

ORIGINAL ARTICLE

Genomic sister-disorders of neurodevelopment: an evolutionary approachBernard Crespi,¹ Kyle Summers² and Steve Dorus³¹ Department of Biosciences, Simon Fraser University, Burnaby, BC, Canada² Department of Biology, East Carolina University, Greenville, NC, USA³ Department of Biology and Biochemistry, University of Bath, Bath, UK**Keywords**

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

Correspondence

Bernard Crespi, Department of Biosciences, Simon Fraser University, Burnaby, BC, Canada V5A 1S6. Tel.: 778 782 3533; fax: 778 782 3496; e-mail: crespis@sfu.ca

Received: 27 September 2008

Accepted: 26 November 2008

First published online: 7 January 2009

doi:10.1111/j.1752-4571.2008.00056.x

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.

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; Korbelt 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 Altshuler 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; Korbelt 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 versus hyperactivity in mice with the *RAII* gene experimentally deleted versus 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, toward 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 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: (i) data on the phenotypes associated with the four best-known human genomic sister-disorders, and (ii) 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 *MCPHI* (Evans et al. 2005; Lencz et al. 2007a), as well as positively selected genes underlying schizophrenia (Crespi et al. 2007). Most generally, this study 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 nonclinical 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 Catarrhini, 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 (Shelley and Robertson 2005; Smith et al. 2005; Girirajan et al. 2006; Martin et al. 2006; Gropman et al. 2007). 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 (Shelley and Robertson 2005; Bi et al. 2006), 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), attention-deficit/hyperactivity disorder (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 has 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

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 Potocki–Lupski	Hemizygous deletion of region at 17p11.2 including <i>RAI1</i> gene; <i>RAI1</i> mutations (Gropman et al. 2007) Duplication of Smith–Magenis region (Potocki et al. 2007)
VCFS region deletion	Deletion of ~30 genes at 22q11.2, effects from <i>COMT</i> , <i>DGCR2</i> , <i>GNB1L</i> , <i>TBX1</i> , <i>UFD1L</i> , 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 <i>CYL2</i> , <i>GTF2I</i> , <i>GTF2IRD1</i> , <i>LIMK1</i> , other genes (Tassabehji 2003; Gray et al. 2006; Edlmann et al. 2007; Young et al. 2008)
Williams-syndrome region duplication	Duplication of 7q11.23 region (Berg et al. 2007)
Klinefelter	One or more excess X chromosomes; Increased expression of <i>PAR1</i> , <i>PAR2</i> genes and 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 <i>PAR1</i> , <i>PAR2</i> genes and 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	Autistic-spectrum syndromes
<p>Smith–Magenis</p> <p>High levels of sociability (Smith et al. 1998; Sarimski 2004)</p> <p>Relative strength in verbal skills (Dykens et al. 1997)</p> <p>Case reports of ‘bipolar episodes’ (Girirajan et al. 2006)</p> <p>Case report of mood disorder (Bersani et al. 2007)</p>	<p>Potocki–Lupski</p> <p>High rates of autism and autistic behavior (Moog et al. 2004; Potocki et al. 2007)</p>
<p>Velocardiofacial</p> <p>Better verbal than visual–spatial skills (Bearden et al. 2001; Lajiness-O’Neill et al. 2006)</p> <p>High rates of schizophrenia, schizoaffective disorders, bipolar, depression, anxiety, phobia (Gothelf 2007)</p>	<p>Velocardiofacial-region duplications</p> <p>Hyperactivity, attention deficits, anxiety, depression, seizures, speech problems, impulsivity (Ensenauer et al. 2003; Yobb et al. 2005; Alberti et al. 2007)</p> <p>Case report of autism (Mukaddes and Herguner 2007)</p> <p>Case report of Asperger syndrome (Hassed et al. 2004b)</p> <p>Two cases of autism (Marshall et al. 2008)</p> <p>Two cases of autism (Christian et al. 2008)</p>
<p>Williams</p> <p>Better verbal than visual–spatial skills (Vicari et al. 2004)</p> <p>Hypersociability, fascination with faces (Doyle et al. 2004)</p> <p>Dyslexia (Temple 2006)</p> <p>High rates of anxiety and phobias (Meyer-Lindenberg et al. 2006; Lincoln et al. 2007)</p>	<p>Williams-region duplications</p> <p>Severe language impairment, visual-spatial skills spared (Berg et al. 2007)</p> <p>High rates of autism and autistic behavior (Berg et al. 2007; Depienne et al. 2007)</p>
<p>Klinefelter</p> <p>Dyslexia (Geschwind et al. 2000)</p> <p>Poor verbal skills, preserved visual- spatial skills (Money 1993; DeLisi et al. 2005)</p> <p>High rates of schizophrenia, schizoaffective disorder, schizotypy, bipolar disorder, anxiety, depression (DeLisi et al. 2005; van Rijn et al. 2005; Boks et al. 2007)*</p>	<p>Turner</p> <p>Hyperlexia (Temple and Carney 1996)</p> <p>Good verbal skills, impaired visual- spatial skills (Money 1993; Kesler 2007)</p> <p>Gaze aversion (Lawrence et al. 2003)</p> <p>High rates of autism and autistic traits in maternal-X cases (Skuse et al. 1997)</p> <p>Reduced incidence of schizophrenia plus bipolar disorder (Mors et al. 2001)</p>
<p>Idiopathic schizophrenia</p> <p>Low birth weight (Wahlbeck et al. 2001; Nilsson et al. 2005)</p> <p>Slow growth (Niemi et al. 2005)</p> <p>Small head, brain size (Gur et al. 2007)</p> <p>Better verbal than visual–spatial skills (Kravariti et al. 2006)</p> <p>Dyslexia (Bersani et al. 2006; Revheim et al. 2006)</p> <p>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)</p>	<p>Idiopathic autism</p> <p>High or average birth weight (Sacco et al. 2007; Mraz et al. 2007; Sugie et al. 2005)</p> <p>Overgrowth, faster body growth (Dissanayake et al. 2006; Mills et al. 2007; Mraz et al. 2007; Fukumoto et al. 2008)</p> <p>Macrocephaly (Lainhart et al. 2006; Stanfield et al. 2008)</p> <p>Hyperlexia (Newman et al. 2007)</p> <p>Better visual–spatial than verbal skills in subset of cases (Caron et al. 2006)</p>

‘Psychotic-spectrum’ syndromes involve an increased incidence of psychotic-spectrum psychiatric conditions (mainly schizophrenia, schizoaffective disorder, bipolar disorder, depression, anxiety, and phobias), and ‘autistic-spectrum’ syndromes involve autistic traits, autism and Asperger syndrome.

*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.

genes immediately proximal and distal to *RAI1*, *PENT* 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 (Girirajan et al. 2007; Potocki et al. 2007). Two individuals with this syndrome were formally diagnosed with autism (Moog et al. 2004; Potocki et al. 2007), 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–chimpanzee 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 seven 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 (VCFS) involves congenital malformation of the heart, face and limbs, usually due to a 3-Mb 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,b; 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

Table 3. Evidence for positive selection on genes associated with human neurogenetic sister-disorders, from maximum likelihood analyses.

Gene	Gene symbol	Lineage	–2Δln	Positively selected codons (posterior probability)
Pseudoautosomal region 1				
<i>Interleukin 3 receptor, alpha</i>	<i>IL3RA</i>	Primate	5.32*	None
<i>GTP binding protein 6</i>	<i>GTPBP6</i>	Primate	8.04**	Leu 125 (0.982)
<i>Acetylserotonin O-methyltransferase-like</i>	<i>ASTML</i>	Primate	6.20*	None
<i>Purinergic receptor P2Y, G-protein coupled, 8</i>	<i>P2R8Y</i>	Primate	9.82**	None
Velocardiofacial syndrome				
<i>claudin 5</i>	<i>CLDN5</i>	Primate	6.70**	None
<i>Guanine nucleotide binding protein, beta polypeptide 1-like</i>	<i>GNB1L</i>	Primate	4.86*	Ser 119 (0.961)
<i>Zinc finger protein 74</i>	<i>ZNF74</i>	Primate	9.94**	Ala 84 (0.961) Thr 321 (0.991)
<i>Catechol-O-methyltransferase</i>	<i>COMT</i>	Primate	8.02**	Pro 324 (0.972)
<i>Ubiquitin fusion degradation 1 like</i>	<i>UFD1L</i>	Human	6.58*	His 221 (0.983)
Smith–Magenis syndrome				
<i>Retinoic acid induced 1</i>	<i>RAI1</i>	Primate	5.68*	None
Williams syndrome				
<i>Replication factor C 2</i>	<i>RFC2</i>	Primate	3.78	None

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.

* $P < 0.05$, ** $P < 0.01$.

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, obsessive-compulsive disorder, generalized anxiety disorder, panic disorder, ADHD, pervasive developmental disorder – not otherwise specified (PDD-NOS), and psychotic symptoms. VCFS 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 (Paylor et al. 2006; Zweier et al. 2007), 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; Gothelf et al. 2005; Wonodi 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 (Hassed et al. 2004a; Portnoï et al. 2005; Yobb et al. 2005; Alberti et al. 2007; Mukaddes and Herguner 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 two of 275 females referred for fragile X testing (Yobb et al. 2005).

