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Neural phenotypes of common and rare genetic variants

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Abstract

Neuroimaging methods offer a powerful way to bridge the gaps between genes, neurobiology and behavior. Such investigations may be further empowered by complementary strategies involving chromosomal abnormalities associated with particular neurobehavioral phenotypes, which can help to localize causative genes and better understand the genetics of complex traits in the general population. Here we review the evidence from studies using these convergent approaches to investigate genetic influences on brain structure: 1) Studies of common genetic variation associated with particular neuroanatomic phenotypes, and 2) Studies of possible ‘genetic subtypes’ of neuropsychiatric disorders with very high penetrance, with a focus on neuroimaging studies using novel computational brain mapping algorithms. Finally, we discuss the contribution of behavioral neurogenetics research to our understanding of the genetic basis of neuropsychiatric disorders in the broader population.

Keywords

Brain; Genetic; Neuroimaging; Psychosis; Chromosome 22q11.2; Fragile X; COMT; velocardiofacial syndrome; Williams Syndrome; neurofibromatosis I

INTRODUCTION

Investigation of the genetic mechanisms underlying neuropsychiatric disorders is an extremely challenging task. Although highly heritable, with biological bases in the brain, these disorders

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are multifactorial, complex syndromes that pose enormous challenges to biomedical discovery due to their complexity and the large gaps between basic science models and clinical phenomena. It is increasingly clear that these psychiatric illnesses are unlikely to be caused by a single gene of large effect (Lander & Schork, 1994); but rather, in the majority of cases, it is the interaction of multiple genes, together with environmental effects, which may cause an individual to reach the 'threshold' for meeting disease criteria. As such, the 'common disease common variant' hypothesis postulates that highly prevalent disorders, such as Type II diabetes and major depression, are attributable to a small number of predisposing alleles with relatively high frequencies, which each increase risk for disease only slightly (Lander, 1996).

The identification of intermediate phenotypes (endophenotypes), which may have a simpler genetic architecture than disease diagnoses, is likely to greatly enhance the power of mapping studies of psychiatric disorders, which have traditionally relied on categorical disease phenotypes (Bearden & Freimer, 2006; Gottesman & Gould, 2003). This approach may also help to resolve the carrier status of family members of affected probands, given that these individuals may carry predisposing genotypes but not meet criteria for the disorder (incomplete penetrance). As such, the research agenda for the next Diagnostic and Statistical Manual of Mental Disorders (DSM-V) emphasizes the importance of translating findings from multiple physiological levels, including the neural systems and cellular and molecular levels, into a new classification system for psychiatric disorders that is based on pathophysiologic and etiologic processes rather than overt symptom clusters (Charney & Babich, 2002; Phillips, 2007).

In other areas of medicine, there is rapidly accruing evidence that it is feasible to identify genes underlying quantitative variation in complex human phenotypes. Through linkage-based localization of quantitative trait loci (QTLs) several such genes have been identified, including those underlying QTLs for immunoglobulin E serum levels and asthma (Zhang et al., 2003), osteoporosis (Streeten et al., 2006; Stykarsdottir et al., 2003) and coronary artery disease (Shah et al., 2006). Such methods offer a means for us to ultimately identify specific genes influencing brain structure (Glahn, Thompson, & Blangero, 2007). It is increasingly clear that the genes influencing liability to psychiatric disorders are likely to impact multiple neural systems known to be affected in these illnesses, including neurotransmitter systems that mediate cognitive and affective processes, such as attention, memory, language, and social cognition (Cannon & Keller, 2006). Thus, more direct anatomical and/or physiological assays of these brain systems are likely to yield promising endophenotypes for these syndromes. Defining these new phenotypes at a neural-systems level could yield dramatic advances in neuropsychiatric therapeutics.

New image processing methodologies are now able to define brain phenotypes associated with neuropsychiatric disorders with increasing precision (Schaer & Eliez, 2007). Here we review the contribution of structural neuroimaging to advancing our understanding of the pathogenetic processes underlying brain development in common and rare disorders of cognition and emotion, with a particular focus on novel image processing methodologies. Specifically, we discuss studies using converging methods to investigate genetic influences on brain structure: 1) Studies of common genetic variation associated with particular neuroanatomic phenotypes, using the COMT Val¹⁵⁸Met polymorphism as a particular example, and 2) Studies of possible 'genetic subtypes' of neuropsychiatric disorders with very high penetrance. Here, we will specifically focus on the examples of the 22q11.2 deletion syndrome (velocardiofacial syndrome; 22q11.2DS), Williams syndrome, fragile X syndrome, and neurofibromatosis I (NF1), as they each present with distinct neurobehavioral phenotypes, thus providing unique insight into the neural systems and possible genetic bases underlying these phenotypic features more generally. Some of these syndromes are considered to be models for broader neurodevelopmental pathologies of heterogeneous and unclear origin; in particular, 22q11.2 deletion syndrome is often viewed as a developmental model for psychosis, whereas fragile X

is considered to be a model for autism (Schaer & Eliez, 2007). Williams syndrome represents a genetic deletion syndrome with profound effects on visuospatial cognition and social development (Meyer-Lindenberg & Zink, 2007). Finally, the development of a mouse model for NF1 has provided unique insights into the genetic basis of learning difficulties associated with the disorder, and their underlying cellular and molecular mechanisms (Costa et al., 2002).

Neuroanatomic measures as valuable endophenotypes

A major issue in applying endophenotypes to gene mapping is that heritability has not yet been established for many such features. Brain morphometric features are potential endophenotypic variables that have demonstrated high heritability (Baare et al., 2001; P. Thompson, Cannon, & Toga, 2002; I. C. Wright, Sham, Murray, Weinberger, & Bullmore, 2002). Recent advances in neuroimaging methods have made it possible to examine structural and functional neuroanatomy across a wide range of neuropsychiatric conditions, providing important insights in the pathophysiology of these illnesses and promising avenues for the development of novel treatments (Glahn et al., 2007). In addition to advancing our understanding of pathophysiologic processes underlying a given disorder, brain imaging endophenotypes also have the potential to improve our ability to identify subgroups of individuals who will respond preferentially to a specific treatment (Phillips, 2007). As such, these measures could help to guide treatment choice very early in the illness course.

However, one of the greatest difficulties inherent in studying the genetic basis of any of these neuropsychiatric disorders is heterogeneity. Current classification schemas are based on particular clusters of symptoms and clinical course descriptors that do not necessarily describe homogeneous conditions, but rather reflect final common pathways of various pathophysiological processes (Charney & Babich, 2002; Hasler, Drevets, Gould, Gottesman, & Manji, 2006). At the same time, the same disease phenotype can potentially be caused by mutations in different genetic loci (locus heterogeneity), which poses a major obstacle for mapping genes that influence complex genetic traits (Lin & Biswas, 2004). One way to gain traction on these difficulties is to study defined neurogenetic syndromes, which can serve as ideal candidates to advance our understanding of neurodevelopmental pathways that “might otherwise be obscured when investigating more heterogeneous pathologies” (Reiss, Eliez, Schmitt, Patwardhan, & Haberecht, 2000) (Figure 1).

Rare Mutations and Neurogenetic Disorders

This complementary approach to the search for susceptibility genes for complex traits involves the study of chromosomal abnormalities such as translocations, duplications, and deletions, which might segregate with the disorder. Research efforts on other complex diseases - for example, the strong association between early-onset dementia and Down's syndrome - suggest that this strategy may be particularly valuable for understanding the genetics and underlying pathophysiology of diseases with complex inheritance patterns (K.C. Murphy, 2002).

Another important advantage of this approach is that it facilitates the use of translational models, as the genetic cause of the disorder is well characterized. Mouse models for individual candidate genes provide an opportunity to investigate the function of these genes, and how they may impact on cognitive and neural phenotypic features associated with a given syndrome.

COMT Val¹⁵⁸Met Polymorphism in the General Population—The gene coding for catechol-O-methyl transferase (COMT) located on chromosome 22q11.2, has been extensively studied in relation to both cognitive function and risk for a variety of psychiatric diagnoses, particularly schizophrenia (Akil et al., 2003; Barr et al., 1999; Bray et al., 2003; Dunham, Collins, Wadey, & Scambler, 1992; Egan et al., 2001; Eisenberg et al., 1999; Frisch et al.,

2001). This gene codes for an enzyme which has a major role in the metabolism and regulation of dopamine, particularly in the prefrontal cortex (PFC) (Tunbridge, Harrison, & Weinberger, 2006). The COMT gene contains an evolutionarily recent functional polymorphism (Val¹⁵⁸Met) that determines COMT enzyme activity; homozygosity for the low-activity (Met) allele is associated with a three- to fourfold reduction of COMT enzyme activity compared with homozygotes for the high-activity (Val) variant, resulting in reduced degradation of synaptic catecholamines in Met allele carriers (Lachman et al., 1996). As such, COMT is one of the few genes associated with schizophrenia that has been shown to involve a functional variant (e.g., Akil et al., 2003).

Egan et al. (2001) reported evidence that the Val allele, which promotes more rapid breakdown of synaptic dopamine, leads to prefrontal hypofunction during performance on a working memory task in patients with schizophrenia. These findings have now been extended to show a significant effect of COMT genotype on working memory performance (assayed by the n-back task) for patients with schizophrenia, their healthy siblings, and controls (Goldberg et al., 2003), as well as differential response to amphetamine as a function of COMT genotype, supporting the notion of a characteristic inverted-“U” functional-response curve to increasing prefrontal dopamine signaling (Mattay et al., 2003). However the effect of this variant in the general population can only account for a very small percentage of the variance in working memory function and risk for psychosis (Bilder et al., 2002; Glatt, Faraone, & Tsuang, 2003). While a meta-analysis of case control studies found a significant but weak effect of the COMT Val/Met polymorphism in European samples (Fan et al., 2005), there may be additional functional sites in COMT (Bray et al., 2003); thus, inconsistent findings across genetic association studies may be due to different combinations of alleles at these functional loci in different samples (Meyer-Lindenberg et al., 2006). In addition, COMT may interact with other putative schizophrenia susceptibility genes to modulate their association with schizophrenia. Nicodemus et al. (2007) investigated this possibility in a sibling study and two case-control samples, and found a significant statistical interaction between COMT and polymorphisms in other candidate genes for schizophrenia, many of which had no significant main effect, suggesting that the actions of candidate genes relevant to complex disorders are likely to involve a number of interactions (Nicodemus et al., 2007). Given the multiple complexities involved in detecting modest main effects of these susceptibility genes in general population samples, it may be more informative to examine individuals with more extreme variation in genotype, where the magnitude of the genetic effect on dopaminergic neurotransmission is potentially much greater.

22q11.2 Deletion Syndrome—The 22q11.2 Deletion Syndrome (Velocardiofacial/DiGeorge Syndrome) is a congenital condition resulting from a hemizygous deletion at chromosome 22q11.2. It is believed to have a prevalence of at least 1 in 4,000 - 4,500 live births, making this syndrome one of the most common genetic diseases currently known (Stachon et al., 2007). The most systematically observed manifestations of 22q11.2DS include cleft palate and other craniofacial anomalies, conotruncal heart defects, T-cell abnormalities, and neonatal hypocalcemia (McDonald-McGinn et al., 1999; McDonald-McGinn et al., 1997). There is increasing evidence for a characteristic cognitive phenotype in this syndrome, involving marked deficits in visuospatial cognition, arithmetic (Bearden et al., 2001; Moss et al., 1999; Swillen et al., 1997) and spatial attentional orienting (Simon, Bearden, Mc-Ginn, & Zackai, 2005).

In addition, this syndrome is associated with extremely high rates of psychopathology, including attention deficit hyperactivity disorder in 35 to 55% of children and adolescents with the deletion (ADHD; Antshel, Conchelos, Lanzetta, Fremont, & Kates, 2005; Gothelf, Michaelovsky et al., 2007; Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2001), obsessive-compulsive disorder (OCD; Gothelf, Presburger, Zohar et al., 2004), and autistic spectrum

disorder (Fine et al., 2005; Niklasson et al., 2001). Most notably, twenty-five to 30% of adults with this syndrome develop schizophrenia or affective psychosis, making 22q11.2DS one of the greatest known risk factors for psychotic illness identified to date (K.C. Murphy, 2002). Interestingly, a high prevalence of bipolar spectrum disorders has also been reported in patients with 22q11.2 deletions (Arnold, Siegel-Bartelt, Cytrynbaum, Teshima, & Schachar, 2001; Papolos et al., 1996). The 22q11.2 region is one of the few regions of the genome for which significant linkage findings have been observed for both schizophrenia and bipolar disorder (Badner & Gershon, 2002), which highlights the possible etiologic overlap between these diagnostic categories.

