

# Diametric gene-dosage effects as windows into neurogenetic architecture

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Gene expression can be modulated in two opposite directions, towards higher or lower amounts of product. How do diametric changes in gene dosage influence neurological development and function? Recent studies of transgenic and knockout mouse models, genomic copy-number variants, imprinted-gene expression alterations, and sex-chromosome aneuploidies are revealing examples of 'mirror-extreme' brain and behavior phenotypes, which provide unique insights into neurodevelopmental architecture. These convergent studies quantitatively connect gene dosages with specific trajectories and outcomes, with important implications for the experimental dissection of normal neurological functions, the genetic analysis of psychiatric disorders, the development of pharmacological therapies, and mechanisms for the evolution of human brain and behavior.

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## Introduction

Causally connecting genetic variation with neurological and behavioral variation remains one of the most challenging enterprises in science, due mainly to the complexities of gene action, gene interaction, and neurodevelopment. The discipline of neurogenetics centers on parsing such intricacies using research systems tractable enough for analysis, yet realistic enough to generate insights relevant to nature. A key feature of gene action, in its relationships with phenotypes, is dosage sensitivity: whether increases and/or decreases in gene expression are reflected in concomitant, quantitative phenotypic changes [1]. To the extent that gene-phenotype relations exhibit linear dosage sensitivity, genetic variation can be directly, causally and quantitatively connected with neurological traits, robustly revealing adaptive gene functions rather than pathological,

secondary byproducts of perturbations. One-to-one dosage-phenotype mappings also reveal neurodevelopmental architecture: what phenotypes, at what levels from synapse, to modular function, to higher-order connectivity, and to cognition and emotion, genes with neurological effects actually underpin. Understanding this architecture is fundamental to not just how the brain works and how it has evolved, but also to the causes and forms of neurological and psychiatric disorders [2].

The purpose of this article is to highlight a set of genomic and genetic alterations that are providing novel insights into neurogenetic causation, because diametric alterations to gene dosages mirror diametric alterations to phenotypes. Such loci are dosage sensitive with linear connections to brain and behavior traits that are chosen *a priori* or emerge from larger-scale phenomic study. I first review the range of gene-dosage effects on neurological phenotypes, and their possible physiological causes. I then focus on recent studies that have demonstrated diametric gene-dosage effects, at scales from gene to chromosome, and discuss implications for future work.

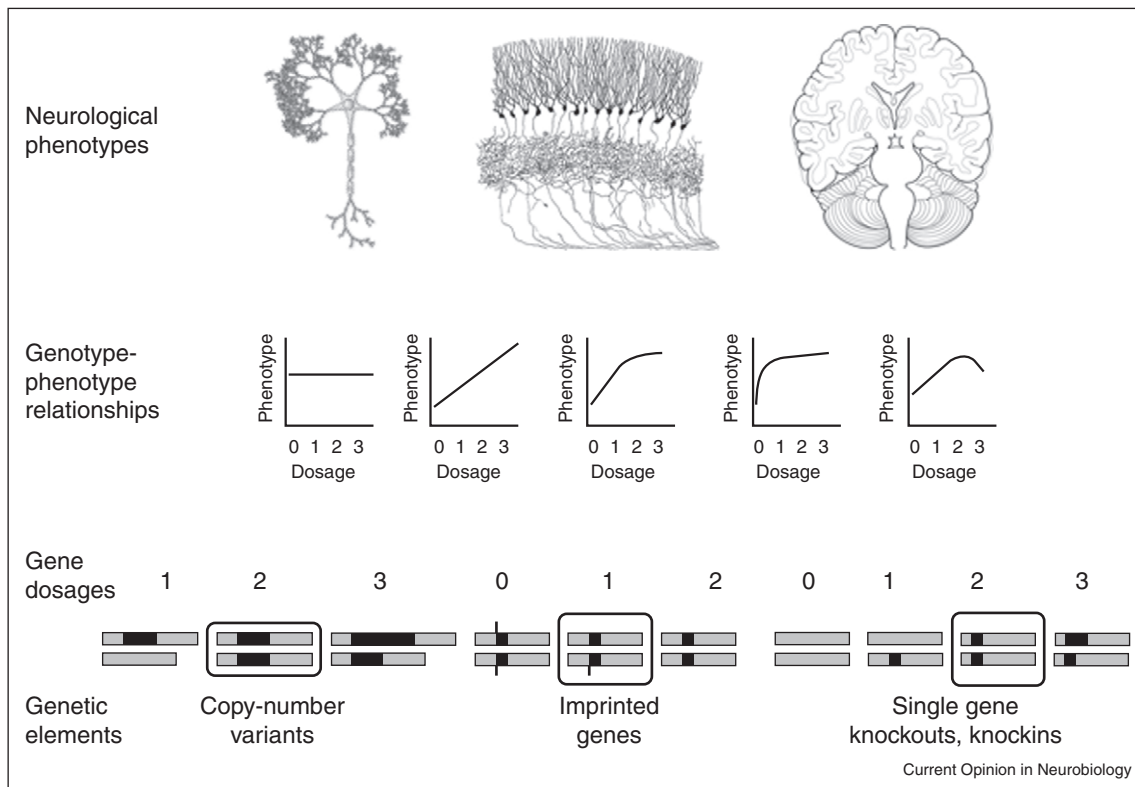
## Gene dosage effects in neurogenetics

Gene dosage effects mediate between genetic alterations and neurological-scale phenotypes. Such effects may be either flat (canalized), linear (codominant), curvilinear (dominant/recessive), or inverted-U shaped, depending on the genes and phenotypes under consideration (Figure 1). Variation in gene dosage effects is known to depend partly on gene function. For example, transcription factors and tissue-specific proteins synthesized in large quantities commonly show codominant effects, whereas metabolic enzymes often exhibit dominance and recessiveness [1,3]. Such general associations of function with dosage-effect remain purely statistical, however, such that for any given gene, experimental or natural-variation studies are essential to determine if and how dosages affect phenotypes. Ideally, such studies involve bidirectional changes from normality, since gene dosages, and developmental/physiological systems, can be perturbed naturally or experimentally in two opposite directions. Over the past 5–10 years, an increasing set of studies has emerged providing such crucial evidence.

