill et al. 2006) -High rates of schizophrenia, schizoaffective disorders, bipolar, depression, anxiety, phobia (Gothelf 2007)	Velocardiofacial-region duplications -Hyperactivity, attention deficits, anxiety, depression, seizures, speech problems, impulsivity (Yobb et al. 2005; Alberti et al. 2007; Ensenauer et al. 2003) -Case report of autism (Mukaddes and Herguner 2007) -Case report of Asperger syndrome (Hassed et al. 2004b) -Two cases of autism (Marshall et al. 2008) -Two cases of autism (Christian et al. 2008)

Psychotic-spectrum syndromes	Autistic-spectrum syndromes
Williams -Better verbal than visual-spatial skills (Vicari et al. 2004) -Hypersociability, fascination with faces (Doyle et al. 2004) -Dyslexia (Temple 2006) -High rates of anxiety and phobias (Meyer-Lindenberg et al. 2006; Lincoln et al. 2007)	Williams-region duplications -Severe language impairment, visual-spatial skills spared (Berg et al. 2007) -High rates of autism and autistic behavior (Berg et al. 2007; Depienne et al. 2007)
Klinefelter -Dyslexia (Geschwind et al. 2000) -Poor verbal skills, preserved visual-spatial skills (Money 1993; DeLisi et al. 2005) -High rates of schizophrenia, schizoaffective disorder, schizotypy, bipolar disorder, anxiety, depression DeLisi et al. 2005; van Rijn et al. 2005; Boks et al. 2007) [1]	Turner -Hyperlexia (Temple and Carney 1996) -Good verbal skills, impaired visual-spatial skills (Money 1993; Kesler 2007) -Gaze aversion (Lawrence et al. 2003) -High rates of autism and autistic traits in maternal-X cases (Skuse et al. 1997) -Reduced incidence of schizophrenia plus bipolar disorder (Mors et al. 2001)

Idiopathic schizophrenia	Idiopathic autism
-Low birth weight (Nilsson et al. 2005; Wahlbeck et al. 2001) -Slow growth (Niemi et al. 2005) -Small head, brain size (Gur et al. 2007) -Better verbal than visual-spatial skills (Kravariti et al. 2006) -Dyslexia (Bersani et al. 2006; Revheim et al. 2006) -Overlap in genetic basis with bipolar disorder, major depression, and schizotypy (Craddock and Forty 2006; Van Den Bogaert et al. 2006; Blackwood et al. 2007; Fanous et al. 2007; Potash 2006)	-High or average birth weight (Sacco et al. 2008; Mraz et al. 2007; Sugie et al. 2005) -Overgrowth, faster body growth (Dissanayake et al. 2006; Fukumoto et al. 2008; Mills et al. 2007; Mraz et al. 2007) -Macrocephaly (Lainhart et al. 2006; Stanfield et al. 2008) -Hyperlexia (Newman et al. 2007) -Better visual-spatial than verbal skills in subset of cases (Caron et al. 2006)

[1] Two case studies have described autism or autism-spectrum disorders (PDD-NOS) in Klinefelter individuals (Jha et al. 2007; Merhar and Manning-Courtney 2007). These cases were characterized by speech delay and introversion, with no evidence of restricted interests or motor stereotypies in the four children described.

Table 3. Evidence for positive selection on genes associated with human neurogenetic sister-disorders, from maximum likelihood analyses. We focused on putatively-causative genes where these were known from studies of single-gene mutations or atypical deletions (in Williams syndrome and Smith-Magenis syndrome), but where the causative genes were unknown (for Klinefelter, Turner, and Velocardiofacial syndromes) we analyzed all of the genes in the affected regions. * = P < 0.05, ** = P < 0.01.

Gene	Gene Symbol	Lineage	-2ΔLn	Positively Selected Codons (posterior probability)
Pseudoautosomal Region 1				
Interleukin 3 receptor, alpha	*IL3RA*	primate	5.32*	none
GTP binding protein 6	*GTPBP6*	primate	8.04**	Leu 125 (.982)
Acetylserotonin O-methyltransferase-like	*ASTML*	primate	6.20*	none
Purinergic receptor P2Y, G-protein coupled, 8	*P2R8Y*	primate	9.82**	none
Velocardiofacial syndrome				
claudin 5	*CLDN5*	primate	6.70**	none
Guanine nucleotide binding protein, beta polypeptide 1-like	*GNB1L*	primate	4.86*	Ser 119 (.961)
Zinc finger protein 74	*ZNF74*	primate	9.94**	Ala 84 (.961) Thr 321 (.991)
Catechol-O-methyltransferase	*COMT*	primate	8.02**	Pro 324 (.972)
Ubiquitin fusion degradation 1 like	*UFD1L*	human	6.58*	His 221 (.983)
Smith-Magenis syndrome				
Retinoic acid induced 1	*RAI1*	primate	5.68*	none
Williams syndrome				
Replication factor C 2	*RFC2*	primate	3.78	none