The greatly increased risk for psychosis in this syndrome suggests that a gene or genes within the 22q11.2 deletion region may contribute to schizophrenia susceptibility in the broader population. Support for this notion is provided by genetic linkage and association studies implicating genes within the 22q region in schizophrenia. Although the COMT gene has been the most widely studied in relation to a variety of phenotypes, several other genes in the region have been implicated in risk for schizophrenia, most recently the *Gnb11* gene (Williams et al., 2008), as well as proline dehydrogenase (PRODH), *ZDHHC8*, and G-protein-coupled receptor kinase (GRK3; Karayiorgou et al., 1995; Mukai et al., 2004; Paterlini et al., 2005). In addition, mice heterozygously deleted for some of the genes in this region have sensorimotor gating and memory impairments similar to those observed in schizophrenia (Gogos et al., 1998; Gogos et al., 1999; Paylor et al., 2006; Paylor et al., 2001). As such, it has been proposed that individuals with this syndrome may have genetically determined differences in brain anatomy that predispose to schizophrenia (T. van Amelsvoort et al., 2004).

COMT Genotype in 22q11.2DS

In particular, given its known effects on metabolic degradation of dopamine and norepinephrine (Lachman et al., 1996), the COMT gene is a biologically relevant candidate gene. Although at present there is little evidence that this gene is responsible for increased risk for a categorical diagnosis of schizophrenia in this syndrome (Bassett, Caluseriu, Weksberg, Young, & Chow, 2007; K. C. Murphy, Jones, & Owen, 1999), it does demonstrate observable effects on cognitive and neuroanatomic traits. While some studies in children with 22q11.2DS have found that presence of the COMT Met allele on the single intact chromosome was associated with better performance on measures of prefrontal cognitive function, as compared to Val allele carriers (Bearden, Jawad et al., 2004; Shashi et al., 2006), another study failed to replicate these findings (Glaser et al., 2006). In addition, Val genotype was associated with a more than 4-fold increase in risk for clinically significant behavior problems in 22q11.2DS (Bearden et al., 2005). These data are consistent with previous findings of increased psychopathology associated with Val genotype in normal individuals, suggesting that this polymorphism may influence both prefrontal cognition and behavior in individuals with COMT haploinsufficiency. However, there is some evidence for developmental changes in the effect of COMT genotype on both cognition and neuroanatomy: in a longitudinal study, Gothelf and colleagues (Gothelf, Eliez et al., 2005), found that the Met allele was a risk factor for a reduction in prefrontal cortical volume, cognition and the development of psychotic symptoms in adolescence. Moreover, another study of adults with 22q11.2DS found that Val hemizygotes had significantly increased frontal lobe volume, as well as increased gray matter volume in the cerebellum, brainstem and parahippocampal gyrus, and decreased cerebellar white matter density, relative to Met allele carriers (T van Amelsvoort et al., 2007). Thus, while COMT genotype does appear to play a role in the neurocognitive and neuroanatomic expression of the syndrome (Bassett et al., 2007), findings vary considerably across studies, which may be partially attributable to developmental factors that require longitudinal studies for proper elucidation. Nevertheless, it is unlikely that this gene in isolation is responsible for the lion's share of the variance in the behavioral phenotype of 22q11.2DS; rather, given the multiple

genes in this region that are highly expressed in the developing brain, and known to affect early neuronal migration, it is likely that deficiency in more than one gene in the deleted region contributes to the strikingly increased risk for psychosis (Karayiorgou & Gogos, 2004).

In addition, some cases of terminal 22q microduplication have recently been reported (Okamoto et al., 2007). These patients appear to share some overlap in physical features with the 22q11.2 deletion syndrome, including characteristic craniofacial abnormalities, and growth and developmental deficiencies, suggesting that both over- and underexpression of genes in this region may lead to similar disruptions of developmental processes. Notably, the trisomic region in these patients included the *SHANK3* gene, which is important for synaptic scaffolding; mutations in this gene have also been associated with autism (Durand et al., 2007).

Neuroanatomy and 22q11.2DS

Several recent studies have significantly advanced our knowledge of 22qDS-associated cortical dysmorphology. As detailed in Table 1, the disorder is associated with developmental midline anomalies, including callosal dysmorphology (Antshel et al., 2005; Machado et al., 2007; Shashi et al., 2004), volume reduction in the cerebellar vermis and pons (Bish et al., 2006; Eliez, Schmitt, White, Wellis, & Reiss, 2001), and increased prevalence of cavum septum pellucidum (Chow, Zipursky, Mikulis, & Bassett, 2002; T. van Amelsvoort et al., 2001). In children and adolescents with this syndrome, quantitative analyses of brain volume have revealed a pattern of relative frontal preservation and disproportionate reduction in parieto-occipital brain regions (Eliez, Schmitt, White, & Reiss, 2000; Kates et al., 2001; Simon, Ding et al., 2005).

Using cortical pattern matching methodology in order to model and control for individual differences in gyral and sulcal patterning, we mapped cortical thickness in millimeters based on structural MRI images of 21 children with confirmed 22q11.2 deletions and 13 demographically matched healthy comparison subjects (Bearden et al., 2007). All participants with 22q11.2DS had the same 3 Mb typical deletion. Thickness was mapped at 65,536 homologous points, based on the 3D distance from the cortical gray-white matter interface to the external gray-CSF boundary (P. M. Thompson et al., 2005). A pattern of regionally specific cortical thinning was observed in superior parietal cortices and the right parieto-occipital cortex, regions critical for visuospatial processing (Figure 3). The observed gray matter deficits appear to be of functional significance, as gray matter volume was highly correlated with both verbal and nonverbal IQ in the children with 22q11.2DS ($r=0.65$; $p=0.002$), although this relationship was not significant in the control sample. These findings thus suggest a specific neural basis for the deficits in visuospatial processing observed in 22q11.2DS, and suggest a possible mechanism by which regional cortical abnormalities may affect human visuospatial cognition.

Neuroanatomy in 22q11.2DS vs. Schizophrenia

Interestingly, the cortical anomalies most frequently observed in children and adolescents with 22q11.2 deletions do not closely resemble those seen in adults with schizophrenia, where prefrontal and temporal regions show the greatest gray matter deficits (I. Wright et al., 2000). Developmental factors are likely to play an important role in these differences. As seen in Figure 4, we observed a moderate inverse relationship between age and cortical thickness in our cross-sectional study, in both patients with 22q11.2DS and healthy controls, although qualitative inspection of the maps suggests that there may be a more pronounced effect of age on cortical thickness in 22q11.2DS as compared to typically developing controls. Consistent with independent studies of cortical development and aging (Gogtay et al., 2004; Sowell et al., 2003; Vidal et al., 2006), controls showed localized regions of cortical thinning in superior parietal, cingulate and middle temporal regions associated with increasing age. However, children with 22q11.2DS showed a more posterior and widespread pattern of age-associated

cortical thinning, particularly in the inferior temporal gyrus bilaterally, and in ventromedial parieto-occipital regions (Figure 4).

Using identical cortical pattern matching methods, (P. M. Thompson et al., 2001) and (Vidal et al., 2006) mapped cortical changes over time in adolescents with childhood onset of schizophrenia (see Figure 3). This study revealed that early deficits in parietal brain regions progressed anteriorly into temporal lobes, engulfing sensorimotor and dorsolateral prefrontal cortices over a 5-year period. This trajectory appears to be an exaggeration of the normal sequence of dendritic pruning and myelination (Gogtay et al., 2004). Only the latest changes involved the dorsolateral prefrontal cortex and superior temporal gyri, regions of deficit observed most consistently in adult studies, suggesting that these structural changes occur later in the course of illness.

Although we did not find evidence for differences in patterns of cortical thickness between 22q11.2DS patients with and without psychiatric disorders, using a continuous measure, we found a relationship between reduced temporal gray matter and elevated Thought Problems, as assessed by the Child Behavior Checklist (Bearden, van Erp et al., 2004). Consistent with this, Campbell and colleagues (2006) found that severity of schizotypy score was positively correlated with gray matter density in temporo-occipital regions and the basal ganglia in children and adolescents with 22q11.2 deletions. This study also found that emotional and social problems were associated with gray matter concentration in frontostriatal regions, suggesting that quantitative indices of psychopathology may be related to differences in brain development in 22q11.2DS, even in the absence of categorical syndrome-based group differences.

Fragile X syndrome—Fragile X syndrome (FraX) is the most common inherited form of mental disability, occurring in approximately 1 in 2000-6000 live births (Gustavson, Blomquist, & Holmgren, 1986; Gustavson, Holmgren, & Blomquist, 1987; Reddy, 2005). The “full mutation” form of FraX results from a specific single gene mutation of the fragile X mental retardation 1 (*FMR1*) gene (Xq27.3). As expected with an X-linked disorder, affected women, who carry the mutation on only one of their two X chromosomes, have a milder form of the syndrome relative to males. For example, females with FraX typically exhibit cognitive abilities ranging from mild mental retardation to average function, though difficulties in socialization, anxiety, and learning and attention deficits may be present regardless of intellectual level (Hinton et al., 1992; Tsiouris & Brown, 2004). In contrast, with only a single X chromosome, males with the syndrome frequently have moderate to severe mental retardation, with particular deficits in executive function, visuospatial skills, and visuomotor coordination (see Reiss & Dant (2003) for a review).

The neurobehavioral profile of FraX overlaps with autism, a disorder defined by particular constellations of behavioral symptoms. Fifteen to 30% of males with FraX meet criteria for autism, although a much higher percentage have behaviors in the autistic spectrum (Baumgardner, Reiss, Freund, & Abrams, 1995; Freund, Reiss, Hagerman, & Vinogradov, 1992; Mazzocco, Kates, Baumgardner, Freund, & Reiss, 1997; Reiss, Abrams, Greenlaw, Freund, & Denckla, 1995). Unlike idiopathic autism however, the cause of FraX is known: an abnormally expanded number of trinucleotide repeats (>200), with consequent hypermethylation of the fragile X mental retardation gene (*FMR1*) leads to loss of, or reduction in the *FMR1* protein (FMRP). Pre-mutation carriers of FraX (with 55-200 CGG trinucleotide repeats) were originally considered unaffected. However, evolving research suggests that a portion of carriers of premutation alleles may have mild social, emotional and cognitive problems (Dorn, Mazzocco, & Hagerman, 1994; C. J. Moore et al., 2004), and, if male, are also at significant risk for a late-onset neurodegenerative disorder, fragile X-associated tremor/ataxia syndrome (FXTAS) (P. J. Hagerman & Hagerman, 2007; R. J. Hagerman et al., 2004).

Because FXTAS is not seen in adults with transcriptionally silent full mutation alleles, and elevated FMRI mRNA levels are present in premutation carriers, it has been proposed that FXTAS is caused by a toxic 'gain of function' of the FMR1 mRNA (Tassone, Iwahashi, & Hagerman, 2004).

The FMRP protein is normally expressed in neurons throughout the brain, with particularly high expression in the cerebellum, hippocampus and nucleus basalis (Tamanini et al., 1996). In particular, this protein is thought to be critical for synaptic development, given delayed dendritic spine maturation in both patients with FraX and in *Fmr1* knockout mice. Lu and colleagues (2004) found that FMRP plays an important role in controlling cytoskeletal organization during neuronal development, via regulation of microtubule associated protein 1B (MAP1B).

Brain imaging studies have been able to establish links between reduction of FMRP and specific neuroanatomic abnormalities in individuals with FraX (Table 1; also see (Reiss & Dant, 2003)). Some of the most consistently observed abnormalities include hypoplasia of the cerebellar vermis and enlargement of the caudate, both of which may be relevant to neurodevelopmental aspects of the syndrome (Reiss, Aylward, Freund, Joshi, & Bryan, 1991; Reiss, Freund, Tseng, & Joshi, 1991). Indeed, Gothelf and colleagues (2007) recently applied a receiver operating characteristic curve analysis to MRI scans obtained from a large sample of children and adolescents with the fragile X full mutation, in order to identify brain regions that best distinguish between subjects with FraX and typically developing controls. The caudate was identified first (73.5% of subjects with large caudate had FraX), posterior vermis was identified second, and amygdala third. Of 56 subjects with small amygdala and small posterior vermis and large caudate, 91.5% had FraX, indicating that the combination of the three neuroanatomic abnormalities distinguishes between FraX and control subjects with a specificity of 91.5%. In addition, large caudate and small posterior cerebellar vermis were correlated with lower FMRP levels and more severe cognitive deficits and behavior abnormalities (Figure 5).

Functional MRI findings have also helped to advance our knowledge of subthreshold neurophysiologic abnormalities associated with the FraX premutation (Hessl et al., 2007). Relative to controls, men with the FMR1 premutation showed reduced activity in the amygdala and other brain regions important for social cognition (i.e., orbitofrontal cortex and superior temporal sulcus), while viewing fearful faces. Premutation carriers also displayed a lack of startle potentiation while viewing fearful faces and reduced skin conductance response when greeting an unfamiliar experimenter. Reduction in amygdala activation was significantly associated with self-report of psychological symptoms. These results suggest a possible etiology for mild deficits in social cognition observed in some children and adults with the premutation, involving elevated *FMR1* mRNA and/or reduced FMR1 protein.