## Single-gene diametric alterations

Gene knockout mice have been a mainstay of neurobiological study for many years, but engineering of mice to overexpress specific genes or transcripts has received much less attention until recently. Direct comparisons

Figure 1



Alternative mappings between genetic alterations, gene dosages, and neurological phenotypic changes. Normal genetic-elements states are enclosed within boxes, and a set of representative genotype–phenotype relationships are depicted. Linear dosage–phenotype mappings involve diametric phenotypes, which indicates direct, quantitative effects of gene products on development and function.

of underexpressing and overexpressing mouse models have revealed a set of genes for which opposite alterations yield opposite phenotypes, as well as patterns of genotype–phenotype relation that provide important new insights into neurogenetic processes (Table 1). Phenotypes showing diametric alterations with increases versus decreases in gene expression, in mouse models and/or humans, include (1) head/brain size (DYRK1A, FMR1); (2) anxiety (alpha-CaMKII, BDNF, FMR1, RAI1); (3) memory (AC1, COMT, CREB); (4) activity levels (FMRP, RAI1); (5) responsivity to stress (COMT); (6) seizure susceptibility (BDNF); (7) social interaction (FMR1, GTF2I, NR2B, SEPT5); (8) dominance/aggression (RAI1); and (9) prepulse inhibition (RELN). This set of phenotypes reflects, to a large degree, neurologically salient, and measurable, mouse-model traits, which commonly vary among strains as well as between males and females. Given that for only a subset of the genes in Table 1 have overexpression and underexpression studies been conducted using the same strains, and the exact same protocols, a priority for future work will involve standardized behavioral analysis of mice subject to diametric gene-dosage alterations, coupled with neurophysiological studies of proposed mechanisms that mediate linear

genotype–phenotype mappings. For mouse disease models, such studies are central to determining the degree to which pathways affected by human single-gene alterations (such as SNPs, SNVs and CNVs associated with human neurodevelopmental conditions) can be regulated pharmacologically, and assessing the effects of overmodulation or undermodulation of gene dosages. Mouse models of underexpression versus overexpression indeed provide excellent opportunities for evaluating potential therapies that involve gene-dosage modulation: for example, overexpression of RELN protects against the expression of schizophrenia-related symptoms in mice [4•] possibly via downregulation of NR2B-mediated neurotransmission.

### Copy-number variation

Copy number variants (CNVs) represent deletions or duplications of the same genomic region, which may span a single gene or many dozens of genes [5–7]. Such variation has recently been documented as a ubiquitous feature of eukaryotic genomes, and has been demonstrated to cause, at least approximately, the expected variation in gene dosages, usually deviating from two (normal) to one (deletion) or three (duplication) [8•].

**Table 1****Genes whose underexpression versus overexpression generates diametric changes to neurologically relevant phenotypes, in mice and/or humans**

Gene (human symbol)	Mouse alterations and phenotypes	Relevance to human phenotypes and disease	Comments	References
AC1	Overexpression leads to enhanced hippocampal LTP and better memory functions; knockouts show reduced spatial memory and LTP	AC1 is neuron-specific $CA^{++}$ -stimulated adenylyl cyclase involved in cAMP signalling, learning and memory	Memory enhancements are task specific and age-dependent	Garelick [51]
BDNF	Lower anxiety-like behavior and increased seizure susceptibility in transgenic overexpressing mice; opposite in heterozygote knockout mice	Decreased serum BDNF in epilepsy; links of BDNF with anxiety	Some overexpression effects sex specific; different knockout studies show heterogeneous results	Bianchin [52] Papaleo [53] Bath [54]
CAMK2A	Overexpression in forebrain leads to increase in suite of anxiety-related behavior and offensive aggression; knockout shows lower anxiety and higher defensive aggression	SNPs linked to conduct disorder	Overexpression and underexpression in mice also lead to learning and memory deficits	Hasegawa [55] Jian [56]
COMT	Overexpression results in impaired working memory, blunted stress responses and pain sensitivity; underexpression (null) shows reverse	Polymorphisms involved in metabolism of catecholamines, including dopamine, epinephrine and norepinephrine, associated with many disease and psychological phenotypes	Authors suggest role of COMT in tradeoff between cognitive and affective functions	Papaleo [57]
CREB1	Overexpression in forebrain associated with enhanced memory functions; loss of function impairs memory consolidation	Genetic variation associated with mood disorders; target for memory enhancement in Alzheimer's	Gene dosage effects appear specific to memory consolidation (long-term but not short-term memory)	Suzuki [58]
DYRK1A	Gene copy number directly related to (1) brain size (positively); and (2) neuron density, positively in thalamic nuclei, but negatively in cortex	Deletion or truncation in humans associated with microcephaly; gene overexpressed in Down syndrome, associated with Alzheimer's syndrome	Overexpression reduces proliferation and increases differentiation of neural progenitor cells	Oegema [59] Yabut [60] Guedj [61*]
FMR1	Overexpression associated with hypoactivity, low exploratory behavior; knockout (null) shows reverse	Loss of expression causes Fragile X syndrome, which involves hyperactivity and altered levels of anxiety	In humans, Fragile X characterized by macrocephaly, and duplications including FMR1 gene can involve microcephaly	Peier [62] Rio [63]
GTF2I	Overexpression involves increased social anxiety (separation anxiety); underexpression associated with decreased social anxiety (increased social interaction)	Deletion associated with hypersociality, and expressive language phenotype in Williams syndrome; duplication associated with ASD, language impairment, and high separation anxiety (with regard to parent)	Social behavior tests differ between studies; GTF2I shows higher expression from paternal chromosome, and increase in expression along human lineage	Sikela [64] Collette [65] Sakurai [66] Mervis [67*]
NR2B	Overexpression leads to enhanced social recognition memory; replacement of NR2B by NR2A leads to social deficits	Core subunit component of NMDA receptor, whose function is central to schizophrenia, other conditions	NR2B knockout is lethal	Wang [68] Jacobs [69*]