Mukaddes 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 3 Mb 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 five 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

Velocardiofacial syndrome 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: (i) the notable proportion of VCFS-region genes inferred as subject to positive selection for the primate-origin lineage, (ii) the HapMap selection signal across a block of genes in three populations, and (iii) 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 (Berg et al. 2007; Depienne et al. 2007; Kirchoff 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, hypervocal 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 (Poerber and Dykens 1996; Doyle et al. 2004; Feinstein and Singh 2007; 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 (Tager-Flusberg and Sullivan 2000; Reiss et al. 2004; Vicari et al. 2004; Porter and Coltheart 2005). 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, Poerber 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), 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 (Laws and Bishop 2004; Fidler et al. 2007; Klein-Tasman et al. 2007). However, theory of mind skills has been reported as comparable to matched controls in Williams syndrome, and levels of empathy appear to be elevated above controls (Sullivan and Tager-Flusberg 1999; Tager-Flusberg and Sullivan 2000). 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 nonautistic (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, has 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; Edelman 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 *Gtf2IRD1* 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 *GTF2I* to *LIMK1* demonstrated statistical significance in maximum-likelihood analyses, although *RFC2* showed borderline nonsignificance ($0.05 < P < 0.06$) 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 and 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: (i) normal or enhanced verbal skills, especially with regard to reading level, accuracy and comprehension, including a relatively high incidence of hyperlexia, (ii) notable impairments of visual–spatial skills as assayed, for example, via tests of mental rotation, block design, object assembly and mathematical ability, and (iii) impaired social skills (Money 1993; Temple and Carney 1996; Lawrence et al. 2003; Nijhuis-van der Sanden 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 (Lawrence et al. 2003; Weiss et al. 2007). 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 et al. 1997; Skuse 2000, 2005).

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 (Varrela 1984; Ratcliffe et al. 1990, 1994; 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 (Graham et al. 1988; Geschwind et al. 2000; Boone et al. 2001; Fales et al. 2003; Itti et al. 2003, 2006; Simpson et al. 2003; 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 syndrome include anxiety, depression, bipolar disorder, schizoaffective disorder and schizophrenia (Mizukami et al. 1989; DeLisi et al. 1994, 2005; Everman and Stoudermire 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- to 10-fold increase (DeLisi et al. 1994, 2005; van Rijn et al. 2006). In 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 higher 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 et al. 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) (Ross et al. 2006; Zinn et al. 2007). 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 versus 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 the 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 PAR1, 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) ($\chi^2 = 5.03$, $P = 0.025$).

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, as 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) is 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

concur with the results of recent studies showing that a notable proportion of cases of autism can be ascribed to the 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). In 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 VCFS by Gothelf (2007, Table 2), as well as for Klinefelter syndrome (Mizukami et al. 1989; Everman and Stoudemire 1994; DeLisi et al. 2005; 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 2008b; Crespi and Badcock 2008). 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 toward 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 the 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 that 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.

Acknowledgements

C. Feinstein, U. Franke and R. Weksberg kindly provided useful comments on earlier versions of this paper. This work was funded by grants from NSERC and the Canada Council for the Arts to B. C., an ECU College Research Award to K. S., and an NIH Ruth L. Kirschstein National Research Service Award to S. D.

Literature cited

Alberti, A., C. Romano, M. Falco, F. Cali, P. Schinocca, O. Galesi, A. Spalletta *et al.* 2007. 1.5 mb de novo 22q11.21

- microduplication in a patient with cognitive deficits and dysmorphic facial features. *Clinical Genetics* **71**:177–182.
- Allen, N. C., S. Bagade, M. B. McQueen, J. P. A. Ioannidis, F. K. Kavvoura, M. J. Khoury, R. E. Tanzi *et al.* 2008. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. *Nature Genetics* **40**:827–834.
- Altshuler, L. L., S. Y. Bookheimer, J. Townsend, M. A. Proenza, N. Eisenberger, F. Sabb, J. Mintz *et al.* 2005. Blunted activation in orbitofrontal cortex during mania: a functional magnetic resonance imaging study. *Biological Psychiatry* **58**:763–769.
- Antonell, A., O. de Luis, X. Domingo-Roura, and L. A. Pérez-Jurado. 2005. Evolutionary mechanisms shaping the genomic structure of the Williams-Beuren syndrome chromosomal region at human 7q11.23. *Genome Research* **15**:1179–1188.
- Antshel, K. M., W. R. Kates, N. Roizen, W. Fremont, and R. J. Shprintzen. 2005. 22q11.2 deletion syndrome: genetics, neuroanatomy and cognitive/behavioral features keywords. *Child Neuropsychology* **11**:5–19.
- Antshel, K. M., A. Aneja, L. Strunge, J. Peebles, W. P. Fremont, K. Stallone, N. Abdulsabur *et al.* 2007. Autistic spectrum disorders in velo-cardio-facial syndrome (22q11.2 deletion). *Journal of Autism and Developmental Disorders* **37**:1776–1786.
- Babcock, M., S. Yatsenko, J. Hopkins, M. Brenton, Q. Cao, P. de Jong, P. Stankiewicz *et al.* 2007. Hominoid lineage specific amplification of low-copy repeats on 22q11.2 (LCR22s) associated with velo-cardio-facial/digeorge syndrome. *Human Molecular Genetics* **16**:2560–2571.
- Baker, K. D., and D. H. Skuse. 2005. Adolescents and young adults with 22q11 deletion syndrome: psychopathology in an at-risk group. *British Journal of Psychiatry* **186**:115–120.
- Bassett, A. S., and E. W. C. Chow. 2008. Schizophrenia and 22q11.2 deletion syndrome. *Current Psychiatry Reports* **10**:148–157.
- Bearden, C. E., M. F. Woodin, P. P. Wang, E. Moss, D. McDonald-McGinn, E. Zackai, B. Emmanuel *et al.* 2001. The neurocognitive phenotype of the 22q11.2 deletion syndrome: selective deficit in visual-spatial memory. *Journal of Clinical and Experimental Neuropsychology* **23**:447–464.
- Bearden, C. E., P. P. Wang, and T. J. Simon. 2002. Williams syndrome cognitive profile also characterizes Velocardiofacial/DiGeorge syndrome. *American Journal of Medical Genetics* **114**:689–692.
- Beaudet, A. L., and J. W. Belmont. 2008. Array-based DNA diagnostics: let the revolution begin. *Annual Review of Medicine* **59**:113–129.
- Beckmann, J. S., X. Estivill, and S. E. Antonarakis. 2007. Copy number variants and genetic traits: closer to the resolution of phenotypic to genotypic variability. *Nature Reviews. Genetics* **8**:639–646.
- Berg, J. S., N. Brunetti-Pierri, S. U. Peters, S. L. Kang, C. Fong, J. Salamone, D. Freedenberg *et al.* 2007. Speech delay and autism spectrum behaviors are frequently associated with duplication of the 7q11.23 Williams-Beuren syndrome region. *Genetics in Medicine* **9**:427–441.
- Bersani, G., M. L. Maneschi, E. Tarolla, and P. Pancheri. 2006. Dyslexia as a possible aspect of neurocognitive impairment in schizophrenia. *Schizophrenia Research* **82**:265–266.
- Bersani, G., D. Russo, L. Limpido, and D. Marconi. 2007. Mood disorder in a patient with Smith-Magenis syndrome: a case report. *Neuroendocrinology Letters* **28**:7–10.
- Bi, W., G. M. Saifi, S. Girirajan, X. Shi, B. Szomju, H. Firth, R. E. Magenis *et al.* 2006. RAI1 point mutations, CAG repeat variation, and SNP analysis in non-deletion Smith-Magenis syndrome. *American Journal of Medical Genetics. Part A* **140**:2454–2463.
- Bi, W., J. Yan, X. Shi, L. A. Yuva-Paylor, B. A. Antalffy, A. Goldman, J. W. Yoo *et al.* 2007. Rai1 deficiency in mice causes learning impairment and motor dysfunction, whereas Rai1 heterozygous mice display minimal behavioral phenotypes. *Human Molecular Genetics* **16**:1802–1813.
- Blackwood, D. H. R., B. J. Pickard, P. A. Thomson, K. L. Evans, D. J. Porteous, and W. J. Muir. 2007. Are some genetic risk factors common to schizophrenia, bipolar disorder and depression? Evidence from DISC1, GRIK4 and NRG1. *Neurotoxicity Research* **11**:73–83.
- Boks, M. P. M., M. H. T. de Vette, I. E. Sommer, S. van Rijn, J. C. Giltay, H. Swaab, and R. S. Kahn. 2007. Psychiatric morbidity and X-chromosomal origin in a Klinefelter sample. *Schizophrenia Research* **93**:399–402.
- Bonnefont, J., S. I. Nikolaev, A. L. Perrier, S. Guo, L. Cartier, S. Sorce, T. Laforge *et al.* 2008. Evolutionary forces shape the human RFPL1,2,3 genes toward a role in neocortex development. *American Journal of Human Genetics* **83**:208–218.
- Boone, K. B., R. S. Swerdloff, B. L. Miller, D. H. Geschwind, J. Razani, A. Lee, I. G. Gonzalo *et al.* 2001. Neuropsychological profiles of adults with Klinefelter syndrome. *Journal of the International Neuropsychological Society* **7**:446–456.
- Brandes, B. M., and H. O. Mesrobian. 2005. Evaluation and management of genital anomalies in two patients with Klinefelter syndrome and review of literature. *Urology* **65**:976–979.
- Brock, J. 2007. Language abilities in Williams syndrome: a critical review. *Development and Psychopathology* **19**:97–127.
- Brunet, A., L. Armengol, T. Pelaez, R. Guilat, V. Valles, E. Gabau, X. Estivill *et al.* 2008. Failure to detect the 22q11.2 duplication syndrome among patients with schizophrenia. *Behavioral and Brain Functions* **4**:10.
- Buchanan, J. A., and S. W. Scherer. 2008. Contemplating effects of genomic structural variation. *Genetics in Medicine* **10**:639–647.
- Bulayeva, K. B., S. M. Leal, T. A. Pavlova, R. M. Kurbanov, S. J. Glatt, O. A. Bulayev, and M. T. Tsuang. 2005. Mapping genes of complex psychiatric diseases in Daghestan genetic