Thus, converging approaches across these multiple levels of inquiry provide evidence that FraX, which arises from disruption of a single gene leading to the loss of a specific protein, is associated with a cascade of neurodevelopmental aberrations, resulting in structural and functional brain abnormalities. In turn, these neuroanatomic alterations lead to early disruption in emotion, cognition, and behavior in this syndrome (Reiss & Dant, 2003).

Association of De Novo Mutations with Autism

Recent work on the genetics of idiopathic autism suggests that chromosomal aberrations, in the form of submicroscopic de novo copy number variants (CNVs), may play a greater role in the etiology of autistic spectrum disorders (ASD) than was previously believed (Sebat et al., 2007). A recent review estimated that cytogenetically detectable chromosomal abnormalities are found in 7.4% of ASD cases (Vorstman et al., 2006). Interestingly, mutations have most

convincingly been reported in the synaptic scaffolding protein gene *SHANK3*, near the 22q11.2DS locus on chromosome 22q (Durand et al., 2007), as well as two neuroligin (*NLGN3* and *NLGN4*) genes on the X chromosome (Jamain et al., 2003). Mutations in these genes are known to affect synaptic cell-adhesion molecules, suggest that a defect of synaptogenesis may be involved in the pathoetiology of autism (Jamain et al., 2003). Most recently, a novel, recurrent microdeletion and a reciprocal microduplication at chromosome 16p11.2 were detected, which appear to account for about 1% of cases of autism overall (Weiss et al., 2008). Several genes in this region are involved in neurodevelopment; given that either duplication or deletion of the region was associated with autism, one or more genes at this locus may be particularly dosage sensitive (Weiss et al., 2008), although the mechanisms leading to the autism phenotype in these individuals is not yet understood.

Williams Syndrome—Most individuals with Williams syndrome (WS) have a ~1.6 Mb deletion in chromosome 7q11.23 that encompasses at least 21 genes, including the elastin (*ELN*) gene, *LIMK1* (which encodes a protein tyrosine kinase expressed in the developing brain), and *STX1A* (which encodes a component of the synaptic apparatus) (Colleen A. Morris & Mervis, 1999; C. A. Morris et al., 2003). Studies of patients with deletions or mutations confined to *ELN* showed that hemizygosity for elastin is responsible for the cardiac defects commonly associated with WS (Ewart, Jin, Atkinson, Morris, & Keating, 1994; Ewart et al., 1993). Individuals with WS characteristically show profound impairments in spatial cognition and visual-motor skills, but have relatively spared skills in face recognition. Children with WS also demonstrate relative strengths in verbal abilities, and possess a distinct auditory sensitivity, involving particular attraction to music, strong aversion to certain sounds (hyperacusis/phonophobia), and relatively spared auditory rote memory abilities. WS individuals are often described as hypersociable, although they also exhibit elevated rates of nonsocial anxiety and specific phobias (e.g. Bellugi, Lichtenberger, Jones, Lai, & St. George, 2000; Bellugi, Lichtenberger, Mills, Galaburda, & Korenberg, 1999; Cassidy & Morris, 2002; Mervis & Klein-Tasman, 2000).

The *LIMK1* gene encodes a protein that regulates dynamic aspects of the cell cytoskeleton, and studies of families with atypical deletions have implicated this gene in the marked impairment in visuospatial constructive cognition characteristic of the syndrome (Frangiskakis et al., 1996); but see Tassabehji et al., 1999). *LIMK1* hemizygosity may lead to defects during brain development; a *LIMK1* knockout mouse model demonstrated changes in hippocampus-dependent learning and hippocampal physiology (Meng et al., 2002). Consistent with the murine model, a multimodal neuroimaging study recently investigated hippocampal structure, function, and metabolic integrity in WS and found marked reduction in resting blood flow, as well as a lack of differential response to visual stimuli in the anterior hippocampal formation, concomitant with subtle alterations in hippocampal morphology (Meyer-Lindenberg et al., 2005).

Overall brain size is reduced in WS, particularly in parieto-occipital cortex (Boddaert et al., 2006; Eckert, Galaburda, Mills et al., 2006; Meyer-Lindenberg A, 2004; Reiss, Eliez, Schmitt, Straus et al., 2000) although unlike 22q11.2DS and FraX, cerebellar size appears to be preserved (Table 1). Other studies employing novel neuroimaging methodologies have observed multiple indices of abnormal brain development, including atypical Sylvian fissure patterning (Eckert, Galaburda, Karchemskiy et al., 2006), temporo-parietal gyrification differences (Eckert, Galaburda, Karchemskiy et al., 2006) and increased cortical complexity (Gaser et al., 2006; P. M. Thompson et al., 2005; Tosun et al., 2006). While the specific genetic mechanisms underlying these abnormalities remained to be determined, it is likely they may be causally linked to one or more of the genes in the 7q11.23 region, and that careful study of the proteins expressed by these genes could lead to new insights about cortical development.

Neurofibromatosis type I (NF1)—NF1, or von Recklinghausen disease, is associated with a chromosome 17q11.2 mutation and is transmitted in autosomal dominant fashion, but spontaneous mutations account for about 50% of reported cases (Friedman & Birch, 1997). Pathological mutations range from single nucleotide substitutions to large-scale deletions throughout the gene (M. J. Lee & Stephenson, 2007). As a tumor-suppressor gene, the NF1 gene protein product, neurofibromin, plays an important role in the development of tumors. Neurofibromin is expressed early during embryonic development, with high levels of expression in the brain, suggesting that is important for the orderly differentiation of CNS neurons (K. North, 2000). Cafe-au-lait spots and fibromatous skin tumors are consistent clinical features. Some NF1 patients also exhibit gross neuropathological changes such as optic pathway gliomas and astrogliosis (M. J. Lee & Stephenson, 2007). Importantly, cognitive deficits and specific learning disabilities occur in approximately 30 to 50% of patients, even in the absence of ostensible neural pathology. Similar to the other genetic syndromes described above, visual-spatial impairment has long been considered a hallmark feature of the disorder (Cutting, Koth, Burnette et al., 2000; Cutting, Koth, & Denckla, 2000; K. N. North et al., 1997), with the most commonly reported findings being visuo-perceptual deficits, executive dysfunction, motor coordination problems, and borderline to low average IQ (e.g., K. N. North et al., 1997; Ozonoff, 1999).

MRI scans of human NF1 patients have revealed areas of increased signal intensity, known as unidentified bright objects (UBOs; Truhan & Filipek, 1993) which occur throughout the brain, but are especially prominent in the basal ganglia and cerebellum. Some studies, but not others, have reported a significant correlation between the presence of UBOs and cognitive deficits in NF1 (Denckla et al., 1996; K. North et al., 1994); but see Hyman, Gill, Shores, Steinberg, & North, 2007). Interestingly, UBOs have been frequently reported in children but appear to be less prevalent among adult NF1 patients, potentially indicating an age-related modification or compensation process. In one of the few longitudinal studies to date to examine the evolution of UBOs over time, Kraut et al. (2004) found a complex, non-linear pattern for the regional distribution of UBOs, as well as the number and total volume occupied by UBOs in a given region. UBOs were initially found in most of the brain regions examined, followed by a decrease during the pre-teen years, and then a progressive increase in UBOs to earlier childhood levels after age 12-14 years. Nevertheless, the neuroanatomic and pathogenic basis for these changes remains unclear. The limited pathologic data available suggest that the UBO's may reflect spongiform changes in white matter (DiPaolo et al., 1995), associated with brain dysplasia. Using proton spectroscopy, Alkan et al. (2003) found metabolite differences between the NF1 and control groups in normal-appearing white matter, which could possibly indicate demyelination or gliosis.

The origins and significance of other brain changes in NF1, such as macrocephaly and subcortical white matter increases, are equally obscure, although gray and white matter volume increases relative to healthy control subjects have been consistently documented in several studies (e.g., Cutting et al., 2002; Greenwood et al., 2005; B. D. Moore, 3rd, Slopis, Jackson, De Winter, & Leeds, 2000; Steen et al., 2001; Table 1). In addition, increased corpus callosum area and/or callosal thickening also appears to be characteristic of NF1 (Dubovsky et al., 2001; Kayl, Moore, Slopis, Jackson, & Leeds, 2000; Margariti et al., 2007). Increased severity of attention problems was related to smaller callosal area, suggesting that ADHD symptoms may be associated with neuroanatomic variation in patients with NF1 (Kayl et al., 2000). It has been hypothesized that a malfunction of neurofibromin, the NF1 gene product, may lead to disruption of normal processes of programmed cell death (apoptosis) (B. D. Moore, 3rd et al., 2000), although this possibility remains speculative.

A compelling animal model of NF1 has been developed; similar to human patients, mice harboring a targeted mutation of the NF1 gene show pronounced deficits on spatial learning

tests (Silva, Elgersma, Friedman, Stern, & Kogan, 1998; Silva et al., 1997). These mice lack exon 23a, which modifies the GTPase-activating protein (GAP) domain of Nf1, and are physically normal but show specific learning impairments. Silva and colleagues also found that these exon deleted mice have specific deficits in long-term potentiation, which can be rescued by genetic and pharmacological manipulations that decrease Ras gene function (Costa et al., 2002), indicating that the learning deficits associated with NF1 may be caused by excessive Ras gene activity. These findings have important implications for the development of cognitive remediation treatments for both individuals with NF1 and for individuals with cognitive disabilities more generally.

Neuroanatomic Correlates of Overlapping Cognitive Deficits Across Syndromes

Notably, the characteristic 22q11.2DS cognitive profile -involving relative strengths in verbal memory, in contrast to marked deficits in visuospatial memory - resembles that seen in Williams Syndrome (Bearden, Wang, & Simon, 2002), although the magnitude of effect may be greater in WS. Unlike WS, however, patients with 22q11.2DS are not generally reported to show appetitive social behavior, or particular strengths in musical ability (Karmiloff-Smith et al., 2004). Cortical thickness mapping methods revealed a failure of cortical maturation in patients with WS, involving a zone of right hemisphere perisylvian cortex that was 5-10% thicker in WS than in matched controls, despite pervasive gray and white matter deficits, but with corresponding deficits in the adjacent dorsal stream, including superior parietal brain regions (P. M. Thompson et al., 2005). Similar to patients with 22q11.2DS, WS patients also evidenced cortical thinning in the most inferior portion of the inferior frontal gyrus (*pars orbitalis*), a key area for language development (see Figures 3 and 6).

Using functional brain imaging during visual processing tasks, Meyer-Lindenberg and colleagues (Meyer-Lindenberg A, 2004) identified a pattern of hypoactivation in subjects with WS in the parietal portion of the dorsal stream, concomitant with gray matter volume reduction in the immediately adjacent parieto-occipital/intraparietal sulcus. Path analysis provided support for their hypothesis that structural abnormalities in the parietal region may serve as a 'roadblock' to dorsal stream information flow in WS. Notably, a similar finding of functional and structural anomaly in the right intraparietal sulcus has been observed in an X-linked neurogenetic disorder (monosomy X) also associated with pronounced impairment in visuospatial skills and arithmetic abilities, Turner Syndrome (Molko et al., 2003). Given converging evidence from lesion and neuroimaging studies that the parietal lobe is critical for accurate visual-spatial perception and mental transformation of images in typically developing individuals. (e.g. (Alivisatos & Petrides, 1997; Barnea-Goraly, Eliez, Menon, Bammer, & Reiss, 2005; Shomstein & Yantis, 2006)), it is tempting to speculate that a similar neuroanatomic substrate, involving localized thickness deficits in parieto-occipital brain regions, may underlie the visuospatial impairments characteristic of patients with 22q11.2DS, by affecting the flow of information through distributed neural systems. This hypothesis awaits further testing using multi-modal imaging approaches.

Using tensor-based morphometry (TBM), an approach which detects and automatically quantifies subtle and distributed patterns of gray and white matter volume differences, based on fluid registration of structural brain images. (e.g. A. Leow et al., 2005; A. D. Leow et al., 2006; Shen & Davatzikos, 2003), we examined the three-dimensional pattern of brain abnormalities in FraX (A. D. Lee et al., 2007) and WS (Chiang et al., 2007). As evident in Figure 7, patients with FraX show substantial expansion of subcortical regions, particularly basal ganglia, whereas patients with WS show relative reductions in these regions. In contrast, occipital reduction appears common to both syndromes.

While it is thus possible that the particular genetic abnormality in each of these syndromes may be directly relevant to specific aspects of the neurobehavioral phenotype, it is particularly

informative to examine both unique and overlapping neural and behavioral phenotypic features across syndromes. It is likely that some of these similarities are due to the downstream effects of these profound genetic mutations on early neuronal migration and brain development, which may result in similar nonverbal learning disability profiles across syndromes.