**Table 1** (Continued)

Gene (human symbol)	Mouse alterations and phenotypes	Relevance to human phenotypes and disease	Comments	References
RAI1	Overexpressing mice hypoactive; lower-expression mice hyperactive; decreased anxiety and dominance-like behavior in 17p11.2 deletion mouse model, opposite changes in duplication	Primary gene involved in Smith–Magenis syndrome (deletion or loss of function) and reciprocal duplication	Effects of reduced expression differ according to mouse model studied; comparison of mouse-model with human phenotypes challenging	Bi [70] Girirajan [71] Carmona-Mora [72]
RELN	Overexpression in mice protects against PPI deficits caused by NMDA antagonist; heterozygous knockouts show PPI deficits in some studies	Codes for large secreted extracellular glycoprotein that mediates neuronal migration; genetic variation has been linked with schizophrenia and autism	Extensive variation found between studies in PPI-deficit effects for heterozygote knockout mice	Teixeira [4*]
SEPT5	Overexpression involves increased social interactions; reduced expression shows reverse	Gene is deleted in 22q11.2 deletions (Velocardiofacial syndrome), with high rates of schizophrenia	Rearing of C57BL/6J mice under low stress led to higher SEPT5 expression	Harper [73*]

Over the past five years, a suite of studies has linked rare copy-number variants with liability to psychiatric and cognitive conditions, especially autism, schizophrenia, and intellectual disability [5–7,9,10\*]. Sets of individuals with these and some other conditions show evidence of increased burdens of rare CNVs, especially large deletions and *de novo* variants [10\*,11]. However, specific CNVs show notably variable penetrance and expressivity, sometimes being found in apparently unaffected individuals, and sometimes affecting risk of multiple conditions [10\*,12].

Recently, opposite phenotypes, some of which have been related to these two conditions, have been reported in comparisons of individuals with rare deletions versus duplications of the same genomic regions. At two loci, 1q21.1 and 16p11.2, reciprocal deletions versus duplications have been associated with diametric differences in human head size. For 1q21.1, Brunetti-Pierri *et al.* [13] and Mefford *et al.* [6] have shown that individuals with a 1.35 Mb deletion exhibit a notable incidence of microcephaly, while individuals with a duplication of the same region demonstrate macrocephaly. Of the genes in this deletion/duplication interval, one, a paralog of the ciliary-function HYDIN gene, has been independently linked with cerebral cortex growth [14], and represents a strong candidate for these diametric gene-dosage effects.

At 16p11.2, which harbors a reciprocal 600 kb deletion/duplication, McCarthy *et al.* [5] showed that head circumference was significantly larger in individuals with the deletion than with the duplication. Shinawi *et al.* [7] extended these observations by showing that individuals with the microdeletion exhibited a high incidence of absolute or relative (adjusted for body size) macrocephaly, whereas individuals with microduplications exhibited head circumference statistically smaller than in

controls. A recent paper by Golzio *et al.* [15\*\*] has identified a single gene as the apparent cause of these ‘mirrored neuroanatomical phenotypes’ owing to CNVs at this locus. In this study, each human transcript, from the 29 deleted or duplicated genes in the 16p11.2 human CNV interval, was variably expressed in zebra fish; of these genes, alterations to only the KCTD13 gene recapitulated the human microcephaly–macrocephaly variation. Analysis of early neurodevelopment in zebra fish and mice also demonstrated that this cerebral cortex growth variation was mediated by changes to neuronal progenitor cell proliferation and/or apoptosis.

These similar findings for 1q21.1 and 16p11.2 are of particular interest because the head-size variation found in deletions versus duplications appears to parallel links of these CNVs to risks of autism and schizophrenia. Thus, both of the CNVs involving larger head size (duplications of 1q21.1 and deletions of 16p11.2) have been strongly associated with increased risk of autism [16], findings that corroborate well-replicated reports of larger head size during childhood in idiopathic autism [17]. By contrast, the CNVs connected with smaller head size (deletions of 1q21.1 and duplications of 16p11.2) show clear associations with higher risk of schizophrenia [16], a condition for which reduced head and brain size have been identified as correlates in idiopathic cases as well [18]. Taken together, these results suggest that variation in number of copies, and expression levels, of dosage-sensitive genes affecting brain growth may exert strong effects on liability to neurodevelopmental disorders.

Reciprocal alterations of CNVs at 16p11.2 and a different locus, 17p11.2, mediate a set of neurophysiological as well as neuroanatomical and psychiatric phenotypes. At both of these loci, deletions are associated with obesity, higher body mass index, and metabolic, energy-balance

phenotypes resembling the human 'metabolic syndrome', whereas duplications are associated with the reverse [19\*,20\*\*]. For 16p11.2, these alterations have been related to hyperphagia compared to low, highly selective food intake. By contrast, for 17q11.2, analysis of mouse models of deletions versus duplications shows that the reciprocal phenotypes do not involve alterations to food intake, but generate opposite changes in weight, obesity, low-density lipoprotein levels, and insulin sensitivity by other means. These mouse-model differences appear to correspond to phenotypes observed in human subjects with either deletions (Smith–Magenis syndrome) or duplications (Potocki–Lupski syndrome) [19\*], although further data focusing on metabolic traits in these syndromes are required. As for 1q21.1 and 16p11.2, deletions and duplications at 17p11.2 are known to also be associated with psychiatric and behavioral phenotypes: Potocki–Lupski syndrome is characterized by autism spectrum disorders [21], while individuals with Smith–Magenis syndrome exhibit high levels of attention-seeking and friendliness, but also mood dysregulation, high impulsivity and underdeveloped social-cognitive skills [22,23]. For neither 16p11.2 or 17p11.2 have the specific genes involved in the reciprocal metabolic phenotypes been identified. At 17p11.2, selective *RAI1* deletion appears to be linked with some metabolic alterations, but *RAI1* duplications do not generate the CNV duplication metabolic phenotypes.