- isolates. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics* **132**:76–84.
- Bulayeva, K. B., S. J. Glatt, O. A. Bulayev, T. A. Pavlova, and M. T. Tsuang. 2007. Genome-wide linkage scan of schizophrenia: a cross-isolate study. *Genomics* **89**:167–177.
- Burns, J. K. 2004. An evolutionary theory of schizophrenia: cortical connectivity, metarepresentation, and the social brain. *Behavioral and Brain Sciences* **27**:831–855.
- Cantor, R. M., and D. H. Geschwind. 2008. Schizophrenia: genome, interrupted. *Neuron* **58**:165–167.
- Caron, M.-J., L. Mottron, C. Rainville, and S. Chouinard. 2004. Do high functioning persons with autism present superior spatial abilities? *Neuropsychologia* **42**:467–481.
- Caron, M.-J., L. Mottron, C. Berthiaume, and M. Dawson. 2006. Cognitive mechanisms, specificity and neural underpinnings of visuospatial peaks in autism. *Brain* **129**:1789–1802.
- Carrel, L., and H. F. Willard. 2005. X-inactivation profile reveals extensive variability in X-linked gene expression in females. *Nature* **434**:400–404.
- Chiang, M., A. L. Reiss, A. D. Lee, U. Bellugi, A. M. Galaburda, J. R. Korenberg, D. L. Mills *et al.* 2007. 3D pattern of brain abnormalities in Williams syndrome visualized using tensor-based morphometry. *Neuroimage* **36**:1096–1109.
- Chow, E. W. C., M. Watson, D. A. Young, and A. S. Bassett. 2006. Neurocognitive profile in 22q11 deletion syndrome and schizophrenia. *Schizophrenia Research* **87**:270–278.
- Christian, S. L., C. W. Brune, J. Sudi, R. A. Kumar, S. Liu, S. Karamohamed, J. A. Badner, *et al.* 2008. Novel submicroscopic chromosomal abnormalities detected in autism spectrum disorder. *Biological Psychiatry* **63**:1111–1117.
- Cooper, G. M., D. A. Nickerson, and E. E. Eichler. 2007. Mutational and selective effects on copy-number variants in the human genome. *Nature Genetics* **39**:22–29.
- Cosoff, S. J., and R. J. Hafner. 1998. The prevalence of comorbid anxiety in schizophrenia, schizoaffective disorder and bipolar disorder. *Australian and New Zealand Journal of Psychiatry* **32**:67–72.
- Courtens, W., I. Schramme, and A. Laridon. 2008. Microduplication 22q11.2: a benign polymorphism or a syndrome with a very large clinical variability and reduced penetrance? – Report of two families. *American Journal of Medical Genetics. Part A* **146**:758–763.
- Craddock, N., and L. Forty. 2006. Genetics of affective (mood) disorders. *European Journal of Human Genetics* **14**:660–668.
- Craig, I. W., E. Harper, and C. S. Loat. 2004. The genetic basis for sex differences in human behaviour: role of the sex chromosomes. *Annals of Human Genetics* **68**:269–284.
- Crespi, B. J. 2008a. Turner syndrome and the evolution of human sexual dimorphism. *Evolutionary Applications* **1**: 449–461.
- Crespi, B. J. 2008b. Genomic imprinting in the development and evolution of psychotic spectrum conditions. *Biological Reviews* **83**:441–493.
- Crespi, B., and C. Badcock. 2008. Psychosis and autism as diametrical disorders of the social brain. *Behavioral and Brain Sciences* **31**:241–320.
- Crespi, B., K. Summers, and S. Dorus. 2007. Adaptive evolution of genes underlying schizophrenia. *Proceedings of the Royal Society of London, Series B. Biological Sciences* **274**:2801–2810.
- Crow, T. J. 2008. The ‘big bang’ theory of the origin of psychosis and the faculty of language. *Schizophrenia Research* **102**:31–52.
- Davies, W., and L. S. Wilkinson. 2006. It is not all hormones: alternative explanations for sexual differentiation of the brain. *Brain Research* **1126**:36–45.
- Debbané, M., B. Glaser, M. K. David, C. Feinstein, and S. Eliez. 2006. Psychotic symptoms in children and adolescents with 22q11.2 deletion syndrome: neuropsychological and behavioral implications. *Schizophrenia Research* **84**:187–193.
- DeLisi, L. E., U. Friedrich, J. Wahlstrom, A. Boccio-Smith, A. Forsman, K. Eklund, and T. J. Crow. 1994. Schizophrenia and sex chromosome anomalies. *Schizophrenia Bulletin* **20**:495–505.
- DeLisi, L. E., A. M. Maurizio, C. Svetina, B. Ardekani, K. Szulc, J. Nierenberg, J. Leonard *et al.* 2005. Klinefelter’s syndrome (XXY) as a genetic model for psychotic disorders. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics* **135**:15–23.
- Demuth, J. P., T. De Bie, J. E. Stajich, N. Cristianini, and M. W. Hahn. 2006. The evolution of mammalian gene families. *PLoS ONE* **1**:e85.
- Depienne, C., D. Heron, C. Betancur, B. Benyahia, O. Trouillard, D. Bouteiller, A. Verloes *et al.* 2007. Autism, language delay and mental retardation in a patient with 7q11 duplication. *Journal of Medical Genetics* **44**:452–458.
- Dissanayake, C., Q. M. Bui, R. Huggins, and D. Z. Loesch. 2006. Growth in stature and head circumference in high-functioning autism and Asperger disorder during the first 3 years of life. *Development and Psychopathology* **18**:381–393.
- Donnelly, S. L., C. M. Wolpert, M. M. Menold, M. P. Bass, J. R. Gilbert, M. L. Cuccaro, G. R. Delong *et al.* 2000. Female with autistic disorder and monosomy X (Turner syndrome): parent-of-origin effect of the X chromosome. *American Journal of Medical Genetics* **96**:312–316.
- Doyle, T. F., U. Bellugi, J. R. Korenberg, and J. Graham. 2004. “Everybody in the world is my friend” hypersociability in young children with Williams syndrome. *American Journal of Medical Genetics. Part A*. **124**:263–273.
- Dumas, L., Y. H. Kim, A. Karimpour-Fard, M. Cox, J. Hopkins, J. R. Pollack, and J. M. Sikela. 2007. Gene copy number variation spanning 60 million years of human and primate evolution. *Genome Research* **17**:1266–1277.
- Dykens, E. M. 2003. Anxiety, fears, and phobias in persons with Williams syndrome. *Developmental Neuropsychology* **23**:291–316.