In addition, there is some overlap in the particular psychiatric conditions associated with these syndromes. Elevated rates of attention deficit/hyperactivity disorder (ADHD) occur in all four disorders (Bastain et al., 2002; Gothelf, Presburger, Levy et al., 2004; Sullivan et al., 2006), and both 22q11.2DS and fragile X are associated with elevated rates of autistic spectrum disorders in childhood, although the autism phenotype in 22q11.2DS differs to some extent from that of idiopathic autism (Kates et al., 2007). The extent to which cognitive delay accounts for some common features of the autism/ADHD phenotypes across these syndromes is not yet clear. However, high rates of psychotic illness appear to be relatively specific to 22q11.2DS, suggesting that there may be a gene particularly relevant to development of psychosis in the 22q11 region. Nevertheless, another genetic disorder, Prader-Willi syndrome (PWS), which results from the loss of several paternally expressed genes in the 15q11-13 region (Khan & Wood, 1999) appears to be associated with elevated rates of atypical psychotic disorder which resembles catatonia, as well as affective illness (Verhoeven & Tuinier, 2006). Psychotic illness is strongly associated with the maternal uniparental disomy subtype of PWS, but not the deletion subtype (Boer et al., 2002; Soni et al., 2008). In addition, those with maternal uniparental disomy are also at greater risk for autistic symptomatology. This is intriguing given recent evidence that maternal duplications of this same chromosomal region are involved in idiopathic autism (see Dykens, Sutcliffe, & Levitt (2004) for a review). In addition, functional alterations of genes in the 15q11-13 region are associated with social deficits in a variety of neurodevelopmental disorders (Dimitropoulos & Schultz, 2007). It has been hypothesized that gamma-aminobutyric acid (GABA)-ergic pathways may be implicated in all of these conditions, as genes which code for GABA receptors lie within this region, and GABA receptor abnormalities have been observed in patients with Prader-Willi Syndrome (Dykens et al., 2004; Verhoeven & Tuinier, 2006). In contrast, other genetic mutations may lead to deficits in attention and social behavior via multiple neurodevelopmental pathways.

As seen in Table 1, reduction of the cerebellar vermis is consistently observed in fragile X and 22q11.2DS, both of which present with marked social difficulties and high levels of autistic spectrum disorders; cerebellar hypoplasia is also frequently observed in idiopathic autism (Courchesne, Townsend, & Saitoh, 1994). In contrast, the cerebellum is typically enlarged in persons with Williams Syndrome, who tend to have increased social drive (e.g., (Schmitt, Eliez, Warsofsky, Bellugi, & Reiss, 2001b). This distinction suggests that the cerebellar vermis may be an important neuroanatomic substrate for social behavior (Gothelf, Furfaro, Penniman, Glover, & Reiss, 2005). Supporting this notion, in girls with FraX, Mazzocco and colleagues (1997) found that reduction in size of the posterior cerebellar vermis was associated with higher levels of stereotypic behavior, communication dysfunction, and other autistic-like behaviors, as assessed by parental interview.

Furthermore, both fragile X and 22q11.2DS involve disproportionate enlargement of the caudate nucleus. The caudate is a subcortical nucleus that is well known for involvement in movement. It is also believed to play an important role in cortical-subcortical loops related to emotion and cognition, via connections with non-motor frontal cortical regions (e.g., (Cummings, 1993)). Disturbances of these circuits can result in disturbances of attention and spatial working memory, mood regulation, and social behavior (Masterman & Cummings, 1997). Many of the cognitive and behavioral disturbances observed in FraX (e.g. stereotyped and perseverative behaviors, attention deficits, and impulse control problems) are thus consistent with disruption of prefrontal-striatal circuitry (Reiss & Dant, 2003).

Although the molecular and cellular basis for enlargement of particular brain structures in some neurogenetic syndromes is not known, it is possible that such enlargement may represent pathological failure of normal cortical maturation processes. Interestingly, measures of cognitive performance in Fragile X fail to show the normal correlations with volumetric brain measures (Eliez, Blasey, Freund, Hastie, & Reiss, 2001). Similarly, in individuals with NF1, the normal positive association between gray matter volume and IQ was not observed (Greenwood et al., 2005); additionally, (B. D. Moore, 3rd et al., 2000) found that poorer performance on measures of visual-spatial and motor skills and academic achievement was associated with greater corpus callosum size. Taken together, these findings suggest that normal neurodevelopmental patterns of brain specialization are adversely impacted in individuals with these syndromes.

Conclusions

In the neurogenetic syndromes reviewed above, the genetic 'lesion' is well characterized; however, neuropsychiatric phenotypes associated with most genetic risk variants can typically be detected only in large scale group comparisons. Recent findings from the Wellcome Trust Case Control Consortium (WTCCC, 2007) corroborate this notion; in the largest genome-wide association scan to date, the WTCCC has examined the genetic underpinnings of seven common human diseases, including bipolar disorder. Here the strongest signal for bipolar disorder was located at chromosome 16p12; although this finding was not additionally supported in a replication analysis, the authors note that several genes in the 16p12 region may have relevance to the pathophysiology of bipolar disorder. In general, the findings of this landmark study confirm that, for traits associated with common disease, there will be few susceptibility genes of large effect, a small number of modest effects, and a substantial number of genes which contribute small increases in disease risk.

Although common mental disorders (e.g., schizophrenia, bipolar disorder, and attention deficit/hyperactivity disorder) are highly heritable, they differ from rare Mendelian disorders in that they are likely the end products of multiple causes (Cannon & Keller, 2006). Furthermore, there is increasing evidence for an overlap in genetic susceptibility between disorders previously viewed as distinct diagnostic categories, particularly bipolar disorder and schizophrenia. Significant association findings have been reported for both disorders at the *DISC1* locus (disrupted in schizophrenia 1), as well as *DAOA* (D-amino acid oxidase activator), *NRG1* (neuregulin1) and *DTNBP1* (dystrobrevin binding protein 1) (Craddock, O'Donovan, & Owen, 2005). Although it is difficult to quantify the functional impact of common genetic variation, imaging genetics approaches have considerably advanced our understanding of the neural mechanisms associated with these variants (Meyer-Lindenberg & Zink, 2007).

At the same time, defined genetic syndromes with characteristic neurobehavioral phenotypes offer a rare opportunity for investigating linkages between genes, neurobiology, and cognition. Investigation of these etiologically more homogeneous disorders enables more precise quantification and characterization of genetic risk, providing further insights into the complex pathophysiology of neuropsychiatric disorders. In addition, subtle de novo chromosomal aberrations may play a larger role in the etiology of complex neuropsychiatric diseases than was previously thought, as has been demonstrated by recent advances in the genetics of idiopathic autism (Sebat et al., 2007).

From a clinical perspective, it is important for mental health care professionals to consider the possibility of a previously undiagnosed chromosomal abnormality when confronted with a child with psychiatric symptoms, cognitive delays, and minor physical anomalies. This underscores the need for thorough medical history-taking as part of a standard psychiatric

evaluation, as individuals with these syndromes are highly likely to be encountered in the context of a psychiatric clinic.

In summary, research using these convergent approaches has the potential to substantially advance our knowledge of the neural basis of cognitive and neurobehavioral alterations in particular neurogenetic disorders of known etiology, as well as in the broader population. As the accumulation of genomic and gene expression knowledge accelerates, the ability to use more refined neural endophenotypes will be critical to the success of this research. In particular, by combining information across multiple levels of phenotypic expression, we can advance definitions of phenotypes that can lead to novel research paths. Progress in this area raises the possibility of genomically targeted therapeutic approaches, which may correct or compensate for the specific neurocognitive, behavioral and neurobiological changes associated with these disorders.

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REFERENCES

- Akil M, Kolachana BS, Rothmond DA, Hyde TM, Weinberger DR, Kleinman JE. Catechol-O-methyltransferase genotype and dopamine regulation in the human brain. *Journal of Neuroscience* 2003;23(6):2008–2013. [PubMed: 12657658]
- Alivisatos B, Petrides M. Functional activation of the human brain during mental rotation. *Neuropsychologia* 1997;35(2):111–118. [PubMed: 9025115]
- Alkan A, Sarac K, Kutlu R, Yakinci C, Sigirci A, Aslan M, et al. Proton MR spectroscopy features of normal appearing white matter in neurofibromatosis type 1. *Magn Reson Imaging* 2003;21(9):1049–1053. [PubMed: 14684211]
- Alkan A, Sigirci A, Kutlu R, Ozcan H, Erdem G, Aslan M, et al. Neurofibromatosis type 1: diffusion weighted imaging findings of brain. *Eur J Radiol* 2005;56(2):229–234. [PubMed: 15963674]
- Antshel KM, Conchelos J, Lanzetta G, Fremont W, Kates WR. Behavior and corpus callosum morphology relationships in velocardiofacial syndrome (22q11.2 deletion syndrome). *Psychiatry Res* 2005;138(3):235–245. [PubMed: 15854791]
- Arnold PD, Siegel-Bartelt J, Cytrynbaum C, Teshima I, Schachar R. Velocardio-facial syndrome: Implications of microdeletion 22q11 for schizophrenia and mood disorders. *Am J Med Genet* 2001;105(4):354–362. [PubMed: 11378850]
- Baare WF, Hulshoff Pol HE, Boomsma DI, Posthuma D, de Geus EJ, Schnack HG, et al. Quantitative genetic modeling of variation in human brain morphology. *Cereb Cortex* 2001;11(9):816–824. [PubMed: 11532887]
- Badner JA, Gershon ES. Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. *Mol Psychiatry* 2002;7(4):405–411. [PubMed: 11986984]
- Barnea-Goraly N, Eliez S, Hedeus M, Menon V, White CD, Moseley M, et al. White matter tract alterations in fragile X syndrome: preliminary evidence from diffusion tensor imaging. *Am J Med Genet B Neuropsychiatr Genet* 2003;118(1):81–88. [PubMed: 12627472]
- Barnea-Goraly N, Eliez S, Menon V, Bammer R, Reiss AL. Arithmetic ability and parietal alterations: a diffusion tensor imaging study in velocardiofacial syndrome. *Brain Res Cogn Brain Res* 2005;25(3):735–740. [PubMed: 16260124]

- Barnea-Goraly N, Menon V, Krasnow B, Ko A, Reiss A, Eliez S. Investigation of white matter structure in velocardiofacial syndrome: a diffusion tensor imaging study. *Am J Psychiatry* 2003;160(10):1863–1869. [PubMed: 14514502]
- Barr CL, Wigg K, Malone M, Schachar R, Tannock R, Roberts W, et al. Linkage study of catechol-O-methyltransferase and attention-deficit hyperactivity disorder. *American Journal of Medical Genetics* 1999;88(6):710–713. [PubMed: 10581494]
- Bassett AS, Caluseriu O, Weksberg R, Young DA, Chow EW. Catechol-O-methyl transferase and expression of schizophrenia in 73 adults with 22q11 deletion syndrome. *Biol Psychiatry* 2007;61(10):1135–1140. [PubMed: 17217925]
- Bastain TM, Lewczyk CM, Sharp WS, James RS, Long RT, Eagen PB, et al. Cytogenetic abnormalities in attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2002;41(7):806–810. [PubMed: 12108805]
- Baumgardner TL, Reiss AL, Freund LS, Abrams MT. Specification of the neurobehavioral phenotype in males with fragile X syndrome. *Pediatrics* 1995;95(5):744–752. [PubMed: 7724315]
- Bearden CE, Freimer NB. Endophenotypes for psychiatric disorders: ready for primetime? *Trends Genet* 2006;22(6):306–313. [PubMed: 16697071]
- Bearden CE, Jawad AF, Lynch DR, Monterosso JR, Sokol S, McDonald-McGinn DM, et al. Effects of COMT genotype on behavioral symptomatology in the 22q11.2 Deletion Syndrome. *Child Neuropsychol* 2005;11(1):109–117. [PubMed: 15846854]
- Bearden CE, Jawad AF, Lynch DR, Sokol S, Kanes SJ, McDonald-McGinn DM, et al. Effects of a functional COMT polymorphism on prefrontal cognitive function in patients with 22q11.2 deletion syndrome. *Am J Psychiatry* 2004;161(9):1700–1702. [PubMed: 15337663]
- Bearden CE, van Erp TG, Dutton RA, Tran H, Zimmermann L, Sun D, et al. Mapping cortical thickness in children with 22q11.2 deletions. *Cereb Cortex* 2007;17(8):1889–1898. [PubMed: 17056649]
- Bearden CE, van Erp TG, Monterosso JR, Simon TJ, Glahn DC, Saleh PA, et al. Regional brain abnormalities in 22q11.2 deletion syndrome: association with cognitive abilities and behavioral symptoms. *Neurocase* 2004;10(3):198–206. [PubMed: 15788257]
- Bearden CE, Wang PP, Simon TJ. Williams syndrome cognitive profile also characterizes Velocardiofacial/DiGeorge syndrome. *Am J Med Genet* 2002;114(6):689–692. [PubMed: 12210289]
- Bearden CE, Woodin MF, Wang PP, Moss E, McDonald-McGinn D, Zackai E, et al. The neurocognitive phenotype of the 22q11.2 deletion syndrome: selective deficit in visual-spatial memory. *J Clin Exp Neuropsychol* 2001;23(4):447–464. [PubMed: 11780945]
- Bellugi U, Lichtenberger L, Jones W, Lai Z, George M St. The neurocognitive profile of Williams syndrome: A complex pattern of strengths and weaknesses. *Journal of Cognitive Neuroscience* 2000;12(Suppl1):7–29. [PubMed: 10953231]
- Bellugi U, Lichtenberger L, Mills D, Galaburda A, Korenberg J. Bridging cognition, the brain and molecular genetics: Evidence from Williams syndrome. *Trends in Neurosciences* 1999;22(5):197–207. [PubMed: 10322491]
- Bilder RM, Volavka J, Czobor P, Malhotra AK, Kennedy JL, Ni X, et al. Neurocognitive correlates of the COMT Val(158)Met polymorphism in chronic schizophrenia. *Biological Psychiatry* 2002;52(7):701–707. [PubMed: 12372660]
- Bish JP, Nguyen V, Ding L, Ferrante S, Simon TJ. Thalamic reductions in children with chromosome 22q11.2 deletion syndrome. *Neuroreport* 2004;15(9):1413–1415. [PubMed: 15194864]
- Bish JP, Pendyal A, Ding L, Ferrante H, Nguyen V, McDonald-McGinn D, et al. Specific cerebellar reductions in children with chromosome 22q11.2 deletion syndrome. *Neurosci Lett* 2006;399(3):245–248. [PubMed: 16517069]
- Boddaert N, Mochel F, Meresse I, Seidenwurm D, Cachia A, Brunelle F, et al. Parieto-occipital grey matter abnormalities in children with Williams syndrome. *Neuroimage* 2006;30(3):721–725. [PubMed: 16380272]
- Boer H, Holland A, Whittington J, Butler J, Webb T, Clarke D. Psychotic illness in people with Prader Willi syndrome due to chromosome 15 maternal uniparental disomy. *Lancet* 2002;359(9301):135–136. [PubMed: 11809260]