Opposite alterations to energy balance, comparable to those reported for 16p11.2 and 17p11.2, have also been reported for the *GNAS* locus at 20q13, at which loss of *Gαs* expression in the CNS of mice leads to decreased energy expenditure, severe insulin resistance, and extreme obesity; by contrast, mouse knockouts of an *XLαs* transcript from this locus lead to higher energy expenditure, higher insulin sensitivity, and reduced adiposity [24]. These dramatic, diametric changes, which are mediated partly by alterations to sympathetic nerve activity under the control of melanocortins [24] are not due directly to gene-dosage alterations, but may still be functionally diametric in that an *XLαs* transcript has been proposed to act as a dominant negative regulator of *Gαs*, such that loss of the transcript increases its activity. Determining the neurogenetic causes of the opposite shifts in metabolic phenotypes from diametric alterations at 16p11.2, 17p11.2, and 20q13, which appear to center on hypothalamic function [25], should provide new insights into the causes and control of human energy balance and obesity.

Finally, the 17q21.31 locus in humans exhibits a pair of reciprocal deletion/duplication syndromes, whose phenotypic effects, at least for the deletion, have recently been traced to effects from the gene *KANSL1* [26,27]. Individuals with the deletion, or loss of *KANSL1* function owing to mutation causing haploinsufficiency, are characterized by a friendly, amiable disposition, as well as severe

speech and language delays [28,29]. By contrast, individuals with the duplication exhibit poor social interactions, temper outbursts and aggressiveness, and variably affected verbal skills [30,31]; some individuals with the duplication have also been diagnosed with autism (Suppl. data in [32,33]). This locus and gene are of particular interest because they show strong signatures of recent positive selection in some human populations, which appear to be linked with altered expression or function of *KANSL1* [34,35].

### Imprinted-gene effects

Genomic imprinting refers to the silencing of one of an individual's two copies of a gene (for autosomal loci), depending on its parent of origin. Whereas copy number variation leads to haploidy, diploidy, or triploidy for the affected locus, alterations to imprinted regions may result in either a complete loss, or a doubling, of gene expression, from the usual gene-expression complement of one (Figure 1). The *GNAS* locus described above is subject to imprinting, with *Gαs* maternally expressed in some tissues, while *XLαs* transcripts are expressed from the paternal chromosome [24]. However, mouse models overexpressing the relevant transcripts have yet to be developed.

Two reciprocal imprinted-gene syndromes are emerging as important foci for neurogenetic research in humans. First, Beckwith–Wiedemann (BWS) and Silver–Russell (SRS) syndromes are caused by opposite genetic or epigenetic alterations to imprinted loci at 11p15.5 [36]. These syndromes result in either somatic overgrowth (in BWS, usually owing to increased expression of *IGF2* or decreased expression of *CDKN1C*), or undergrowth (in SRS, commonly owing to the opposite alterations of these two genes). BWS and SRS have generally not been considered as conditions with neurological effects. However, Kent *et al.* [37] recently reported a notably elevated incidence of autism (about 8%) among BWS patients, and one of the first neuroimaging studies of individuals with this syndrome reported a high incidence of alterations to the posterior fossa [38]. Given the frequency of cerebellar abnormalities (including overgrowth) in idiopathic autism [39], and the recent finding that methylation levels at the imprinting control region at 11p15.5 can account for 25% of observed variation in human cerebellum weight [40\*], these findings suggest that further neurodevelopmental and neurogenetic studies of BWS may provide useful data. Surprisingly, there appear to be no published studies of psychological or neurological phenotypes in SRS, except case reports. Do SRS patients show changes in the posterior fossa opposite to those found in BWS, or higher rates of any neurodevelopmental conditions?

Second, Prader–Willi syndrome (PWS) and Angelman syndrome (AS) are caused by reciprocal alterations



(segmental deletions, or uniparental disomies) involving a suite of imprinted and non-imprinted genes at 15q11–q13 [41]. Although these two syndromes exhibit ‘opposite’ phenotypes with regard to low versus high childhood activity levels and behavioral solicitation, and negative versus positive affect [23,42], their genetic or epigenetic underpinnings appear, curiously, to be quite distinct. Whereas AS is caused by loss of function for the imprinted gene UBE3A, no human single-gene alteration or mouse model that fully recapitulates PWS has been reported. Instead, this syndrome appears to be caused by loss of expression for two or more non-contiguous paternally expressed genes at 15q11–q13. Do these different alterations in PWS and AS impact common neurodevelopmental pathways, but in opposite ways? AS indeed resembles Rett syndrome, and several other monogenic loss of function disorders, for a suite of neurological phenotypes with molecular-genetic links [43<sup>•</sup>]; likewise, PWS-like developmental and behavioral phenotypes have been reported from alterations to over ten different loci (Table 3 in [44]). Uncovering any such pathways is important for two reasons. First, AS, Rett syndrome, and related conditions may represent a neurogenetically linked subset of ASDs, for which similar therapies may be efficacious. Second, PWS owing to uniparental disomy of chromosome 15 represents one of the most highly penetrant known cause of psychosis, with over 50% of individuals affected [45]. As such, it should provide an excellent model system for linking genes with psychosis-related phenotypes via neurodevelopmental analysis of mouse models, or study of synaptic function in human induced pluripotent neuronal stem cells.

### X-chromosome aneuploidies

Losses or gains of entire chromosomes are compatible with life for only the X and Y in humans, with absence of part or all of the X leading to Turner syndrome in females, and gains of one X leading to either Klinefelter syndrome (in males) or XXX syndrome (in females). Recent studies that synthesize data on these aneuploidies [46] show that in both sexes, an extra X chromosome is associated with notably and selectively reduced language skills, with reductions in grey and white matter in XXY males, especially in temporal and frontal lobes, and a smaller amygdala [44]. By contrast, the loss of the X in Turner syndrome leads to preserved or enhanced verbal skills, but reduced visual-spatial abilities, with reduced parietal lobe volumes, and a larger amygdala [47,48]. These psychological and neuroanatomical patterns are paralleled by evidence regarding psychiatric phenotypes, with high levels of autism spectrum conditions in Turner syndrome, and high rates of schizophrenia and schizotypy in Klinefelter and XXX syndromes [44].

What gene or genes might underlie such striking differences in cognitive profiles, neuroanatomy, and psychiatric conditions? The Turner syndrome neurocognitive

phenotype has been mapped to Xp22.3, within pseudoautosomal region 1, which does not show X inactivation [49]. Comparison of gene expression between XY and XXY individuals has demonstrated higher expression in XXY of one gene, GTPBP6, in this region [50]. Moreover, within XXY individuals, higher expression of this gene was significantly, inversely related to verbal skills [50]. Considered together, these data suggest that dosage-sensitive effects of GTPBP6, and perhaps other genes in pseudoautosomal region 1, mediate human verbal abilities or verbal/visual-spatial tradeoffs, at least across individuals with X-chromosomal aneuploidies.