- Dykens, E. M., B. M. Finucane, and C. Gayley. 1997. Brief report: cognitive and behavioral profiles in persons with Smith-Magenis syndrome. *Journal of Autism and Developmental Disorders* **27**:203–211.
- Dykens, E. M., R. M. Hodapp, and B. M. Finucane. 2000. *Genetics and Mental Retardation Syndromes: A New Look at Behavior and Interventions*. Brookes Publishing Company, Baltimore, MD.
- Edelmann, L., A. Prosnitz, S. Pardo, J. Bhatt, N. Cohen, T. Lauriat, L. Ouchanov *et al.* 2007. An atypical deletion of the Williams-Beuren syndrome interval implicates genes associated with defective visuospatial processing and autism. *Journal of Medical Genetics* **44**:136–143.
- Eliez, S. 2007. Autism in children with 22q11.2 deletion syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry* **46**:433–434.
- Elsea, S. H., and S. Girirajan. 2008. Smith-Magenis syndrome. *European Journal of Human Genetics* **16**:412–421.
- Emanuel, B. S., and S. C. Saitta. 2007. From microscopes to microarrays: dissecting recurrent chromosomal rearrangements. *Nature Reviews. Genetics* **8**:869–883.
- Enard, W., M. Przeworski, S. E. Fisher, C. S. L. Lai, V. Wiebe, T. Kitano, A. P. Monaco *et al.* 2002. Molecular evolution of FOXP2, a gene involved in speech and language. *Nature* **418**:869–872.
- Ensenauer, R. E., A. Adeyinka, H. C. Flynn, V. V. Michels, N. M. Lindor, D. B. Dawson, E. C. Thorland *et al.* 2003. Microduplication 22q11.2, an emerging syndrome: clinical, cytogenetic, and molecular analysis of thirteen patients. *American Journal of Human Genetics* **73**:1027–1040.
- Evans, P. D., S. L. Gilbert, N. Mekel-Bobrov, E. J. Vallender, J. R. Anderson, L. M. Vaez-Azizi, S. A. Tishkoff *et al.* 2005. Microcephalin, a gene regulating brain size, continues to evolve adaptively in humans. *Science* **309**:1717–1720.
- Everman, D. B., and A. Stoudemire. 1994. Bipolar disorder associated with Klinefelter's syndrome and other chromosomal abnormalities. *Psychosomatics* **35**:35–40.
- Fales, C. L., B. J. Knowlton, K. J. Holyoak, D. H. Geschwind, R. S. Swerdloff, and I. G. Gonzalo. 2003. Working memory and relational reasoning in Klinefelter syndrome. *Journal of the International Neuropsychological Society* **9**:839–846.
- Fanous, A. H., M. C. Neale, C. O. Gardner, B. T. Webb, R. E. Straub, F. A. O'Neill, D. Walsh *et al.* 2007. Significant correlation in linkage signals from genome-wide scans of schizophrenia and schizotypy. *Molecular Psychiatry* **12**:958–965.
- Feinstein, C., and S. Singh. 2007. Social phenotypes in neurogenetic syndromes. *Child and Adolescent Psychiatric Clinics of North America* **16**:631–647.
- Feinstein, C., S. Eliez, C. Blasey, and A. L. Reiss. 2002. Psychiatric disorders and behavioral problems in children with velocardiofacial syndrome: usefulness as phenotypic indicators of schizophrenia risk. *Biological Psychiatry* **51**:312–318.
- Fidler, D. J., S. L. Hepburn, D. E. Most, A. Philofsky, and S. J. Rogers. 2007. Emotional responsivity in young children with Williams syndrome. *American Journal of Mental Retardation* **112**:194–206.
- Fukumoto, A., T. Hashimoto, H. Ito, M. Nishimura, Y. Tsuda, M. Miyazaki, K. Mori *et al.* 2008. Growth of head circumference in autistic infants during the first year of life. *Journal of Autism and Developmental Disorders* **38**:411–418.
- Geschwind, D. H., K. B. Boone, B. L. Miller, and R. S. Swerdloff. 2000. Neurobehavioral phenotype of Klinefelter syndrome. *Mental Retardation and Developmental Disabilities Research Reviews* **6**:107–116.
- Giedd, J. N., L. S. Clasen, G. L. Wallace, R. K. Lenroot, J. P. Lerch, E. M. Wells, J. D. Blumenthal *et al.* 2007. XXY (Klinefelter syndrome): a pediatric quantitative brain magnetic resonance imaging case-control study. *Pediatrics* **119**:e232–e240.
- Girirajan, S., C. N. Vlangos, B. B. Szomju, E. Edelman, C. D. Trevors, L. Dupuis, M. Nezarati *et al.* 2006. Genotype-phenotype correlation in Smith-Magenis syndrome: evidence that multiple genes in 17p11.2 contribute to the clinical spectrum. *Genetics in Medicine* **8**:417–427.
- Girirajan, S., S. R. Williams, J. Y. Garbern, N. Nowak, E. Hatchwell, and S. H. Elsea. 2007. 17p11.2p12 triplication and del(17)q11.2q12 in a severely affected child with dup(17)p11.2p12 syndrome. *Clinical Genetics* **72**:47–58.
- Girirajan, S., N. Patel, R. E. Slager, M. E. Tokarz, M. Bucan, J. L. Wiley, and S. H. Elsea. 2008. How much is too much? phenotypic consequences of *Rai1* overexpression in mice. *European Journal of Human Genetics* **16**:941–954.
- Good, C. D., K. Lawrence, N. S. Thomas, C. J. Price, J. Ashburner, K. J. Friston, R. S. J. Frackowiak *et al.* 2003. Dosage-sensitive X-linked locus influences the development of amygdala and orbitofrontal cortex, and fear recognition in humans. *Brain* **126**:2431–2446.
- Gothelf, D. 2007. Velocardiofacial syndrome. *Child and Adolescent Psychiatric Clinics of North America* **16**:677–693.
- Gothelf, D., S. Eliez, T. Thompson, C. Hinard, L. Penniman, C. Feinstein, H. Kwon *et al.* 2005. COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome. *Nature Neuroscience* **8**:1500–1502.
- Gothelf, D., L. Penniman, E. Gu, S. Eliez, and A. L. Reiss. 2007a. Developmental trajectories of brain structure in adolescents with 22q11.2 deletion syndrome: a longitudinal study. *Schizophrenia Research* **96**:72–81.
- Gothelf, D., C. Feinstein, T. Thompson, E. Gu, L. Penniman, E. Van Stone, H. Kwon *et al.* 2007b. Risk factors for the emergence of psychotic disorders in adolescents with 22q11.2 deletion syndrome. *American Journal of Psychiatry* **164**:663–669.
- Gothelf, D., M. Schaer, and S. Eliez. 2008. Genes, brain development and psychiatric phenotypes in velo-cardio-facial syndrome. *Developmental Disabilities Research Reviews* **14**:59–68.
- Graham, J. M., A. S. Bashir, R. E. Stark, A. Silbert, and S. Walzer. 1988. Oral and written language abilities of XXY