- Bray NJ, Buckland PR, Williams NM, Williams HJ, Norton N, Owen MJ, et al. A haplotype implicated in schizophrenia susceptibility is associated with reduced COMT expression in human brain. *Am J Hum Genet* 2003;73(1):152–161. [PubMed: 12802784]
- Campbell LE, Daly E, Toal F, Stevens A, Azuma R, Catani M, et al. Brain and behaviour in children with 22q11.2 deletion syndrome: a volumetric and voxel-based morphometry MRI study. *Brain* 2006;129(Pt 5):1218–1228. [PubMed: 16569671]
- Cannon TD, Keller MC. Endophenotypes in the genetic analyses of mental disorders. *Annu Rev Clin Psychol* 2006;2:267–290. [PubMed: 17716071]
- Cassidy SB, Morris CA. Behavioral phenotypes in genetic syndromes: genetic clues to human behavior. *Adv Pediatr* 2002;49:59–86. [PubMed: 12214780]
- Charney DS, Babich KS. Foundation for the NIMH strategic plan for mood disorders research. *Biol Psychiatry* 2002;52(6):455–456. [PubMed: 12361663]
- Chiang MC, Reiss AL, Lee AD, Bellugi U, Galaburda AM, Korenberg JR, et al. 3D pattern of brain abnormalities in Williams syndrome visualized using tensor-based morphometry. *Neuroimage* 2007;36(4):1096–1109. [PubMed: 17512756]
- Chow EW, Zipursky RB, Mikulis DJ, Bassett AS. Structural brain abnormalities in patients with schizophrenia and 22q11 deletion syndrome. *Biological Psychiatry* 2002;51(3):208–215. [PubMed: 11839363]
- Costa RM, Federov NB, Kogan JH, Murphy GG, Stern J, Ohno M, et al. Mechanism for the learning deficits in a mouse model of neurofibromatosis type 1. *Nature* 2002;415(6871):526–530. [PubMed: 11793011]
- Courchesne E, Townsend J, Saitoh O. The brain in infantile autism: posterior fossa structures are abnormal. *Neurology* 1994;44(2):214–223. [PubMed: 8309561]
- Craddock N, O'Donovan MC, Owen MJ. The genetics of schizophrenia and bipolar disorder: dissecting psychosis. *J Med Genet* 2005;42(3):193–204. [PubMed: 15744031]
- Cummings JL. Frontal-subcortical circuits and human behavior. *Arch Neurol* 1993;50(8):873–880. [PubMed: 8352676]
- Cutting LE, Cooper KL, Koth CW, Mostofsky SH, Kates WR, Denckla MB, et al. Megalencephaly in NF1: predominantly white matter contribution and mitigation by ADHD. *Neurology* 2002;59(9):1388–1394. [PubMed: 12427889]
- Cutting LE, Koth CW, Burnette CP, Abrams MT, Kaufmann WE, Denckla MB. Relationship of cognitive functioning, whole brain volumes, and T2-weighted hyperintensities in neurofibromatosis-1. *J Child Neurol* 2000;15(3):157–160. [PubMed: 10757470]
- Cutting LE, Koth CW, Denckla MB. How children with neurofibromatosis type 1 differ from “typical” learning disabled clinic attenders: nonverbal learning disabilities revisited. *Dev Neuropsychol* 2000;17(1):29–47. [PubMed: 10916573]
- Debbane M, Schaer M, Farhoumand R, Glaser B, Eliez S. Hippocampal volume reduction in 22q11.2 deletion syndrome. *Neuropsychologia* 2006;44(12):2360–2365. [PubMed: 16787654]
- Denckla MB, Hofman K, Mazzocco MM, Melhem E, Reiss AL, Bryan RN, et al. Relationship between T2-weighted hyperintensities (unidentified bright objects) and lower IQs in children with neurofibromatosis-1. *Am J Med Genet* 1996;67(1):98–102. [PubMed: 8678124]
- Dimitropoulos A, Schultz RT. Autistic-like symptomatology in Prader-Willi syndrome: a review of recent findings. *Curr Psychiatry Rep* 2007;9(2):159–164. [PubMed: 17389128]
- DiPaolo DP, Zimmerman RA, Rorke LB, Zackai EH, Bilaniuk LT, Yachnis AT. Neurofibromatosis type 1: pathologic substrate of high-signal-intensity foci in the brain. *Radiology* 1995;195(3):721–724. [PubMed: 7754001]
- Dorn MB, Mazzocco MM, Hagerman RJ. Behavioral and psychiatric disorders in adult male carriers of fragile X. *J Am Acad Child Adolesc Psychiatry* 1994;33(2):256–264. [PubMed: 8150798]
- Dubovsky EC, Booth TN, Vezina G, Samango-Sprouse CA, Palmer KM, Brasseux CO. MR imaging of the corpus callosum in pediatric patients with neurofibromatosis type 1. *AJNR Am J Neuroradiol* 2001;22(1):190–195. [PubMed: 11158908]
- Dunham I, Collins J, Wadey R, Scambler P. Possible role for COMT in psychosis associated with velo-cardio-facial syndrome. *Lancet* 1992;340(8831):1361–1362. [PubMed: 1360084]

- Durand CM, Betancur C, Boeckers TM, Bockmann J, Chaste P, Fauchereau F, et al. Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nat Genet* 2007;39(1):25–27. [PubMed: 17173049]
- Dykens EM, Sutcliffe JS, Levitt P. Autism and 15q11-q13 disorders: behavioral, genetic, and pathophysiological issues. *Ment Retard Dev Disabil Res Rev* 2004;10(4):284–291. [PubMed: 15666333]
- Eastwood JD, Fiorella DJ, MacFall JF, Delong DM, Provenzale JM, Greenwood RS. Increased brain apparent diffusion coefficient in children with neurofibromatosis type 1. *Radiology* 2001;219(2):354–358. [PubMed: 11323456]
- Eckert MA, Galaburda AM, Karchemskiy A, Liang A, Thompson P, Dutton RA, et al. Anomalous sylvian fissure morphology in Williams syndrome. *Neuroimage* 2006;33(1):39–45. [PubMed: 16876437]
- Eckert MA, Galaburda AM, Mills DL, Bellugi U, Korenberg JR, Reiss AL. The neurobiology of Williams syndrome: cascading influences of visual system impairment? *Cell Mol Life Sci* 2006;63(16):1867–1875. [PubMed: 16810457]
- Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences USA* 2001;98(12):6917–6922.
- Eisenberg J, Mei-Tal G, Steinberg A, Tartakovsky E, Zohar A, Gritsenko I, et al. Haplotype relative risk study of catechol-O-methyltransferase (COMT) and attention deficit hyperactivity disorder (ADHD): association of the high-enzyme activity Val allele with ADHD impulsive-hyperactive phenotype. *American Journal of Medical Genetics* 1999;88(5):497–502. [PubMed: 10490706]
- Eliez S, Barnea-Goraly N, Schmitt JE, Liu Y, Reiss AL. Increased basal ganglia volumes in velo-cardio-facial syndrome (deletion 22q11.2). *Biol Psychiatry* 2002;52(1):68–70. [PubMed: 12079732]
- Eliez S, Blasey CM, Freund LS, Hastie T, Reiss AL. Brain anatomy, gender and IQ in children and adolescents with fragile X syndrome. *Brain* 2001;124(Pt 8):1610–1618. [PubMed: 11459752]
- Eliez S, Blasey CM, Schmitt E, White C, Hu D, Reiss AL. Velocardiofacial Syndrome; Are Structural Changes in the Temporal and Mesial Temporal Regions Related to Schizophrenia? *American Journal of Psychiatry* 2001;158(3):447–453. [PubMed: 11229987]
- Eliez S, Schmitt JE, White CD, Reiss AL. Children and adolescents with velocardiofacial syndrome: a volumetric MRI study. *American Journal of Psychiatry* 2000;157(3):409–415. [PubMed: 10698817]
- Eliez S, Schmitt JE, White CD, Wellis VG, Reiss AL. A quantitative MRI study of posterior fossa development in velocardiofacial syndrome. *Biological Psychiatry* 2001;49(6):540–546. [PubMed: 11257239]
- Ewart AK, Jin W, Atkinson D, Morris CA, Keating MT. Supravalvular aortic stenosis associated with a deletion disrupting the elastin gene. *J Clin Invest* 1994;93(3):1071–1077. [PubMed: 8132745]
- Ewart AK, Morris CA, Atkinson D, Jin W, Sternes K, Spallone P, et al. Hemizyosity at the elastin locus in a developmental disorder, Williams syndrome. *Nat Genet* 1993;5(1):11–16. [PubMed: 7693128]
- Fan JB, Zhang CS, Gu NF, Li XW, Sun WW, Wang HY, et al. Catechol-O-methyltransferase gene Val/Met functional polymorphism and risk of schizophrenia: a large-scale association study plus meta-analysis. *Biol Psychiatry* 2005;57(2):139–144. [PubMed: 15652872]
- Fine SE, Weissman A, Gerdes M, Pinto-Martin J, Zackai EH, McDonald-McGinn DM, et al. Autism spectrum disorders and symptoms in children with molecularly confirmed 22q11.2 deletion syndrome. *J Autism Dev Disord* 2005;35(4):461–470. [PubMed: 16134031]
- Frangiskakis JM, Ewart AK, Morris CA, Mervis CB, Bertrand J, Robinson BF, et al. LIM-kinase1 hemizyosity implicated in impaired visuospatial constructive cognition. *Cell* 1996;86(1):59–69. [PubMed: 8689688]
- Freund LS, Reiss AL, Hagerman R, Vinogradov S. Chromosome fragility and psychopathology in obligate female carriers of the fragile X chromosome. *Arch Gen Psychiatry* 1992;49(1):54–60. [PubMed: 1728251]
- Friedman JM, Birch PH. Type 1 neurofibromatosis: a descriptive analysis of the disorder in 1,728 patients. *Am J Med Genet* 1997;70(2):138–143. [PubMed: 9128932]
- Frisch A, Laufer N, Danziger Y, Michaelovsky E, Leor S, Carel C, et al. Association of anorexia nervosa with the high activity allele of the COMT gene: a family-based study in Israeli patients. *Molecular Psychiatry* 2001;6(2):243–245. [PubMed: 11317231]