### Conclusions

Diametric gene dosage effects on neurological, behavioral and psychiatric phenotypes have been demonstrated for a rapidly increasing suite of mouse and human genes and genomic regions. Such studies are useful because they provide scaffolds for functional links between gene action, neurodevelopment, and phenotypic outcomes that are more robust and informative than those generated by knockouts alone. In addition, such systems connect directly with (1) natural bidirectional perturbations to gene expression (which generate phenotypic variation upon which natural selection can act), (2) diametricity in traits that can guide choice of phenotypes for focused analysis in CNV-based studies, and (3) strategies for pharmacological modulation of dosage-sensitive pathways. Accelerating progress in neurogenetic technologies, especially transgenic mouse and zebrafish models, and induced human pluripotent stem-cell derived neurons, opens the door to large-scale systematic study of diametric gene-dosage effects, with important implications for our understanding of neurogenetic architecture and disease.

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### References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Huang N, Lee I, Marcotte EM, Hurles ME: **Characterising and predicting haploinsufficiency in the human genome.** *PLoS Genet* 2010, **6**:e1001154.
2. Horev G, Ellegood J, Lerch JP, Son YE, Muthuswamy L, Vogel H, Krieger AM, Buja A, Henkelman RM, Wigler M *et al.*: **Dosage-dependent phenotypes in models of 16p11.2 lesions found in autism.** *Proc Natl Acad Sci USA* 2011, **108**:17076–17081.
3. Dang VT, Kassahn KS, Marcos AE, Ragan MA: **Identification of human haploinsufficient genes and their genomic proximity to segmental duplications.** *Eur J Hum Genet* 2008, **16**:1350–1357.
4. Teixeira CM, Martín ED, Sahún I, Masachs N, Pujadas L, Corvelo A, Bosch C, Rossi D, Martínez A, Maldonado R *et al.*: **Overexpression of reelin prevents the manifestation of behavioral phenotypes related to schizophrenia and bipolar disorder.** *Neuropsychopharmacology* 2011, **36**:2395–2405.

The authors showed that overexpression of RELN in mice led to a reduction in PPI deficits induced by NMDA antagonism, and significantly lowered the degree to which stress increased levels of NMDA NR2B-mediated activity. Their results suggest that modulation of reelin signaling may represent a new domain for pharmacological therapy in schizophrenia and depression.