- boys: implications for anticipatory guidance. *Pediatrics* **81**:795–806.
- Gray, V., A. Karmiloff-Smith, E. Funnell, and M. Tassabehji. 2006. In-depth analysis of spatial cognition in Williams syndrome: a critical assessment of the role of the LIMK1 gene. *Neuropsychologia* **44**:679–685.
- Gropman, A. L., S. Elsea, W. C. Duncan, and A. C. M. Smith. 2007. New developments in Smith-Magenis syndrome (del 17p11.2). *Current Opinion in Neurology* **20**:125–134.
- Gur, R. E., M. S. Keshavan, and S. M. Lawrie. 2007. Deconstructing psychosis with human brain imaging. *Schizophrenia Bulletin* **33**:921–931.
- Haig, D. 2004. Genomic imprinting and kinship: how good is the evidence? *Annual Review of Genetics* **38**:553–585.
- Hassed, S. J., D. Hopcus-Niccum, L. Zhang, S. Li, and J. J. Mulvihill. 2004a. A new genomic duplication syndrome complementary to the velocardiofacial (22q11 deletion) syndrome. *Clinical Genetics* **65**:400–404.
- Hassed, S., S. A. Vaz, J. Lee, J. J. Mulvihill, and S. Li. 2004b. Expanded phenotype of the 22q duplication syndrome. *American Journal of Human Genetics* **75**(Suppl.):151.
- Helena Mangs, A., and B. J. Morris. 2007. The human pseudoautosomal region (PAR): origin, function and future. *Current Genomics* **8**:129–136.
- Herbert, M. R., D. A. Ziegler, N. Makris, P. A. Filipek, T. L. Kemper, J. J. Normandin, H. A. Sanders *et al.* 2004. Localization of white matter volume increase in autism and developmental language disorder. *Annals of Neurology* **55**:530–540.
- Herguner, S., and N. M. Mukaddes. 2006. Autism and Williams syndrome: a case report. *World Journal of Biological Psychiatry* **7**:186–188.
- Hoogenraad, C. C., A. Akhmanova, N. Galjart, and C. I. De Zeeuw. 2004. LIMK1 and CLIP-115: linking cytoskeletal deficits to Williams syndrome. *Bioessays* **26**:141–150.
- Huppert, J. D., and T. E. Smith. 2005. Anxiety and schizophrenia: the interaction of subtypes of anxiety and psychotic symptoms. *CNS Spectrums* **10**:721–731.
- Itti, E., I. T. Gaw Gonzalo, K. B. Boone, D. H. Geschwind, N. Berman, A. Pawlikowska-Haddal, L. Itti *et al.* 2003. Functional neuroimaging provides evidence of anomalous cerebral laterality in adults with Klinefelter's syndrome. *Annals of Neurology* **54**:669–673.
- Itti, E., I. T. Gaw Gonzalo, A. Pawlikowska-Haddal, K. B. Boone, A. Mliktic, L. Itti, F. S. Mishkin *et al.* 2006. The structural brain correlates of cognitive deficits in adults with Klinefelter's syndrome. *Journal of Clinical Endocrinology and Metabolism* **91**:1423–1427.
- Jha, P., D. Sheth, and M. Ghaziuddin. 2007. Autism spectrum disorder and Klinefelter syndrome. *European Child & Adolescent Psychiatry* **16**:305–308.
- Jones, W., U. Bellugi, Z. Lai, M. Chiles, J. Reilly, A. Lincoln, and R. Adolphs. 2000. II. Hypersociability in Williams syndrome. *Journal of Cognitive Neuroscience* **12**(Suppl. 1):30–46.
- Joover, R., C. Benkelfat, A. Toulouse, R. G. Lafrenière, S. Lal, S. Ajroud, G. Turecki *et al.* 1999. Analysis of 14 CAG repeat-containing genes in schizophrenia. *American Journal of Medical Genetics* **88**:694–699.
- Kalscheuer, V. M., D. FitzPatrick, N. Tommerup, M. Bugge, E. Niebuhr, L. M. Neumann, A. Tzschach *et al.* 2007. Mutations in autism susceptibility candidate 2 (AUTS2) in patients with mental retardation. *Human Genetics* **121**:501–509.
- Kates, W. R., K. M. Antshel, W. P. Fremont, R. J. Shprintzen, L. A. Strunge, C. P. Burnette, and A. M. Higgins. 2007. Comparing phenotypes in patients with idiopathic autism to patients with velocardiofacial syndrome (22q11 DS) with and without autism. *American Journal of Medical Genetics. Part A*. **143**:2642–2650.
- Kaufmann, W. E., K. L. Cooper, S. H. Mostofsky, G. T. Capone, W. R. Kates, C. J. Newschaffer, I. Bukelis *et al.* 2003. Specificity of cerebellar vermal abnormalities in autism: a quantitative magnetic resonance imaging study. *Journal of Child Neurology* **18**:463–470.
- Kesler, S. R. 2007. Turner syndrome. *Child and Adolescent Psychiatric Clinics of North America* **16**:709–722.
- Khaitovich, P., W. Enard, M. Lachmann, and S. Pääbo. 2006. Evolution of primate gene expression. *Nature Reviews. Genetics* **7**:693–702.
- Kirchhoff, M., A. Bisgaard, T. Bryndorf, and T. Gerdes. 2007. MLPA analysis for a panel of syndromes with mental retardation reveals imbalances in 5.8% of patients with mental retardation and dysmorphic features, including duplications of the Sotos syndrome and Williams-Beuren syndrome regions. *European Journal of Medical Genetics* **50**:33–42.
- Klein-Tasman, B. P., C. B. Mervis, C. Lord, and K. D. Phillips. 2007. Socio-communicative deficits in young children with Williams syndrome: performance on the autism diagnostic observation schedule. *Child Neuropsychology* **13**:444–467.
- Kobrynski, L. J., and K. E. Sullivan. 2007. Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. *Lancet* **370**:1443–1452.
- Konneker, T., T. Barnes, H. Furberg, M. Losh, C. M. Bulik, and P. F. Sullivan. 2008. A searchable database of genetic evidence for psychiatric disorders. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics* **147**:671–675.
- Korbel, J. O., P. M. Kim, X. Chen, A. E. Urban, S. Weissman, M. Snyder, and M. B. Gerstein. 2008. The current excitement about copy-number variation: how it relates to gene duplications and protein families. *Current Opinion in Structural Biology* **18**:366–374.
- Kravariti, E., T. Touloupoulou, F. Mapua-Filbey, K. Schulze, M. Walshe, P. Sham, R. M. Murray *et al.* 2006. Intellectual asymmetry and genetic liability in first-degree relatives of probands with schizophrenia. *British Journal of Psychiatry* **188**:186–187.
- de La Rochebrochard, C., G. Joly-Hélas, A. Goldenberg, I. Durand, A. Laquerrière, V. Ickowicz, P. Saugier-Verber

- et al.* 2006. The intrafamilial variability of the 22q11.2 microduplication encompasses a spectrum from minor cognitive deficits to severe congenital anomalies. *American Journal of Medical Genetics. Part A* **140**:1608–1613.
- Lainhart, J. E., E. D. Bigler, M. Bocian, H. Coon, E. Dinh, G. Dawson, C. K. Deutsch *et al.* 2006. Head circumference and height in autism: a study by the collaborative program of excellence in autism. *American Journal of Medical Genetics. Part A* **140**:2257–2274.
- Lajiness-O'Neill, R., I. Beaulieu, A. Asamoah, J. B. Titus, E. Bawle, S. Ahmad, J. W. Kirk *et al.* 2006. The neuropsychological phenotype of velocardiofacial syndrome (VCFS): relationship to psychopathology. *Archives of Clinical Neuropsychology* **21**:175–184.
- Lauritsen, M., O. Mors, P. B. Mortensen, and H. Ewald. 1999. Infantile autism and associated autosomal chromosome abnormalities: a register-based study and a literature survey. *Journal of Child Psychology and Psychiatry, and Allied Disciplines* **40**:335–345.
- Lawrence, K., R. Campbell, J. Swettenham, J. Terstegge, R. Akers, M. Coleman, and D. Skuse. 2003. Interpreting gaze in Turner syndrome: impaired sensitivity to intention and emotion, but preservation of social cueing. *Neuropsychologia* **41**:894–905.
- Laws, G., and D. Bishop. 2004. Pragmatic language impairment and social deficits in Williams syndrome: a comparison with Down's syndrome and specific language impairment. *International Journal of Language & Communication Disorders* **39**:45–64.
- Le Hellard, S., T. W. Mühleisen, S. Djurovic, J. Fernø, Z. Ouriaghli, M. Mattheisen, C. Vasilescu *et al.* 2008. Polymorphisms in SREBF1 and SREBF2, two antipsychotic-activated transcription factors controlling cellular lipogenesis, are associated with schizophrenia in German and Scandinavian samples. *Molecular Psychiatry* (in press).
- Lencz, T., K. E. Burdick, P. DeRosse, T. V. Morgan, J. M. Kane, R. Kucherlapati, and A. K. Malhotra. 2007a. *MCPHI* is associated with risk for illness and cognitive ability in patients with schizophrenia. *Biological Psychiatry* **61**(Suppl. 160):609.
- Lencz, T., T. V. Morgan, M. Athanasiou, B. Dain, C. R. Reed, J. M. Kane, R. Kucherlapati *et al.* 2007b. Converging evidence for a pseudoautosomal cytokine receptor gene locus in schizophrenia. *Molecular Psychiatry* **12**:572–580.
- Lewandowski, K. E., V. Shashi, P. M. Berry, and T. R. Kwapil. 2007. Schizophrenic-like neurocognitive deficits in children and adolescents with 22q11 deletion syndrome. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics* **144**:27–36.
- Leyfer, O. T., J. Woodruff-Borden, B. P. Klein-Tasman, J. S. Fricke, and C. B. Mervis. 2006. Prevalence of psychiatric disorders in 4 to 16-year-olds with Williams syndrome. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics* **141**:615–622.
- Lincoln, A. J., Y. M. Searcy, W. Jones, and C. Lord. 2007. Social interaction behaviors discriminate young children with autism and Williams syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry* **46**:323–331.
- Liu, H., S. C. Heath, C. Sobin, J. L. Roos, B. L. Galke, M. L. Blundell, M. Lenane *et al.* 2002. Genetic variation at the 22q11 *PRODH2/DGCR6* locus presents an unusual pattern and increases susceptibility to schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America* **99**:3717–3722.
- Liu, Y., H. Zhang, G. Ju, X. Zhang, Q. Xu, S. Liu, Y. Yu *et al.* 2007. A study of the *PENT* gene in schizophrenia. *Neuroscience Letters* **424**:203–206.
- Lynn, P. M. Y., and W. Davies. 2007. The 39,XO mouse as a model for the neurobiology of Turner syndrome and sex-biased neuropsychiatric disorders. *Behavioural Brain Research* **179**:173–182.
- Marshall, C. R., A. Noor, J. B. Vincent, A. C. Lionel, L. Feuk, J. Skaug, M. Shago *et al.* 2008. Structural variation of chromosomes in autism spectrum disorder. *American Journal of Human Genetics* **82**:477–488.
- Martens, M. A., S. J. Wilson, and D. C. Reutens. 2008. Research review: Williams syndrome: a critical review of the cognitive, behavioral, and neuroanatomical phenotype. *Journal of Child Psychology and Psychiatry, and Allied Disciplines* **49**:576–608.
- Martin, S. C., P. L. Wolters, and A. C. M. Smith. 2006. Adaptive and maladaptive behavior in children with Smith-Magenis syndrome. *Journal of Autism and Developmental Disorders* **36**:541–552.
- Maynard, T. M., G. T. Haskell, J. A. Lieberman, and A. LaMantia. 2002. 22q11 DS: genomic mechanisms and gene function in DiGeorge/velocardiofacial syndrome. *International Journal of Developmental Neuroscience* **20**:407–419.
- McCarroll, S. A., and D. M. Altshuler. 2007. Copy-number variation and association studies of human disease. *Nature Genetics* **39**:s37–s42.
- McClellan, J., D. Breiger, C. McCurry, and S. A. Hlastala. 2003. Premorbid functioning in early-onset psychotic disorders. *Journal of the American Academy of Child and Adolescent Psychiatry* **42**:666–672.
- Meehan, D. W., T. M. Maynard, D. Gopalakrishna, Y. Wu, and A. S. LaMantia. 2007. When half is not enough: gene expression and dosage in the 22q11 deletion syndrome. *Gene Expression* **13**:299–310.
- Mefford, H. C., A. J. Sharp, C. Baker, A. Itsara, Z. Jiang, K. Buysse, S. Huang *et al.* 2008. Recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes. *New England Journal of Medicine* **359**:1685–1699.
- Melke, J., H. Goubran Botros, P. Chaste, C. Betancur, G. Nygren, H. Anckarsäter, M. Rastam *et al.* 2008. Abnormal melatonin synthesis in autism spectrum disorders. *Molecular Psychiatry* **13**:90–98.