- Gaser C, Luders E, Thompson PM, Lee AD, Dutton RA, Geaga JA, et al. Increased local gyrification mapped in Williams syndrome. *Neuroimage* 2006;33(1):46–54. [PubMed: 16901723]
- Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007;447(7145):661–678. [PubMed: 17554300]
- Glahn DC, Thompson PM, Blangero J. Neuroimaging endophenotypes: strategies for finding genes influencing brain structure and function. *Hum Brain Mapp* 2007;28(6):488–501. [PubMed: 17440953]
- Glaser B, Debbane M, Hinard C, Morris MA, Dahoun SP, Antonarakis SE, et al. No evidence for an effect of COMT Val158Met genotype on executive function in patients with 22q11 deletion syndrome. *Am J Psychiatry* 2006;163(3):537–539. [PubMed: 16513880]
- Glatt SJ, Faraone SV, Tsuang MT. Association between a functional catechol O-methyltransferase gene polymorphism and schizophrenia: meta-analysis of case-control and family-based studies. *Am J Psychiatry* 2003;160(3):469–476. [PubMed: 12611827]
- Gogos JA, Morgan M, Luine V, Santha M, Ogawa S, Pfaff D, et al. Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. *Proc Natl Acad Sci U S A* 1998;95(17):9991–9996. [PubMed: 9707588]
- Gogos JA, Santha M, Takacs Z, Beck KD, Luine V, Lucas LR, et al. The gene encoding proline dehydrogenase modulates sensorimotor gating in mice. *Nat Genet* 1999;21(4):434–439. [PubMed: 10192398]
- Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A* 2004;101(21):8174–8179. [PubMed: 15148381]
- Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, et al. Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. *Arch Gen Psychiatry* 2003;60(9):889–896. [PubMed: 12963670]
- Gothelf D, Eliez S, Thompson T, Hinard C, Penniman L, Feinstein C, et al. COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome. *Nat Neurosci* 2005;8(11):1500–1502. [PubMed: 16234808]
- Gothelf D, Furfaro JA, Hoeft F, Eckert MA, Hall SS, O'Hara R, et al. Neuroanatomy of fragile X syndrome is associated with aberrant behavior and the fragile X mental retardation protein (FMRP). *Ann Neurol*. 2007
- Gothelf D, Furfaro JA, Penniman LC, Glover GH, Reiss AL. The contribution of novel brain imaging techniques to understanding the neurobiology of mental retardation and developmental disabilities. *Ment Retard Dev Disabil Res Rev* 2005;11(4):331–339. [PubMed: 16240408]
- Gothelf D, Michaelovsky E, Frisch A, Zohar AH, Presburger G, Burg M, et al. Association of the low-activity COMT 158Met allele with ADHD and OCD in subjects with velocardiofacial syndrome. *Int J Neuropsychopharmacol* 2007;10(3):301–308. [PubMed: 16734939]
- Gothelf D, Presburger G, Levy D, Nahmani A, Burg M, Berant M, et al. Genetic, developmental, and physical factors associated with attention deficit hyperactivity disorder in patients with velocardiofacial syndrome. *Am J Med Genet B Neuropsychiatr Genet* 2004;126(1):116–121. [PubMed: 15048660]
- Gothelf D, Presburger G, Zohar AH, Burg M, Nahmani A, Frydman M, et al. Obsessive-compulsive disorder in patients with velocardiofacial (22q11 deletion) syndrome. *Am J Med Genet B Neuropsychiatr Genet* 2004;126(1):99–105. [PubMed: 15048657]
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 2003;160(4):636–645. [PubMed: 12668349]
- Greenwood RS, Tupler LA, Whitt JK, Buu A, Dombeck CB, Harp AG, et al. Brain morphometry, T2-weighted hyperintensities, and IQ in children with neurofibromatosis type 1. *Arch Neurol* 2005;62(12):1904–1908. [PubMed: 16344348]
- Gustavson KH, Blomquist HK, Holmgren G. Prevalence of the fragile-X syndrome in mentally retarded boys in a Swedish county. *Am J Med Genet* 1986;23(12):581–587. [PubMed: 3953668]
- Gustavson KH, Holmgren G, Blomquist HK. Chromosomal aberrations in mildly mentally retarded children in a northern Swedish county. *Ups J Med Sci Suppl* 1987;44:165–168. [PubMed: 2965442]

- Hagerman PJ, Hagerman RJ. Fragile X-associated tremor/ataxia syndrome--an older face of the fragile X gene. *Nat Clin Pract Neurol* 2007;3(2):107–112. [PubMed: 17279084]
- Hagerman RJ, Leavitt BR, Farzin F, Jacquemont S, Greco CM, Brunberg JA, et al. Fragile-X-associated tremor/ataxia syndrome (FXTAS) in females with the FMR1 premutation. *Am J Hum Genet* 2004;74(5):1051–1056. [PubMed: 15065016]
- Hasler G, Drevets WC, Gould TD, Gottesman II, Manji HK. Toward constructing an endophenotype strategy for bipolar disorders. *Biol Psychiatry* 2006;60(2):93–105. [PubMed: 16406007]
- Hessl D, Rivera S, Koldewyn K, Cordeiro L, Adams J, Tassone F, et al. Amygdala dysfunction in men with the fragile X premutation. *Brain* 2007;130(Pt 2):404–416. [PubMed: 17166860]
- Hinton VJ, Dobkin CS, Halperin JM, Jenkins EC, Brown WT, Ding XH, et al. Mode of inheritance influences behavioral expression and molecular control of cognitive deficits in female carriers of the fragile X syndrome. *American Journal of Medical Genetics* 1992;43(12):87–95. [PubMed: 1605240]
- Hoeft F, Barnea-Goraly N, Haas BW, Golarai G, Ng D, Mills D, et al. More is not always better: increased fractional anisotropy of superior longitudinal fasciculus associated with poor visuospatial abilities in Williams syndrome. *J Neurosci* 2007;27(44):11960–11965. [PubMed: 17978036]
- Hyman SL, Gill DS, Shores EA, Steinberg A, North KN. T2 hyperintensities in children with neurofibromatosis type 1 and their relationship to cognitive functioning. *J Neurol Neurosurg Psychiatry* 2007;78(10):1088–1091. [PubMed: 17299016]
- Jakala P, Hanninen T, Ryyanen M, Laakso M, Partanen K, Mannerman A, et al. Fragile-X: neuropsychological test performance, CGG triplet repeat lengths, and hippocampal volumes. *J Clin Invest* 1997;100(2):331–338. [PubMed: 9218509]
- Jamain S, Quach H, Betancur C, Rastam M, Colineaux C, Gillberg IC, et al. Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nat Genet* 2003;34(1):27–29. [PubMed: 12669065]
- Karayorgou M, Gogos JA. The molecular genetics of the 22q11-associated schizophrenia. *Brain Res Mol Brain Res* 2004;132(2):95–104. [PubMed: 15582150]
- Karayorgou M, Morris MA, Morrow B, Shprintzen RJ, Goldberg R, Borrow J, et al. Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. *Proceedings of the National Academy of Sciences USA* 1995;92(17):7612–7616.
- Karmiloff-Smith A, Thomas M, Annaz D, Humphreys K, Ewing S, Brace N, et al. Exploring the Williams syndrome face-processing debate: the importance of building developmental trajectories. *J Child Psychol Psychiatry* 2004;45(7):1258–1274. [PubMed: 15335346]
- Kates WR, Antshel KM, Fremont WP, Shprintzen RJ, Strunge LA, Burnette CP, et al. Comparing phenotypes in patients with idiopathic autism to patients with velocardiofacial syndrome (22q11 DS) with and without autism. *Am J Med Genet A* 2007;143(22):2642–2650. [PubMed: 17937445]
- Kates WR, Burnette CP, Bessette BA, Folley BS, Strunge L, Jabs EW, et al. Frontal and caudate alterations in velocardiofacial syndrome (deletion at chromosome 22q11.2). *J Child Neurol* 2004;19(5):337–342. [PubMed: 15224707]
- Kates WR, Burnette CP, Jabs EW, Rutberg J, Murphy AM, Grados M, et al. Regional cortical white matter reductions in velocardiofacial syndrome: a volumetric MRI analysis. *Biological Psychiatry* 2001;49(8):677–684. [PubMed: 11313035]
- Kates WR, Folley BS, Lanham DC, Capone GT, Kaufmann WE. Cerebral growth in Fragile X syndrome: review and comparison with Down syndrome. *Microsc Res Tech* 2002;57(3):159–167. [PubMed: 12112452]
- Kates WR, Miller AM, Abdulsabur N, Antshel KM, Conchelos J, Fremont W, et al. Temporal lobe anatomy and psychiatric symptoms in velocardiofacial syndrome (22q11.2 deletion syndrome). *J Am Acad Child Adolesc Psychiatry* 2006;45(5):587–595. [PubMed: 16670653]
- Kayl AE, Moore BD 3rd, Slopis JM, Jackson EF, Leeds NE. Quantitative morphology of the corpus callosum in children with neurofibromatosis and attention-deficit hyperactivity disorder. *J Child Neurol* 2000;15(2):90–96. [PubMed: 10695893]
- Khan NL, Wood NW. Prader-Willi and Angelman syndromes: update on genetic mechanisms and diagnostic complexities. *Curr Opin Neurol* 1999;12(2):149–154. [PubMed: 10226746]

- Kraut MA, Gerring JP, Cooper KL, Thompson RE, Denckla MB, Kaufmann WE. Longitudinal evolution of unidentified bright objects in children with neurofibromatosis-1. *Am J Med Genet A* 2004;129(2):113–119. [PubMed: 15316979]
- Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM. Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics* 1996;6(3):243–250. [PubMed: 8807664]
- Lander ES. The new genomics: global views of biology. *Science* 1996;274(5287):536–539. [PubMed: 8928008]
- Lander ES, Schork NJ. Genetic dissection of complex traits. *Science* 1994;265(5181):2037–2048. [PubMed: 8091226]
- Lee AD, Leow AD, Lu A, Reiss AL, Hall S, Chiang MC, et al. 3D pattern of brain abnormalities in Fragile X syndrome visualized using tensor-based morphometry. *Neuroimage* 2007;34(3):924–938. [PubMed: 17161622]
- Lee MJ, Stephenson DA. Recent developments in neurofibromatosis type 1. *Curr Opin Neurol* 2007;20(2):135–141. [PubMed: 17351482]
- Leow A, Yu CL, Lee SJ, Huang SC, Protas H, Nicolson R, et al. Brain structural mapping using a novel hybrid implicit/explicit framework based on the level-set method. *Neuroimage* 2005;24(3):910–927. [PubMed: 15652325]
- Leow AD, Klunder AD, Jack CR Jr, Toga AW, Dale AM, Bernstein MA, et al. Longitudinal stability of MRI for mapping brain change using tensor-based morphometry. *Neuroimage* 2006;31(2):627–640. [PubMed: 16480900]
- Lin S, Biswas S. On modeling locus heterogeneity using mixture distributions. *BMC Genet* 2004;5:29. [PubMed: 15458576]
- Lu R, Wang H, Liang Z, Ku L, O'Donnell W, Li W, et al. The fragile X protein controls microtubule-associated protein 1B translation and microtubule stability in brain neuron development. *Proc Natl Acad Sci U S A* 2004;101(42):15201–15206. [PubMed: 15475576]
- Machado AM, Simon TJ, Nguyen V, McDonald-McGinn DM, Zackai EH, Gee JC. Corpus callosum morphology and ventricular size in chromosome 22q11.2 deletion syndrome. *Brain Res* 2007;1131(1):197–210. [PubMed: 17169351]
- Marenco S, Siuta MA, Kippenhan JS, Grodofsky S, Chang WL, Kohn P, et al. Genetic contributions to white matter architecture revealed by diffusion tensor imaging in Williams syndrome. *Proc Natl Acad Sci U S A* 2007;104(38):15117–15122. [PubMed: 17827280]
- Margariti PN, Blekas K, Katzioti FG, Zikou AK, Tzoufi M, Argyropoulou MI. Magnetization transfer ratio and volumetric analysis of the brain in macrocephalic patients with neurofibromatosis type 1. *Eur Radiol* 2007;17(2):433–438. [PubMed: 16733674]
- Masterman DL, Cummings JL. Frontal-subcortical circuits: the anatomic basis of executive, social and motivated behaviors. *J Psychopharmacol* 1997;11(2):107–114. [PubMed: 9208374]
- Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, et al. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proc Natl Acad Sci U S A* 2003;100(10):6186–6191. [PubMed: 12716966]
- Mazzocco MM, Kates WR, Baumgardner TL, Freund LS, Reiss AL. Autistic behaviors among girls with fragile X syndrome. *J Autism Dev Disord* 1997;27(4):415–435. [PubMed: 9261667]
- McDonald-McGinn DM, Kirschner R, Goldmuntz E, Sullivan K, Eicher P, Gerdes M, et al. The Philadelphia story: the 22q11.2 deletion: report on 250 patients. *Genet Couns* 1999;10(1):11–24. [PubMed: 10191425]
- McDonald-McGinn DM, LaRossa D, Goldmuntz E, Sullivan K, Eicher P, Gerdes M, et al. The 22q11.2 deletion: screening, diagnostic workup, and outcome of results; report on 181 patients. *Genetics Testing* 1997;1(2):99–108.
- Meng Y, Zhang Y, Tregoubov V, Janus C, Cruz L, Jackson M, et al. Abnormal spine morphology and enhanced LTP in LIMK-1 knockout mice. *Neuron* 2002;35(1):121–133. [PubMed: 12123613]
- Mervis CB, Klein-Tasman BP. Williams syndrome: cognition, personality, and adaptive behavior. *Mental Retardation & Developmental Disabilities Research Reviews* 2000;6(2):148–158. [PubMed: 10899809]