5. McCarthy SE, Makarov V, Kirov G, Addington AM, McClellan J, Yoon S, Perkins DO, Dickel DE, Kusenda M, Krastoshevsky O *et al.*: **Microduplications of 16p11.2 are associated with schizophrenia.** *Nat Genet* 2009, **41**:1223-1227.
  6. Mefford HC, Sharp AJ, Baker C, Itsara A, Jiang Z, Buysse K, Huang S, Maloney VK, Crolla JA, Baralle D *et al.*: **Recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes.** *N Engl J Med* 2008, **359**:1685-1699.
  7. Shinawi M, Liu P, Kang SH, Shen J, Belmont JW, Scott DA, Probst FJ, Craigen WJ, Graham BH, Pursley A *et al.*: **Recurrent reciprocal 16p11.2 rearrangements associated with global developmental delay, behavioural problems, dysmorphism, epilepsy, and abnormal head size.** *J Med Genet* 2010, **47**:332-341.
  8. Luo R, Sanders SJ, Tian Y, Voineagu I, Huang N, Chu SH, Klei L, Cai C, Ou J, Lowe JK *et al.*: **Genome-wide transcriptome profiling reveals the functional impact of rare de novo and recurrent CNVs in autism spectrum disorders.** *Am J Hum Genet* 2012. [Epub ahead of print].
- Using lymphoblasts from probands and relatives with autism spectrum conditions, the authors demonstrated that underexpression or overexpression was increased in autistic individuals specifically for neural-pathway genes. Degrees of expression change owing to CNVs were also indicated as a novel prioritization criterion for evaluating which genes underlie autism-related phenotypes.
9. Crespi B, Stead P, Elliot M: **Comparative genomics of autism and schizophrenia.** *Proc Natl Acad Sci USA* 2010, **107**(Suppl 1):1736-1741.
  10. Girirajan S, Brkanac Z, Coe BP, Baker C, Vives L, Vu TH, Shafer N, Bernier R, Ferrero GB, Silengo M *et al.*: **Relative burden of large CNVs on a range of neurodevelopmental phenotypes.** *PLoS Genet* 2011, **7**:e1002334.
- Using CNV data from a cohort of individuals with neurological conditions, the authors showed that the burden of large CNVs was positively associated with severity of childhood disability, being highest for intellectual disability with multiple congenital anomalies, intermediate for autism, and lowest (and indistinguishable from controls) for dyslexia.
11. Doherty JL, O'Donovan MC, Owen MJ: **Recent genomic advances in schizophrenia.** *Clin Genet* 2012, **81**:103-109.
  12. Coe BP, Girirajan S, Eichler EE: **The genetic variability and commonality of neurodevelopmental disease.** *Am J Med Genet C Semin Med Genet* 2012, **160C**:118-129.
  13. Brunetti-Pierri N, Berg JS, Scaglia F, Belmont J, Bacino CA, Sahoo T, Lalani SR, Graham B, Lee B, Shinawi M *et al.*: **Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioral abnormalities.** *Nat Genet* 2008, **40**:1466-1471.
  14. Ponting CP: **A novel domain suggests a ciliary function for ASPM, a brain size determining gene.** *Bioinformatics* 2006, **22**:1031-1035.
  15. Golzio C, Willer J, Talkowski ME, Oh EC, Taniguchi Y, Jacquemont S, Reymond A, Sun M, Sawa A, Gusella JF *et al.*: **KCTD13 is a major driver of mirrored neuroanatomical phenotypes of the 16p11.2 copy number variant.** *Nature* 2012, **485**:363-367.
- Overexpression in zebrafish of each human transcript from 29 genes duplicated in an 16p11.2 CNV showed that KCTD13 mediated the diametric changes in brain size seen in duplications compared to deletions at this locus. The method developed here can be used to help determine which dosage-sensitive genes contribute to disease-related phenotypes underlain by CNVs.
16. Crespi B, Crofts H: **Association testing of copy number variants in autism and schizophrenia.** *J Neurodev Dis* 2012. [Epub ahead of print].
  17. Courchesne E, Mouton PR, Calhoun ME, Semendeferi K, Ahrens-Barbeau C, Hallet MJ, Barnes CC, Pierce K: **Neuron number and size in prefrontal cortex of children with autism.** *JAMA* 2011, **306**:2001-2010.
  18. Rimol LM, Nesvåg R, Hagler DJ Jr, Bergmann O, Fennema-Notestine C, Hartberg CB, Haukvik UK, Lange E, Pung CJ, Server A *et al.*: **Cortical volume, surface area, and thickness in schizophrenia and bipolar disorder.** *Biol Psychiatry* 2012, **71**:552-560.
  19. Lacaria M, Saha P, Potocki L, Bi W, Yan J, Girirajan S, Burns B, Elsea S, Walz K, Chan L *et al.*: **A duplication CNV that conveys traits reciprocal to metabolic syndrome and protects against diet-induced obesity in mice and men.** *PLoS Genet* 2012, **8**:e1002713.
- This study analyzed phenotypic variation in metabolic phenotypes for mouse models of the reciprocal copy-number variants at 17p11.2 that cause Smith-Magenis syndrome and Potocki-Lupski syndrome. Mice with the duplication CNV exhibited a suite of physiological traits directly opposite to those found in the human 'metabolic syndrome', and were protected against weight gain and metabolic changes induced by a high fat diet; by contrast, mouse models of the deletion CNV exhibited the opposite suite of metabolic phenotypes.
20. Jacquemont S, Reymond A, Zufferey F, Harewood L, Walters RG, Kutalik Z, Martinet D, Shen Y, Valsesia A, Beckmann ND *et al.*: **Mirror extreme BMI phenotypes associated with gene dosage at the chromosome 16p11.2 locus.** *Nature* 2011, **478**:97-102.
- The authors document opposite growth, morphological, metabolic, and eating-behavior traits among individuals with deletions versus duplications of a region at 16p11.2. The phenotypes are associated with variation in transcript levels for genes in the CNV interval, and may be jointly underlain by effects on energy balance.
21. Potocki L, Bi W, Treadwell-Deering D, Carvalho CM, Eifert A, Friedman EM, Glaze D, Krull K, Lee JA, Lewis RA *et al.*: **Characterization of Potocki-Lupski syndrome (dup(17)(p11.2p11.2)) and delineation of a dosage-sensitive critical interval that can convey an autism phenotype.** *Am J Hum Genet* 2007, **80**:633-649.
  22. Laje G, Morse R, Richter W, Ball J, Pao M, Smith AC: **Autism spectrum features in Smith-Magenis syndrome.** *Am J Med Genet C Semin Med Genet* 2010, **154C**:456-462.
  23. Crespi BJ, Summers K, Dorus S: **Genomic sister-disorders of neurodevelopment: an evolutionary approach.** *Evol Appl* 2009, **2**:81-100.
  24. Weinstein LS, Xie T, Qasem A, Wang J, Chen M: **The role of GNAS and other imprinted genes in the development of obesity.** *Int J Obes (Lond)* 2010, **34**:6-17.
  25. Chen M, Berger A, Kablan A, Zhang J, Gavrilova O, Weinstein LS: **Gsα deficiency in the paraventricular nucleus of the hypothalamus partially contributes to obesity associated with Gsα mutations.** *Endocrinology* 2012. [Epub ahead of print].
  26. Zollino M, Orteschi D, Murdolo M, Lattante S, Battaglia D, Stefanini C, Mercuri E, Chiurazzi P, Neri G, Marangi G: **Mutations in KANSL1 cause the 17q21.31 microdeletion syndrome phenotype.** *Nat Genet* 2012, **44**:636-638.
  27. Koolen DA, Kramer JM, Neveling K, Nillesen WM, Moore-Barton HL, Elmslie FV, Toutain A, Amiel J, Malan V, Tsai AC *et al.*: **Mutations in the chromatin modifier gene KANSL1 cause the 17q21.31 microdeletion syndrome.** *Nat Genet* 2012, **44**:639-641.
  28. Sharkey FH, Morrison N, Murray R, Iremonger J, Stephen J, Maher E, Tolmie J, Jackson AP: **17q21.31 microdeletion syndrome: further expanding the clinical phenotype.** *Cytogenet Genome Res* 2009, **127**:61-66.
  29. Koolen DA, Sharp AJ, Hurst JA, Firth HV, Knight SJ, Goldenberg A, Saugier-Verber P, Pfundt R, Vissers LE, Destree A *et al.*: **Clinical and molecular delineation of the 17q21.31 microdeletion syndrome.** *J Med Genet* 2008, **45**:710-720.
  30. Grisart B, Willatt L, Destree A, Frys JP, Rack K, de Ravel T, Rosenfeld J, Vermeesch JR, Verellen-Dumoulin C, Sandford R: **17q21.31 microduplication patients are characterised by behavioural problems and poor social interaction.** *J Med Genet* 2009, **46**:524-530.
  31. Kitsiou-Tzeli S, Frysira H, Giannikou K, Symrou A, Kosma K, Kakourou G, Leze E, Sofocleous C, Kanavakis E, Tzetzis M: **Microdeletion and microduplication 17q21.31 plus an**