- Meng, Y., Y. Zhang, V. Tregoubov, C. Janus, L. Cruz, M. Jackson, W. Y. Lu *et al.* 2002. Abnormal spine morphology and enhanced LTP in LIMK-1 knockout mice. *Neuron* **35**: 121–133.
- Merhar, S. L., and P. Manning-Courtney. 2007. Two boys with 47, XXY and autism. *Journal of Autism and Developmental Disorders* **37**:840–846.
- Merla, G., C. Howald, C. N. Henrichsen, R. Lyle, C. Wyss, M. Zobot, S. E. Antonarakis *et al.* 2006. Submicroscopic deletion in patients with Williams-Beuren syndrome influences expression levels of the nonhemizygous flanking genes. *American Journal of Human Genetics* **79**:332–341.
- Mervis, C. B., C. A. Morris, B. P. Klein-Tasman, J. Bertrand, S. Kwitny, L. G. Appelbaum, and C. E. Rice. 2003. Attentional characteristics of infants and toddlers with Williams syndrome during triadic interactions. *Developmental Neuropsychology* **23**:243–268.
- Meyer-Lindenberg, A., A. R. Hariri, K. E. Munoz, C. B. Mervis, V. S. Mattay, C. A. Morris, and K. F. Berman. 2005. Neural correlates of genetically abnormal social cognition in Williams syndrome. *Nature Neuroscience* **8**:991–993.
- Meyer-Lindenberg, A., C. B. Mervis, and K. F. Berman. 2006. Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behaviour. *Nature Reviews. Neuroscience* **7**:380–393.
- Miller, D. T., Y. Shen, L. A. Weiss, J. Korn, I. Anslern, C. Bridgemohan, G. F. Cox, *et al.* 2008. Microdeletion / duplication at 15q13.2q13.3 among individuals with features of autism and other neuropsychiatric disorders. *Journal of Medical Genetics* (in press).
- Mills, J. L., M. L. Hediger, C. A. Molloy, G. P. Chrousos, P. Manning-Courtney, K. F. Yu, M. Brasington *et al.* 2007. Elevated levels of growth-related hormones in autism and autism spectrum disorder. *Clinical Endocrinology* **67**:230–237.
- Mizukami, K., J. Koizumi, H. Shiraishi, and S. Nagase. 1989. A clinical case of Klinefelter's syndrome with various psychiatric symptoms. *Japanese Journal of Psychiatry and Neurology* **43**:639–644.
- Molina, J., P. Carmona-Mora, J. Chrast, P. M. Krall, C. P. Canales, J. R. Lupski, A. Reymond *et al.* 2008. Abnormal social behaviors and altered gene expression rates in a mouse model for Potocki-Lupski syndrome. *Human Molecular Genetics* **17**:2486–2495.
- Molko, N., A. Cachia, D. Riviere, J. F. Mangin, M. Bruandet, D. LeBihan, L. Cohen *et al.* 2004. Brain anatomy in Turner syndrome: evidence for impaired social and spatial-numerical networks. *Cerebral Cortex* **14**:840–850.
- Money, J. 1993. Specific neuro-cognitive impairments associated with Turner (45,X) and Klinefelter (47,XXY) syndromes: a review. *Social Biology* **40**:147–151.
- Moog, U., J. J. Engelen, B. W. Weber, M. Van Gelderen, J. Steyaert, F. Baas, H. M. Sijstermans *et al.* 2004. Hereditary motor and sensory neuropathy (HMSN) IA, developmental delay and autism related disorder in a boy with duplication (17)(p11.2p12). *Genetic Counseling* **15**:73–80.
- Mors, O., P. B. Mortensen, and H. Ewald. 2001. No evidence of increased risk for schizophrenia or bipolar affective disorder in persons with aneuploidies of the sex chromosomes. *Psychological Medicine* **31**:425–430.
- Mraz, K. D., J. Green, T. Dumont-Mathieu, S. Makin, and D. Fein. 2007. Correlates of head circumference growth in infants later diagnosed with autism spectrum disorders. *Journal of Child Neurology* **22**:700–713.
- Mukaddes, N. M., and S. Herguner. 2007. Autistic disorder and 22q11.2 duplication. *World Journal of Biological Psychiatry* **8**:127–130.
- Mulle, J. G. 2008. Genomic structural variation and schizophrenia. *Current Psychiatry Reports* **10**:171–177.
- Murphy, K. C. 2002. Schizophrenia and velo-cardio-facial syndrome. *Lancet* **359**:426–430.
- Nakamura, K., A. Anitha, K. Yamada, M. Tsujii, Y. Iwayama, E. Hattori, T. Toyota *et al.* 2008. Genetic and expression analyses reveal elevated expression of syntaxin 1A (STX1A) in high functioning autism. *International Journal of Neuropsychopharmacology* **2**:1–12.
- Newman, T. M., D. Macomber, A. J. Naples, T. Babitz, F. Volkmar, and E. L. Grigorenko. 2007. Hyperlexia in children with autism spectrum disorders. *Journal of Autism and Developmental Disorders* **37**:760–774.
- Nguyen, D., C. Webber, and C. P. Ponting. 2006. Bias of selection on human copy-number variants. *Plos Genetics* **2**:e20.
- Nguyen, D. Q., C. P. Webber, J. Hehir-Kwa, R. Pfundt, J. Veltman, and C. P. Ponting. 2008. Reduced purifying selection prevails over positive selection in human copy number variant evolution. *Genome Research* **18**:1711–1723.
- Niemi, L. T., J. M. Suvisaari, J. K. Haukka, and J. K. Lönqvist. 2005. Childhood growth and future development of psychotic disorder among Helsinki high-risk children. *Schizophrenia Research* **76**:105–112.
- Nijhuis-van der Sanden, M. W. G., P. A. T. M. Eling, and B. J. Otten. 2003. A review of neuropsychological and motor studies in Turner syndrome. *Neuroscience and Biobehavioral Reviews* **27**:329–338.
- Niklasson, L., P. Rasmussen, S. Oskarsdóttir, and C. Gillberg. 2001. Neuropsychiatric disorders in the 22q11 deletion syndrome. *Genetics in Medicine* **3**:79–84.
- Nilsson, E., G. Stålberg, P. Lichtenstein, S. Cnattingius, P. O. Olausson, and C. M. Hultman. 2005. Fetal growth restriction and schizophrenia: a Swedish twin study. *Twin Research and Human Genetics* **8**:402–408.
- O'Driscoll, M., W. B. Dobyns, J. M. van Hagen, and P. A. Jeggo. 2007. Cellular and clinical impact of haploinsufficiency for genes involved in ATR signaling. *American Journal of Human Genetics* **81**:77–86.
- Ogdie, M. N., I. L. Macphie, S. L. Minassian, M. Yang, S. E. Fisher, C. Francks, R. M. Cantor *et al.* 2003. A genome-wide scan for attention-deficit/hyperactivity disorder in