- Meyer-Lindenberg A, K. P., Mervis CB, Kippenhan JS, Olsen RK, Morris CA, Berman KF. Neural basis of genetically determined visuospatial construction deficit in Williams syndrome. *Neuron* 2004;43(5): 623–631. [PubMed: 15339645]
- Meyer-Lindenberg A, Mervis CB, Sarpal D, Koch P, Steele S, Kohn P, et al. Functional, structural, and metabolic abnormalities of the hippocampal formation in Williams syndrome. *J Clin Invest* 2005;115(7):1888–1895. [PubMed: 15951840]
- Meyer-Lindenberg A, Nichols T, Callicott JH, Ding J, Kolachana B, Buckholtz J, et al. Impact of complex genetic variation in COMT on human brain function. *Mol Psychiatry* 2006;11(9):867–877. 797. [PubMed: 16786032]
- Meyer-Lindenberg A, Zink CF. Imaging genetics for neuropsychiatric disorders. *Child Adolesc Psychiatr Clin N Am* 2007;16(3):581–597. [PubMed: 17562580]
- Molko N, Cachia A, Riviere D, Mangin JF, Bruandet M, Le Bihan D, et al. Functional and structural alterations of the intraparietal sulcus in a developmental dyscalculia of genetic origin. *Neuron* 2003;40(4):847–858. [PubMed: 14622587]
- Moore BD 3rd, Slopis JM, Jackson EF, De Winter AE, Leeds NE. Brain volume in children with neurofibromatosis type 1: relation to neuropsychological status. *Neurology* 2000;54(4):914–920. [PubMed: 10690986]
- Moore CJ, Daly EM, Schmitz N, Tassone F, Tysoe C, Hagerman RJ, et al. A neuropsychological investigation of male premutation carriers of fragile X syndrome. *Neuropsychologia* 2004;42(14): 1934–1947. [PubMed: 15381024]
- Morris, CA.; Mervis, CB. Williams syndrome. In: Goldstein, Sam; Reynolds, Cecil R., editors. *Handbook of neurodevelopmental and genetic disorders in children*. The Guilford Press; New York, US: 1999. p. 555-590.
- Morris CA, Mervis CB, Hobart HH, Gregg RG, Bertrand J, Ensing GJ, et al. GTF2I hemizygosity implicated in mental retardation in Williams syndrome: genotype-phenotype analysis of five families with deletions in the Williams syndrome region. *Am J Med Genet A* 2003;123(1):45–59. [PubMed: 14556246]
- Moss EM, Batshaw ML, Solot CB, Gerdes M, McDonald-McGinn DM, Driscoll DA, et al. Psychoeducational profile of the 22q11.2 microdeletion: A complex pattern [see comments]. *Journal of Pediatrics* 1999;134(2):193–198. [PubMed: 9931529]
- Mostofsky SH, Mazzocco MM, Aakalu G, Warsofsky IS, Denckla MB, Reiss AL. Decreased cerebellar posterior vermis size in fragile X syndrome: correlation with neurocognitive performance. *Neurology* 1998;50(1):121–130. [PubMed: 9443468]
- Mukai J, Liu H, Burt RA, Swor DE, Lai WS, Karayiorgou M, et al. Evidence that the gene encoding ZDHHC8 contributes to the risk of schizophrenia. *Nat Genet* 2004;36(7):725–731. [PubMed: 15184899] Epub 2004 Jun 2006
- Murphy KC. Schizophrenia and velo-cardio-facial syndrome. *Lancet* 2002;359(9304):426–430. [PubMed: 11844533]
- Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Archives of General Psychiatry* 1999;56(10):940–945. [PubMed: 10530637]
- Nicodemus KK, Kolachana BS, Vakkalanka R, Straub RE, Giegling I, Egan MF, et al. Evidence for statistical epistasis between catechol-O-methyltransferase (COMT) and polymorphisms in RGS4, G72 (DAOA), GRM3, and DISC1: influence on risk of schizophrenia. *Hum Genet* 2007;120(6): 889–906. [PubMed: 17006672]
- Niklasson L, Rasmussen P, Oskarsdottir S, Gillberg C. Neuropsychiatric disorders in the 22q11 deletion syndrome. *Genetics in Medicine* 2001;3(1):79–84. [PubMed: 11339385]
- North K. Neurofibromatosis type 1. *Am J Med Genet* 2000;97(2):119–127. [PubMed: 11180219]
- North K, Joy P, Yuille D, Cocks N, Mobbs E, Hutchins P, et al. Specific learning disability in children with neurofibromatosis type 1: significance of MRI abnormalities. *Neurology* 1994;44(5):878–883. [PubMed: 8190291]
- North KN, Riccardi V, Samango-Sprouse C, Ferner R, Moore B, Legius E, et al. 1: consensus statement from the NF1 Cognitive Disorders Task Force. Cognitive function and academic performance in neurofibromatosis. *Neurology* 1997;48(4):1121–1127. [PubMed: 9109916]

- Okamoto N, Kubota T, Nakamura Y, Murakami R, Nishikubo T, Tanaka I, et al. 22q13 Microduplication in two patients with common clinical manifestations: a recognizable syndrome? *Am J Med Genet A* 2007;143(23):2804–2809. [PubMed: 17975801]
- Ozonoff S. Cognitive impairment in neurofibromatosis type 1. *Am J Med Genet* 1999;89(1):45–52. [PubMed: 10469436]
- Papalos DF, Faedda GL, Veit S, Goldberg R, Morrow B, Kucherlapati R, et al. Bipolar spectrum disorders in patients diagnosed with velo-cardio-facial syndrome: does a hemizygous deletion of chromosome 22q11 result in bipolar affective disorder? *American Journal of Psychiatry* 1996;153(12):1541–1547. [PubMed: 8942449]
- Paterlini M, Zakharenko SS, Lai WS, Qin J, Zhang H, Mukai J, et al. Transcriptional and behavioral interaction between 22q11.2 orthologs modulates schizophrenia-related phenotypes in mice. *Nat Neurosci* 2005;8(11):1586–1594. [PubMed: 16234811] Epub 2005 Oct 1523
- Paylor R, Glaser B, Mupo A, Ataliotis P, Spencer C, Sobotka A, et al. Tbx1 haploinsufficiency is linked to behavioral disorders in mice and humans: implications for 22q11 deletion syndrome. *Proc Natl Acad Sci U S A* 2006;103(20):7729–7734. [PubMed: 16684884]
- Paylor R, McIlwain KL, McAninch R, Nellis A, Yuva-Paylor LA, Baldini A, et al. Mice deleted for the DiGeorge/velocardiofacial syndrome region show abnormal sensorimotor gating and learning and memory impairments. *Hum Mol Genet* 2001;10(23):2645–2650. [PubMed: 11726551]
- Phillips ML. The emerging role of neuroimaging in psychiatry: characterizing treatment-relevant endophenotypes. *Am J Psychiatry* 2007;164(5):697–699. [PubMed: 17475723]
- Reddy KS. Cytogenetic abnormalities and fragile-X syndrome in Autism Spectrum Disorder. *BMC Med Genet* 2005;6:3. [PubMed: 15655077]
- Reiss AL, Abrams MT, Greenlaw R, Freund L, Denckla MB. Neurodevelopmental effects of the FMR-1 full mutation in humans. *Nature Medicine* 1995;1(2):159–167.
- Reiss AL, Aylward E, Freund LS, Joshi PK, Bryan RN. Neuroanatomy of fragile X syndrome: the posterior fossa. *Ann Neurol* 1991;29(1):26–32. [PubMed: 1996876]
- Reiss AL, Dant CC. The behavioral neurogenetics of fragile X syndrome: analyzing gene-brain-behavior relationships in child developmental psychopathologies. *Dev Psychopathol* 2003;15(4):927–968. [PubMed: 14984133]
- Reiss AL, Eckert MA, Rose FE, Karchemskiy A, Kesler S, Chang M, et al. An experiment of nature: brain anatomy parallels cognition and behavior in Williams syndrome. *J Neurosci* 2004;24(21):5009–5015. [PubMed: 15163693]
- Reiss AL, Eliez S, Schmitt JE, Patwardhan A, Haberecht M. Brain imaging in neurogenetic conditions: realizing the potential of behavioral neurogenetics research. *Ment Retard Dev Disabil Res Rev* 2000;6(3):186–197. [PubMed: 10982496]
- Reiss AL, Eliez S, Schmitt JE, Straus E, Lai Z, Jones W, et al. IV. Neuroanatomy of Williams syndrome: a high-resolution MRI study. *J Cogn Neurosci* 2000;12(Suppl 1):65–73. [PubMed: 10953234]
- Reiss AL, Freund L, Tseng JE, Joshi PK. Neuroanatomy in fragile X females: the posterior fossa. *Am J Hum Genet* 1991;49(2):279–288. [PubMed: 1867191]
- Reiss AL, Lee J, Freund L. Neuroanatomy of fragile X syndrome: the temporal lobe. *Neurology* 1994;44(7):1317–1324. [PubMed: 8035938]
- Schaer M, Eliez S. From genes to brain: understanding brain development in neurogenetic disorders using neuroimaging techniques. *Child Adolesc Psychiatr Clin N Am* 2007;16(3):557–579. [PubMed: 17562579]
- Schmitt JE, Eliez S, Warsofsky IS, Bellugi U, Reiss AL. Corpus callosum morphology of Williams syndrome: relation to genetics and behavior. *Developmental Medicine & Child Neurology* 2001a;43(3):155–159. [PubMed: 11263684]
- Schmitt JE, Eliez S, Warsofsky IS, Bellugi U, Reiss AL. Enlarged cerebellar vermis in Williams syndrome. *Journal of Psychiatric Research* 2001b;35(4):225–229. [PubMed: 11578640]
- Sebat J, Lakshmi B, Malhotra D, Troge J, Lese-Martin C, Walsh T, et al. Strong association of de novo copy number mutations with autism. *Science* 2007;316(5823):445–449. [PubMed: 17363630]
- Shah SH, Kraus WE, Crossman DC, Granger CB, Haines JL, Jones CJ, et al. Serum lipids in the GENECARD study of coronary artery disease identify quantitative trait loci and phenotypic subsets on chromosomes 3q and 5q. *Ann Hum Genet* 2006;70(Pt 6):738–748. [PubMed: 17044848]