- additional CNV, in patients with intellectual disability, identified by array-CGH.** *Gene* 2012, **492**:319-324.
32. Marshall CR, Noor A, Vincent JB, Lionel AC, Feuk L, Skaug J, Shago M, Moessner R, Pinto D, Ren Y *et al.*: **Structural variation of chromosomes in autism spectrum disorder.** *Am J Hum Genet* 2008, **82**:477-488.
  33. Sanders SJ, Ercan-Sencicek AG, Hus V, Luo R, Murtha MT, Moreno-De-Luca D, Chu SH, Moreau MP, Gupta AR, Thomson SA *et al.*: **Multiple recurrent de novo CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism.** *Neuron* 2011, **70**:863-885.
  34. Boettger LM, Handsaker RE, Zody MC, McCarroll SA: **Structural haplotypes and recent evolution of the human 17q21.31 region.** *Nat Genet* 2012. [Epub ahead of print].
  35. Steinberg KM, Antonacci F, Sudmant PH, Kidd JM, Campbell CD, Vives L, Malig M, Scheinfeldt L, Beggs W, Ibrahim M *et al.*: **Structural diversity and African origin of the 17q21.31 inversion polymorphism.** *Nat Genet* 2012. [Epub ahead of print].
  36. Eggermann T: **Silver-Russell and Beckwith-Wiedemann syndromes: opposite (epi)mutations in 11p15 result in opposite clinical pictures.** *Horm Res* 2009, **71**(Suppl 2): 30-35.
  37. Kent L, Bowdin S, Kirby GA, Cooper WN, Maher ER: **Beckwith Wiedemann syndrome: a behavioral phenotype-genotype study.** *Am J Med Genet B Neuropsychiatr Genet* 2008, **147B**:1295-1297.
  38. Gardiner K, Chitayat D, Choufani S, Shuman C, Blaser S, Terespolosky D, Farrell S, Reiss R, Wodak S, Pu S *et al.*: **Brain abnormalities in patients with Beckwith-Wiedemann syndrome.** *Am J Med Genet A* 2012, **158A**:1388-1394.
  39. Fatemi SH, Aldinger KA, Ashwood P, Bauman ML, Blaha CD, Blatt GJ, Chauhan A, Chauhan V, Dager SR, Dickson PE *et al.*: **Pathological role of the cerebellum in autism.** *Cerebellum* 2012. [Epub ahead of print].
  40. Pidsley R, Dempster E, Troakes C, Al-Sarraj S, Mill J: **Epigenetic and genetic variation at the IGF2/H19 imprinting control region on 11p15.5 is associated with cerebellum weight.** *Epigenetics* 2012, **7**:155-163.
- Using post-mortem samples of human brain, the authors demonstrate that levels of methylation in the imprinting control region at 11p15.5 are strongly correlated with cerebellum weight, and explain 25% of cerebellar weight variation. This association is mediated by parent of origin, indicating that epigenetic variation at imprinted loci exerts substantial effects on brain morphology.
41. Buiting K: **Prader-Willi syndrome and Angelman syndrome.** *Am J Med Genet C Semin Med Genet* 2010, **154C**:365-376.
  42. Crespi B: **The evolutionary biology of child health.** *Proc Biol Sci* 2011, **278**:1441-1449.
  43. Willemsen MH, Rensen JH, van Schrojenstein-Lantman de Valk HM, Hamel BC, Kleefstra T: **Adult phenotypes in Angelman- and Rett-like syndromes.** *Mol Syndromol* 2012, **2**:217-234.
- The authors provide the first comprehensive synthesis of the phenotypic similarities between individuals with Angelman syndrome, Rett syndrome, mutations in EHMT1, TCF4, MECP2, CDKL5, and SCN1A, and 22qter deletions, and describe the overlaps in neurodevelopmental pathways that appear to underlie these similarities. This study provides a foundation for comparative neurogenetic analysis of these conditions that should provide novel insights into autism spectrum conditions as well as normative development.
44. Crespi B: **Genomic imprinting in the development and evolution of psychotic spectrum conditions.** *Biol Rev Camb Philos Soc* 2008, **83**:441-493.
  45. Sinnema M, Boer H, Collin P, Maaskant MA, van Roozendaal KE, Schrander-Stumpel CT, Curfs LM: **Psychiatric illness in a cohort of adults with Prader-Willi syndrome.** *Res Dev Disabil* 2011, **32**:1729-1735.
  46. Lee NR, Lopez K, Adeyemi E, Giedd JN: **Sex chromosome aneuploidies: a window for examining the effects of the X and Y chromosomes on speech, language, and social development.** *Int Rev Res Dev Disabil* 2011, **40**:139-180.
  47. Temple CM, Carney R: **Reading skills in children with Turner's syndrome: an analysis of hyperlexia.** *Cortex* 1996, **32**:335-435.
  48. Mullaney R, Murphy D: **Turner syndrome: neuroimaging findings: structural and functional.** *Dev Disabil Res Rev* 2009, **15**:279-283.
  49. Zinn AR, Roeltgen D, Stefanatos G, Ramos P, Elder FF, Kushner H, Kowal K, Ross JL: **A Turner syndrome neurocognitive phenotype maps to Xp22.3.** *Behav Brain Funct* 2007, **3**:24.
  50. Vawter MP, Harvey PD, DeLisi LE: **Dysregulation of X-linked gene expression in Klinefelter's syndrome and association with verbal cognition.** *Am J Med Genet B Neuropsychiatr Genet* 2007, **144B**:728-734.
  51. Garelick MG, Chan GC, DiRocco DP, Storm DR: **Overexpression of type I adenylyl cyclase in the forebrain impairs spatial memory in aged but not young mice.** *J Neurosci* 2009, **29**:10835-10842.
  52. Bianchin MM, Bragatti JA, Torres CM, Nuernberg GL, Rieder CR: **Decreased serum BDNF levels in patients with epileptic and psychogenic nonepileptic seizures.** *Neurology* 2011, **76**:1772.
  53. Papaleo F, Silverman JL, Aney J, Tian Q, Barkan CL, Chadman KK, Crawley JN: **Working memory deficits, increased anxiety-like traits, and seizure susceptibility in BDNF overexpressing mice.** *Learn Mem* 2011, **18**:534-544.
  54. Bath KG, Chuang J, Spencer-Segal JL, Amso D, Altemus M, McEwen BS, Lee FS: **Variant Brain Derived Neurotrophic Factor (Valine66Methionine) polymorphism contributes to developmental and estrous stage-specific expression of anxiety-like behavior in female mice.** *Biol Psychiatry* 2012. [Epub ahead of print].
  55. Hasegawa S, Furuichi T, Yoshida T, Endoh K, Kato K, Sado M, Maeda R, Kitamoto A, Miyao T, Suzuki R *et al.*: **Transgenic up-regulation of alpha-CaMKII in forebrain leads to increased anxiety-like behaviors and aggression.** *Mol Brain* 2009, **2**:6.
  56. Jian XQ, Wang KS, Wu TJ, Hillhouse JJ, Mullersman JE: **Association of ADAM10 and CAMK2A polymorphisms with conduct disorder: evidence from family-based studies.** *J Abnorm Child Psychol* 2011, **39**:773-782.
  57. Papaleo F, Crawley JN, Song J, Lipska BK, Pickel J, Weinberger DR, Chen J: **Genetic dissection of the role of catechol-O-methyltransferase in cognition and stress reactivity in mice.** *J Neurosci* 2008, **28**:8709-8723.
  58. Suzuki A, Fukushima H, Mukawa T, Toyoda H, Wu LJ, Zhao MG, Xu H, Shang Y, Endoh K, Iwamoto T *et al.*: **Upregulation of CREB-mediated transcription enhances both short- and long-term memory.** *J Neurosci* 2011, **31**:8786-8802.
  59. Oegema R, de Klein A, Verkerk AJ, Schot R, Dumee B, Douben H, Eussen B, Dubbel L, Poddighe PJ, van der Laar I *et al.*: **Distinctive phenotypic abnormalities associated with submicroscopic 21q22 deletion including DYRK1A.** *Mol Syndromol* 2010, **1**:113-120.
  60. Yabut O, Domogauer J, D'Arcangelo G: **Dyrk1A overexpression inhibits proliferation and induces premature neuronal differentiation of neural progenitor cells.** *J Neurosci* 2010, **30**:4004-4014.
  61. Guedj F, Pereira PL, Najas S, Barallobre MJ, Chabert C, Souchet B, Sebie C, Verney C, Herault Y, Arbones M *et al.*: **DYRK1A: a master regulatory protein controlling brain growth.** *Neurobiol Dis* 2012, **46**:190-203.
- Using mouse models with one, two and three copies of DYRK1A, the authors demonstrate that patterns of growth, brain size, and neuron density depend strongly on gene copy number. Strikingly, neuron density was inversely related to gene copy number in the cortex, but positively related in thalamus.
62. Peier AM, McIlwain KL, Kenneson A, Warren ST, Paylor R, Nelson DL: **(Over)correction of FMR1 deficiency with YAC transgenics: behavioral and physical features.** *Hum Mol Genet* 2000, **9**:1145-1159.
  63. Rio M, Malan V, Boissel S, Toutain A, Royer G, Gobin S, Morichon-Delvallez N, Turleau C, Bonnefont JP, Munnich A *et al.*: **Familial interstitial Xq27.3q28 duplication encompassing the FMR1**