- an extended sample: suggestive linkage on 17p11. *American Journal of Human Genetics* **72**:1268–1279.
- Orellana, C., J. Bernabeu, S. Monfort, M. Roselló, S. Oltra, I. Ferrer, R. Quiroga *et al.* 2008. Duplication of the Williams-Beuren critical region: case report and further delineation of the phenotypic spectrum. *Journal of Medical Genetics* **45**:187–189.
- Ou, Z., J. S. Berg, H. Yonath, V. B. Enciso, D. T. Miller, J. Picker, T. Lenzi *et al.* 2008. Microduplications of 22q11.2 are frequently inherited and are associated with variable phenotypes. *Genetics in Medicine* **10**:267–277.
- Paylor, R., B. Glaser, A. Mupo, P. Ataliotis, C. Spencer, A. Sobotka, C. Sparks *et al.* 2006. Tbx1 haploinsufficiency is linked to behavioral disorders in mice and humans: implications for 22q11 deletion syndrome. *Proceedings of the National Academy of Sciences of the United States of America* **103**:7729–7734.
- Peterson, B. S., and J. Panksepp. 2004. *Biological Basis of Childhood Neuropsychiatric Disorders*. Wiley, Hoboken, NJ.
- Pober, B. R., and E. M. Dykens. 1996. Williams syndrome: an overview of medical, cognitive, and behavioral features. *Child and Adolescent Psychiatric Clinics of North America* **5**:929–943.
- Porter, M. A., and M. Coltheart. 2005. Cognitive heterogeneity in Williams syndrome. *Developmental Neuropsychology* **27**:275–306.
- Porter, M. A., M. Coltheart, and R. Langdon. 2007. The neuropsychological basis of hypersociability in Williams and Down syndrome. *Neuropsychologia* **45**:2839–2849.
- Portnoi, M., F. Lebas, N. Gruchy, A. Ardalan, V. Biran-Mucignat, V. Malan, L. Finkel *et al.* 2005. 22q11.2 duplication syndrome: two new familial cases with some overlapping features with DiGeorge/velocardiofacial syndromes. *American Journal of Medical Genetics. Part A* **137**:47–51.
- Potash, J. B. 2006. Carving chaos: genetics and the classification of mood and psychotic syndromes. *Harvard Review of Psychiatry* **14**:47–63.
- Potocki, L., W. Bi, D. Treadwell-Deering, C. M. B. Carvalho, A. Eifert, E. M. Friedman, D. Glaze *et al.* 2007. Characterization of Potocki-Lupski syndrome (dup(17)(p11.2p11.2)) and delineation of a dosage-sensitive critical interval that can convey an autism phenotype. *American Journal of Human Genetics* **80**:633–649.
- Prasad, S. E., S. Howley, and K. C. Murphy. 2008. Candidate genes and the behavioral phenotype in 22q11.2 deletion syndrome. *Developmental Disabilities Research Reviews* **14**:26–34.
- Ratcliffe, S. G., G. E. Butler, and M. Jones. 1990. Edinburgh study of growth and development of children with sex chromosome abnormalities. IV. Birth Defects Original Article Series **26**:1–44.
- Ratcliffe, S. G., N. Masera, H. Pan, and M. McKie. 1994. Head circumference and IQ of children with sex chromosome abnormalities. *Developmental Medicine and Child Neurology* **36**:533–544.
- Redon, R., S. Ishikawa, K. R. Fitch, L. Feuk, G. H. Perry, T. D. Andrews, H. Fiegler *et al.* 2006. Global variation in copy number in the human genome. *Nature* **444**:444–454.
- Reiss, A. L., S. Eliez, J. E. Schmitt, E. Straus, Z. Lai, W. Jones, and U. Bellugi. 2000. IV. Neuroanatomy of Williams syndrome: a high-resolution MRI study. *Journal of Cognitive Neuroscience* **12**(Suppl. 1):65–73.
- Reiss, A. L., M. A. Eckert, F. E. Rose, A. Karchemskiy, S. Kesler, M. Chang, M. F. Reynolds *et al.* 2004. An experiment of nature: brain anatomy parallels cognition and behavior in Williams syndrome. *Journal of Neuroscience* **24**:5009–5015.
- Revheim, N., P. D. Butler, I. Schechter, M. Jalbrzikowski, G. Silipo, and D. C. Javitt. 2006. Reading impairment and visual processing deficits in schizophrenia. *Schizophrenia Research* **87**:238–245.
- Riby, D. M., and P. J. B. Hancock. 2008. Viewing it differently: social scene perception in Williams syndrome and autism. *Neuropsychologia* **46**:2855–2860.
- Ried, K., E. Rao, K. Schiebel, and G. A. Rappold. 1998. Gene duplications as a recurrent theme in the evolution of the human pseudoautosomal region 1: isolation of the gene ASMTL. *Human Molecular Genetics* **7**:1771–1778.
- van Rijn, S., A. Aleman, H. Swaab, and R. S. Kahn. 2005. Neurobiology of emotion and high risk for schizophrenia: role of the amygdala and the X-chromosome. *Neuroscience and Biobehavioral Reviews* **29**:385–397.
- van Rijn, S., A. Aleman, H. Swaab, and R. Kahn. 2006. Klinefelter's syndrome (karyotype 47,XXY) and schizophrenia-spectrum pathology. *British Journal of Psychiatry* **189**:459–460.
- Ross, J. L., C. Samango-Sprouse, N. Lahlou, K. Kowal, F. F. Elder, and A. Zinn. 2005. Early androgen deficiency in infants and young boys with 47,XXY Klinefelter syndrome. *Hormone Research* **64**:39–45.
- Ross, J., D. Roeltgen, and A. Zinn. 2006. Cognition and the sex chromosomes: studies in Turner syndrome. *Hormone Research* **65**:47–56.
- Rovet, J. 2004. Turner syndrome: a review of genetic and hormonal influences on neuropsychological functioning. *Child Neuropsychology* **10**:262–279.
- Russell, H. F., D. Wallis, M. M. M. Mazzocco, T. Moshang, E. Zackai, A. R. Zinn, J. L. Ross *et al.* 2006. Increased prevalence of ADHD in Turner syndrome with no evidence of imprinting effects. *Journal of Pediatric Psychology* **31**:945–955.
- Sacco, R., R. Militerni, A. Froli, C. Bravaccio, A. Gritti, M. Elia, P. Curatolo *et al.* 2007. Clinical, morphological, and biochemical correlates of head circumference in autism. *Biological Psychiatry* **62**:1038–1047.
- Sarimski, K. 2004. Communicative competence and behavioural phenotype in children with Smith-Magenis syndrome. *Genetic Counseling* **15**:347–355.
- Schmitt, J. E., S. Eliez, I. S. Warsofsky, U. Bellugi, and A. L. Reiss. 2001. Enlarged cerebellar vermis in Williams syndrome. *Journal of Psychiatric Research* **35**:225–229.

- Sebat, J., B. Lakshmi, D. Malhotra, J. Troge, C. Lese-Martin, T. Walsh, B. Yamrom *et al.* 2007. Strong association of de novo copy number mutations with autism. *Science* **316**:445–449.
- Sha, K. 2008. A mechanistic view of genomic imprinting. *Annual Review of Genomics and Human Genetics* **9**:197–216.
- Shaikh, T. H., H. Kurahashi, S. C. Saitta, A. M. O'Hare, P. Hu, B. A. Roe, D. A. Driscoll *et al.* 2000. Chromosome 22-specific low copy repeats and the 22q11.2 deletion syndrome: genomic organization and deletion endpoint analysis. *Human Molecular Genetics* **9**:489–501.
- Sharp, A. J., S. Hansen, R. R. Selzer, Z. Cheng, R. Regan, J. A. Hurst, H. Stewart *et al.* 2006. Discovery of previously unidentified genomic disorders from the duplication architecture of the human genome. *Nature Genetics* **38**:1038–1042.
- Shelley, B. P., and M. M. Robertson. 2005. The neuropsychiatry and multisystem features of the Smith-Magenis syndrome: a review. *Journal of Neuropsychiatry and Clinical Neurosciences* **17**:91–97.
- Shelley, B. P., M. M. Robertson, and J. Turk. 2007. An individual with Gilles de la Tourette syndrome and Smith-Magenis microdeletion syndrome: is chromosome 17p11.2 a candidate region for Tourette syndrome putative susceptibility genes? *Journal of Intellectual Disability Research* **51**:620–624.
- Shifman, S., A. Levit, M. Chen, C. Chen, M. Bronstein, A. Weizman, B. Yakir *et al.* 2006. A complete genetic association scan of the 22q11 deletion region and functional evidence reveal an association between DGCR2 and schizophrenia. *Human Genetics* **120**:160–170.
- Simon, T. J., C. E. Bearden, D. M. Mc-Ginn, and E. Zackai. 2005a. Visuospatial and numerical cognitive deficits in children with chromosome 22q11.2 deletion syndrome. *Cortex* **41**:145–155.
- Simon, T. J., J. P. Bish, C. E. Bearden, L. Ding, S. Ferrante, V. Nguyen, J. C. Gee *et al.* 2005b. A multilevel analysis of cognitive dysfunction and psychopathology associated with chromosome 22q11.2 deletion syndrome in children. *Development and Psychopathology* **17**:753–784.
- Simpson, J. L., F. de la Cruz, R. S. Swerdloff, C. Samango-Sprouse, N. E. Skakkebaek, J. M. Graham Jr, T. Hassold *et al.* 2003. Klinefelter syndrome: expanding the phenotype and identifying new research directions. *Genetics in Medicine* **5**:460–468.
- Skuse, D. H. 2000. Imprinting, the X-chromosome, and the male brain: explaining sex differences in the liability to autism. *Pediatric Research* **47**:9–16.
- Skuse, D. H. 2005. X-linked genes and mental functioning. *Human Molecular Genetics* **14**:r27–r32.
- Skuse, D. H., R. S. James, D. V. Bishop, B. Coppin, P. Dalton, G. Aamodt-Leeper, M. Bacarese-Hamilton *et al.* 1997. Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. *Nature* **387**:705–708.
- Smith, A. C., E. Dykens, and F. Greenberg. 1998. Behavioral phenotype of Smith-Magenis syndrome (del 17p11.2). *American Journal of Medical Genetics* **81**:179–185.
- Smith, A. C. M., R. E. Magenis, and S. H. Elsea. 2005. Overview of Smith-Magenis syndrome. *Journal of the Association of Genetic Technologists* **31**:163–167.
- Somerville, M. J., C. B. Mervis, E. J. Young, E. Seo, M. del Campo, S. Bamforth, E. Peregrine *et al.* 2005. Severe expressive-language delay related to duplication of the Williams-Beuren locus. *New England Journal of Medicine* **353**:1694–1701.
- Stanfield, A. C., A. M. McIntosh, M. D. Spencer, R. Philip, S. Gaur, and S. M. Lawrie. 2008. Towards a neuroanatomy of autism: a systematic review and meta-analysis of structural magnetic resonance imaging studies. *European Psychiatry* **23**:289–299.
- Stankiewicz, P., and J. R. Lupski. 2002. Genome architecture, rearrangements and genomic disorders. *Trends in Genetics* **18**:74–82.
- Stranger, B. E., M. S. Forrest, M. Dunning, C. E. Ingle, C. Beazley, N. Thorne, R. Redon *et al.* 2007. Relative impact of nucleotide and copy number variation on gene expression phenotypes. *Science* **315**:848–853.
- Sugie, Y., H. Sugie, T. Fukuda, and M. Ito. 2005. Neonatal factors in infants with autistic disorder and typically developing infants. *Autism* **9**:487–494.
- Sugihara, G., K. J. Tsuchiya, and N. Takei. 2008. Distinguishing broad autism phenotype from schizophrenia-spectrum disorders. *Journal of Autism and Developmental Disorders* **38**:667–675.
- Sullivan, K., and H. Tager-Flusberg. 1999. Second-order belief attribution in Williams syndrome: intact or impaired? *American Journal of Mental Retardation* **104**:523–532.
- Sun, S., F. Wang, J. Wei, L. Y. Cao, G. Y. Wu, L. Lu, T. A. Kosten *et al.* 2008. Association between interleukin-3 receptor alpha polymorphism and schizophrenia in the Chinese population. *Neuroscience Letters* **440**:35–37.
- Sybert, V. P., and E. McCauley. 2004. Turner's syndrome. *New England Journal of Medicine* **351**:1227–1238.
- Tager-Flusberg, H., and K. Sullivan. 2000. A componential view of theory of mind: evidence from Williams syndrome. *Cognition* **76**:59–90.
- Tassabehji, M. 2003. Williams-Beuren syndrome: a challenge for genotype-phenotype correlations. *Human Molecular Genetics* **12**:r229–r237.
- Temple, C. M. 2006. Developmental and acquired dyslexias. *Cortex* **42**:898–910.
- Temple, C. M., and R. Carney. 1996. Reading skills in children with Turner's syndrome: an analysis of hyperplexia. *Cortex* **32**:335–345.
- Trikalinos, T. A., A. Karvouni, E. Zintzaras, T. Ylisaukko-oja, L. Peltonen, I. Järvelä, and J. P. A. Ioannidis. 2006. A heterogeneity-based genome search meta-analysis for autism-spectrum disorders. *Molecular Psychiatry* **11**:29–36.
- Turecki, G., P. Grof, E. Grof, V. D'Souza, L. Lebus, C. Marineau, P. Cavazzoni *et al.* 2001. Mapping susceptibil-