**gene but not the MECP2 gene causes a new syndromic mental retardation condition.** *Eur J Hum Genet* 2010, **18**:285-290.

64. Sikela JM: **The jewels of our genome: the search for the genomic changes underlying the evolutionarily unique capacities of the human brain.** *PLoS Genet* 2006, **2**:e80.
  65. Collette JC, Chen XN, Mills DL, Galaburda AM, Reiss AL, Bellugi U, Korenberg JR: **William's syndrome: gene expression is related to parental origin and regional coordinate control.** *J Hum Genet* 2009, **54**:193-198.
  66. Sakurai T, Dorr NP, Takahashi N, McInnes LA, Elder GA, Buxbaum JD: **Haploinsufficiency of Gtf2i, a gene deleted in Williams Syndrome, leads to increases in social interactions.** *Autism Res* 2011, **4**:28-39.
  67. Mervis CB, Dida J, Lam E, Crawford-Zelli NA, Young EJ, Henderson DR, Onay T, Morris CA, Woodruff-Borden J, Yeomans J *et al.*: **Duplication of Gtf2i results in separation anxiety in mice and humans.** *Am J Hum Genet* 2012, **90**:1064-1070.
- In this study the authors documented high rates of separation anxiety in children with duplications of 7q11.23, a region that contains the transcription factor GTF2I whose haploinsufficiency has been implicated in hypersociality in Williams syndrome. In addition, mice with duplications of GTF2I showed significantly higher separation anxiety, as indexed by ultrasonic vocalization, than normal mice and mice with the deletion. The work thus documents diametric effects of this gene on sociality and social anxiety.
68. Wang CC, Held RG, Chang SC, Yang L, Delpire E, Ghosh A, Hall BJ: **A critical role for GluN2B-containing NMDA receptors in cortical development and function.** *Neuron* 2011, **72**:789-805.
  69. Jacobs SA, Tsien JZ: **Genetic overexpression of NR2B subunit enhances social recognition memory for different strains and species.** *PLoS ONE* 2012, **7**:e36387.
- The authors generated transgenic mice that overexpressed the NR2B subunit of the NMDA receptor, and found that they exhibited enhanced relatively long-term social recognition memory for mice of different strains and species compared to controls.
70. Bi W, Yan J, Shi X, Yuva-Paylor LA, Antalffy BA, Goldman A, Yoo JW, Noebels JL, Armstrong DL, Paylor R, Lupski JR: **Rai1 deficiency in mice causes learning impairment and motor dysfunction, whereas Rai1 heterozygous mice display minimal behavioral phenotypes.** *Hum Mol Genet* 2007, **16**:1802-1813.
  71. Girirajan S, Elsea SH: **Abnormal maternal behavior, altered sociability, and impaired serotonin metabolism in Rai1-transgenic mice.** *Mamm Genome* 2009, **20**:247-255.
  72. Carmona-Mora P, Walz K: **Retinoic Acid Induced 1 RAI1: a dosage sensitive gene related to neurobehavioral alterations including autistic behavior.** *Curr Genomics* 2010, **11**:607-617.
  73. Harper KM, Hiramoto T, Tanigaki K, Kang G, Suzuki G, Trimble W, Hiroi N: **Alterations of social interaction through genetic and environmental manipulation of the 22q11.2 gene Sept5 in the mouse brain.** *Hum Mol Genet* 2012. [Epub ahead of print].