- ity genes for bipolar disorder: a pharmacogenetic approach based on excellent response to lithium. *Molecular Psychiatry* **6**:570–578.
- Van Den Bogaert, A., J. Del-Favero, and C. Van Broeckhoven. 2006. Major affective disorders and schizophrenia: a common molecular signature? *Human Mutation* **27**:833–853.
- Varrela, J. 1984. Effects of X chromosome on size and shape of body: an anthropometric investigation in 47,XXY males. *American Journal of Physical Anthropology* **64**:233–242.
- Vawter, M. P., P. D. Harvey, and L. E. DeLisi. 2007. Dysregulation of X-linked gene expression in Klinefelter's syndrome and association with verbal cognition. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics* **144**:728–734.
- Vicari, S., E. Bates, M. C. Caselli, P. Pasqualetti, C. Gagliardi, F. Tonucci, and V. Volterra. 2004. Neuropsychological profile of Italians with Williams syndrome: an example of a dissociation between language and cognition? *Journal of the International Neuropsychological Society* **10**:862–876.
- Vogels, A., W. M. A. Verhoeven, S. Tuinier, K. DeVriendt, A. Swillen, L. M. G. Curfs, and J. P. Frijns. 2002. The psychopathological phenotype of velo-cardio-facial syndrome. *Annales De Génétique* **45**:89–95.
- Voight, B. F., S. Kudravalli, X. Wen, and J. K. Pritchard. 2006. A map of recent positive selection in the human genome. *Plos Biology* **4**:e72.
- Vorstman, J. A. S., W. G. Staal, E. van Daalen, H. van Engeland, P. F. R. Hochstenbach, and L. Franke. 2006. Identification of novel autism candidate regions through analysis of reported cytogenetic abnormalities associated with autism. *Molecular Psychiatry* **11**:18–28.
- Wahlbeck, K., T. Forsén, C. Osmond, D. J. Barker, and J. G. Eriksson. 2001. Association of schizophrenia with low maternal body mass index, small size at birth, and thinness during childhood. *Archives of General Psychiatry* **58**:48–52.
- Weiss, L. A., S. Purcell, S. Waggoner, K. Lawrence, D. Spektor, M. J. Daly, P. Sklar *et al.* 2007. Identification of EFHC2 as a quantitative trait locus for fear recognition in Turner syndrome. *Human Molecular Genetics* **16**:107–113.
- Weiss, L. A., Y. Shen, J. M. Korn, D. E. Arking, D. T. Miller, R. Fossdal, E. Saemundsen *et al.* 2008. Association between microdeletion and microduplication at 16p11.2 and autism. *New England Journal of Medicine* **358**:667–675.
- Williams, N. M., N. Norton, H. Williams, B. Ekholm, M. L. Hamshere, Y. Lindblom, K. V. Chowdari *et al.* 2003. A systematic genomewide linkage study in 353 sib pairs with schizophrenia. *American Journal of Human Genetics* **73**:1355–1367.
- Williams, N. M., B. Glaser, N. Norton, H. Williams, T. Pierce, V. Moskvina, S. Monks *et al.* 2008. Strong evidence that GNB1L is associated with schizophrenia. *Human Molecular Genetics* **17**:555–566.
- Wong, A. H. C., J. Trakalo, O. Likhodi, M. Yusuf, A. Macedo, M. Azevedo, T. Klempan *et al.* 2004. Association between schizophrenia and the syntaxin 1A gene. *Biological Psychiatry* **56**:24–29.
- Wonodi, I., L. E. Hong, M. T. Avila, R. W. Buchanan, W. T. Carpenter, O. C. Stine, B. D. Mitchell *et al.* 2005. Association between polymorphism of the SNAP29 gene promoter region and schizophrenia. *Schizophrenia Research* **78**:339–341.
- Ylisaukko-oja, T., M. Alarcón, R. M. Cantor, M. Auranen, R. Vanhala, E. Kempas, L. von Wendt *et al.* 2006. Search for autism loci by combined analysis of Autism Genetic Resource Exchange and Finnish families. *Annals of Neurology* **59**:145–155.
- Yobb, T. M., M. J. Somerville, L. Willatt, H. V. Firth, K. Harrison, J. MacKenzie, N. Gallo *et al.* 2005. Microduplication and triplication of 22q11.2: a highly variable syndrome. *American Journal of Human Genetics* **76**:865–876.
- Young, E. J., T. Lipina, E. Tam, A. Mandel, S. J. Clapcote, A. R. Bechard, J. Chambers *et al.* 2008. Reduced fear and aggression and altered serotonin metabolism in Gtf2ird1-targeted mice. *Genes, Brain, and Behavior* **7**:224–234.
- Zhang, J., R. Nielsen, and Z. Yang. 2005. Evaluation of an improved branch-site likelihood method for detecting positive selection at the molecular level. *Molecular Biology and Evolution* **22**:2472–2479.
- Zinkstok, J., and T. van Amelsvoort. 2005. Neuropsychological profile and neuroimaging in patients with 22Q11.2 deletion syndrome: a review. *Child Neuropsychology* **11**:21–37.
- Zinn, A. R., D. Roeltgen, G. Stefanatos, P. Ramos, F. F. Elder, H. Kushner, K. Kowal *et al.* 2007. A Turner syndrome neurocognitive phenotype maps to Xp22.3. *Behavioral and Brain Functions* **3**:24.
- Zuberbühler, K. 2006. Language evolution: the origin of meaning in primates. *Current Biology* **16**:R123–R125.
- Zutshi, A., Y. C. J. Reddy, K. Thennarasu, and C. R. Chandrashekar. 2006. Comorbidity of anxiety disorders in patients with remitted bipolar disorder. *European Archives of Psychiatry and Clinical Neuroscience* **256**:428–436.
- Zweier, C., H. Sticht, I. Aydin-Yaylagül, C. E. Campbell, and A. Rauch. 2007. Human TBX1 missense mutations cause gain of function resulting in the same phenotype as 22q11.2 deletions. *American Journal of Human Genetics* **80**:510–517.