- Shashi V, Keshavan MS, Howard TD, Berry MN, Basehore MJ, Lewandowski E, et al. Cognitive correlates of a functional COMT polymorphism in children with 22q11.2 deletion syndrome. *Clin Genet* 2006;69(3):234–238. [PubMed: 16542388]
- Shashi V, Muddasani S, Santos CC, Berry MN, Kwapil TR, Lewandowski E, et al. Abnormalities of the corpus callosum in nonpsychotic children with chromosome 22q11 deletion syndrome. *Neuroimage* 2004;21(4):1399–1406. [PubMed: 15050565]
- Shen D, Davatzikos C. Very high-resolution morphometry using mass-preserving deformations and HAMMER elastic registration. *Neuroimage* 2003;18(1):28–41. [PubMed: 12507441]
- Shomstein S, Yantis S. Parietal cortex mediates voluntary control of spatial and nonspatial auditory attention. *J Neurosci* 2006;26(2):435–439. [PubMed: 16407540]
- Silva AJ, Elgersma Y, Friedman E, Stern J, Kogan J. A mouse model for learning and memory defects associated with neurofibromatosis type I. *Pathol Biol (Paris)* 1998;46(9):697–698. [PubMed: 9885821]
- Silva AJ, Frankland PW, Marowitz Z, Friedman E, Laszlo GS, Cioffi D, et al. A mouse model for the learning and memory deficits associated with neurofibromatosis type I. *Nat Genet* 1997;15(3):281–284. [PubMed: 9054942]
- Simon TJ, Bearden CE, Mc-Ginn DM, Zackai E. Visuospatial and numerical cognitive deficits in children with chromosome 22q11.2 deletion syndrome. *Cortex* 2005;41(2):145–155. [PubMed: 15714897]
- Simon TJ, Ding L, Bish JP, McDonald-McGinn DM, Zackai EH, Gee J. Volumetric, connective, and morphologic changes in the brains of children with chromosome 22q11.2 deletion syndrome: an integrative study. *Neuroimage* 2005;25(1):169–180. [PubMed: 15734353]
- Soni S, Whittington J, Holland AJ, Webb T, Maina EN, Boer H, et al. The phenomenology and diagnosis of psychiatric illness in people with Prader-Willi syndrome. *Psychol Med* 2008;1–10.
- Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. *Nat Neurosci* 2003;6(3):309–315. [PubMed: 12548289]
- Stachon AC, Baskin B, Smith AC, Shugar A, Cytrynbaum C, Fishman L, et al. Molecular diagnosis of 22q11.2 deletion and duplication by multiplex ligation dependent probe amplification. *Am J Med Genet A* 2007;143(24):2924–2930. [PubMed: 18000985]
- Steen RG, Taylor JS, Langston JW, Glass JO, Brewer VR, Reddick WE, et al. Prospective evaluation of the brain in asymptomatic children with neurofibromatosis type 1: relationship of macrocephaly to T1 relaxation changes and structural brain abnormalities. *AJNR Am J Neuroradiol* 2001;22(5):810–817. [PubMed: 11337320]
- Streeten EA, McBride DJ, Pollin TI, Ryan K, Shapiro J, Ott S, et al. Quantitative trait loci for BMD identified by autosome-wide linkage scan to chromosomes 7q and 21q in men from the Amish Family Osteoporosis Study. *J Bone Miner Res* 2006;21(9):1433–1442. [PubMed: 16939402]
- Styrkarsdottir U, Cazier JB, Kong A, Rolfsson O, Larsen H, Bjarnadottir E, et al. Linkage of osteoporosis to chromosome 20p12 and association to BMP2. *PLoS Biol* 2003;1(3):E69. [PubMed: 14691541]
- Sullivan K, Hatton D, Hammer J, Sideris J, Hooper S, Ornstein P, et al. ADHD symptoms in children with FXS. *Am J Med Genet A* 2006;140(21):2275–2288. [PubMed: 17022076]
- Swillen A, Devriendt K, Legius E, Eyskens B, Dumoulin M, Gewillig M, et al. Intelligence and psychosocial adjustment in velocardiofacial syndrome: a study of 37 children and adolescents with VCFS. *Journal of Medical Genetics* 1997;34(6):453–458. [PubMed: 9192263]
- Tamanini F, Meijer N, Verheij C, Willems PJ, Galjaard H, Oostra BA, et al. FMRP is associated to the ribosomes via RNA. *Hum Mol Genet* 1996;5(6):809–813. [PubMed: 8776596]
- Tassabehji M, Metcalfe K, Karmiloff-Smith A, Crette MJ, Grant J, Dennis N, et al. Williams syndrome: use of chromosomal microdeletions as a tool to dissect cognitive and physical phenotypes. *Am J Hum Genet* 1999;64(1):118–125. [PubMed: 9915950]
- Tassone F, Iwahashi C, Hagerman PJ. FMR1 RNA within the intranuclear inclusions of fragile X-associated tremor/ataxia syndrome (FXTAS). *RNA Biol* 2004;1(2):103–105. [PubMed: 17179750]
- Thompson P, Cannon TD, Toga AW. Mapping genetic influences on human brain structure. *Ann Med* 2002;34(78):523–536. [PubMed: 12553492]
- Thompson PM, Cannon TD, Narr KL, van Erp T, Poutanen VP, Huttunen M, et al. Genetic influences on brain structure. *Nat Neurosci* 2001;4(12):1253–1258. [PubMed: 11694885]

- Thompson PM, Lee AD, Dutton RA, Geaga JA, Hayashi KM, Eckert MA, et al. Abnormal cortical complexity and thickness profiles mapped in Williams syndrome. *J Neurosci* 2005;25(16):4146–4158. [PubMed: 15843618]
- Thompson PM, Schwartz C, Toga AW. High-resolution random mesh algorithms for creating a probabilistic 3D surface atlas of the human brain. *Psychiatry Research: Neuroimaging* 1996;3:19–34.
- Thompson PM, Toga AW. A framework for computational anatomy. *Comput Vis Sci* 2002a;5:1–12.
- Thompson PM, Woods RP, Mega MS, Toga AW. Mathematical/computational challenges in creating deformable and probabilistic atlases of the human brain. *Hum Brain Mapp* 2000;9(2):81–92. [PubMed: 10680765]
- Tognini G, Ferrozzi F, Garlaschi G, Piazza P, Patti A, Virdis R, et al. Brain apparent diffusion coefficient evaluation in pediatric patients with neurofibromatosis type 1. *J Comput Assist Tomogr* 2005;29(3):298–304. [PubMed: 15891494]
- Tomauiuolo F, Di Paola M, Caravale B, Vicari S, Petrides M, Caltagirone C. Morphology and morphometry of the corpus callosum in Williams syndrome: a T1-weighted MRI study. *Neuroreport* 2002;13(17):2281–2284. [PubMed: 12488811]
- Tosun, D.; Reiss, A.; Lee, A.; Dutton, R.; Geaga, J.; Hayashi, K., et al. Use of 3-D Cortical Morphometry for Mapping Increased Cortical Gyrification and Complexity in Williams Syndrome; Paper presented at the IEEE International Symposium on Biomedical Imaging; 2006; ISBI2006
- Truhan AP, Filipek PA. Magnetic resonance imaging. Its role in the neuroradiologic evaluation of neurofibromatosis, tuberous sclerosis, and Sturge-Weber syndrome. *Arch Dermatol* 1993;129(2):219–226. [PubMed: 8434982]
- Tsiouris JA, Brown WT. Neuropsychiatric symptoms of fragile X syndrome: pathophysiology and pharmacotherapy. *CNS Drugs* 2004;18(11):687–703. [PubMed: 15330685]
- Tunbridge EM, Harrison PJ, Weinberger DR. Catechol-o-methyltransferase, cognition, and psychosis: Val158Met and beyond. *Biol Psychiatry* 2006;60(2):141–151. [PubMed: 16476412]
- van Amelsvoort T, Daly E, Henry J, Robertson D, Ng V, Owen M, et al. Brain anatomy in adults with velocardiofacial syndrome with and without schizophrenia: preliminary results of a structural magnetic resonance imaging study. *Arch Gen Psychiatry* 2004;61(11):1085–1096. [PubMed: 15520356]
- van Amelsvoort T, Daly E, Robertson D, Suckling J, Ng V, Critchley H, et al. Structural brain abnormalities associated with deletion at chromosome 22q11: quantitative neuroimaging study of adults with velo-cardio-facial syndrome. *British Journal of Psychiatry* 2001;178:412–419. [PubMed: 11331556]
- van Amelsvoort T, Zinkstok J, Figee M, Daly E, Morris R, Owen MJ, et al. Effects of a functional COMT polymorphism on brain anatomy and cognitive function in adults with velo-cardio-facial syndrome. *Psychol Med* 2007:1–12.
- Verhoeven WM, Tuinier S. Prader-Willi syndrome: atypical psychoses and motor dysfunctions. *Int Rev Neurobiol* 2006;72:119–130. [PubMed: 16697294]
- Vidal CN, Rapoport JL, Hayashi KM, Geaga JA, Sui Y, McLemore LE, et al. Dynamically spreading frontal and cingulate deficits mapped in adolescents with schizophrenia. *Arch Gen Psychiatry* 2006;63(1):25–34. [PubMed: 16389194]
- Vorstman JA, Staal WG, van Daalen E, van Engeland H, Hochstenbach PF, Franke L. Identification of novel autism candidate regions through analysis of reported cytogenetic abnormalities associated with autism. *Mol Psychiatry* 2006;11(1):1, 18–28. [PubMed: 16205736]
- Weiss LA, Shen Y, Korn JM, Arking DE, Miller DT, Fossdal R, et al. Association between Microdeletion and Microduplication at 16p11.2 and Autism. *N Engl J Med*. 2008
- Williams NM, Glaser B, Norton N, Williams H, Pierce T, Moskvina V, et al. Strong evidence that GNB1L is associated with schizophrenia. *Hum Mol Genet* 2008;17(4):555–566. [PubMed: 18003636]
- Wright I, Rabe-Hesketh S, Woodruff P, David A, Murray R, Bullmore E. Meta-analysis of regional brain volumes in schizophrenia. *American Journal of Psychiatry* 2000;157:16–25. [PubMed: 10618008]
- Wright IC, Sham P, Murray RM, Weinberger DR, Bullmore ET. Genetic contributions to regional variability in human brain structure: methods and preliminary results. *Neuroimage* 2002;17(1):256–271. [PubMed: 12482082]

Zhang Y, Leaves NI, Anderson GG, Ponting CP, Broxholme J, Holt R, et al. Positional cloning of a quantitative trait locus on chromosome 13q14 that influences immunoglobulin E levels and asthma. *Nat Genet* 2003;34(2):181–186. [PubMed: 12754510]

Strategies for Investigating Neuroanatomic Endophenotypes

Figure 1.

Schematic of convergent strategies for investigating endophenotypes of major neuropsychiatric disorders: Common genes of small effect and rare genetic mutations of high penetrance may result in shared/overlapping neuroanatomic features.

Figure 2.

Literature based-associations of the COMT Val¹⁵⁸Met polymorphism with brain structure and function in the general population (top panel) and in individuals with 22q11.2 deletions (bottom panel). Interestingly, the effects of the COMT Val¹⁵⁸Met polymorphism do not appear to be limited to frontal brain regions in individuals with 22q11.2 deletions, and indeed appear more pronounced in cerebellar regions. Figure created using PubBrain methodology (www.phenowiki.org/pubbrain).

Figure 3.

Figure depicts lateral brain surfaces across three neurodevelopmental disorders, two of which are defined by contiguous gene deletion syndromes (22q11.2DS and Williams syndrome), and one by virtue of behavioral features (child onset schizophrenia). All are mapped using the same cortical pattern matching methodology (P M Thompson, Schwartz, & Toga, 1996; P. M. Thompson & Toga, 2002a; P. M. Thompson, Woods, Mega, & Toga, 2000).

Figure 4.

Developmental effects on cortical thickness in 22q11.2DS. Correlations between medial cortical thickness and age are mapped locally and visualized, separately for children with 22q11.2 deletions and typically developing controls. Figure depicts correlational (r) maps, indicating the strength of the association between cortical thickness and age across the lateral (top panel) and medial surface of the brain (bottom panel), separately for children and adolescents with 22q11.2DS (left) and typically developing controls (right). Red colors indicate brain regions showing the greatest age-associated cortical thinning.

Figure 5. Gene-Brain -Behavior Correlations in Fragile X. (A) Fragile X mental retardation protein (FMRP) protein correlations in females with FraX. (a) r-values (Spearman's rank correlation) that correlate FMRP protein score with tissue volumes are mapped to show the direction of the correlation. The significance of these correlations is shown in (b). Blue colors show correlations that are significant at the uncorrected, voxel level. In the r-maps (a,b,c), red colors indicate regions that show volume reduction with reduction in FMRP protein, whereas blue colors indicate inverse correlations, i.e. greater volume excess associated with FMRP protein reduction. (adapted from A. D. Lee et al., 2007). (B) Surface-based correlational maps showing significant associations between regions of radial caudate nucleus expansion and (a) reduced FMRP levels, (b) Autism Behavior Checklist scores, and (c) Aberrant Behavior Checklist Stereotypy Subscale scores (adapted from Gothelf, Furfaro et al., 2007).

Figure 6.

Cortical thickening in 22q11.2DS and Williams Syndrome. Maps contrast regions of excess in WS compared to demographically matched controls (top) and in 22q11.2DS (bottom). In patients with 22q11.2, no regions of increased cortical thickness were detected, relative to controls. In contrast, patients with WS showed a 10% increase in cortical thickness in perisylvian language-related cortex and adjacent temporal cortex.

Figure 7.

Tensor-Based Morphometry Maps in Two Neurogenetic Syndromes. (A) Significance maps for group differences in local brain volume between FraX and controls. FraX subjects have significant excess volumes in the ventricles and caudate regions (blue colors in panel a). b) depicts significant volume deficits in medial occipital regions and some temporal lobe regions in subjects with FraX (adapted from A. D. Lee et al., 2007). (B) Maps depict neuroanatomic alterations in Williams Syndrome, after adjusting for individual differences in total brain volume. Panel a (top row) shows areas of relative volume preservation in WS, in prefrontal and orbitofrontal areas, anterior cingulate gyrus, inferior parietal regions at the parieto-occipital junction, fusiform gyrus, and cerebellum. Panel b (bottom row): Disproportionate reduction is seen in occipital areas, parietal lobes near the temporo-parietal junction, splenium and posterior body of the corpus callosum, thalamus and the basal ganglia, and midbrain (adapted from Chiang et al., 2007). Abbreviations: Cd: caudate nucleus; OL: occipital lobe; aCG: anterior cingulate gyrus; PF: prefrontal area, IP: inferior parietal region, BG: basal ganglia, PL: parietal lobe, TL: thalamus.

Table 1

Summary of Neuroimaging Studies of Four Neurogenetic Disorders

Brain Structure(s)	Fragile X	22q11.2DS	Williams Syndrome	NF1
Cortex (whole brain volume)*	Children: ↑ (Reiss et al., 1995) (Mostofsky et al., 1998) or = (Kates, Folley, Lanham, Capone, & Kaufmann, 2002)	Children: ↓ (Bearden et al., 2007; Eliez et al., 2000; Eliez, Schmitt et al., 2001) Adults w.SZ: ↓ (vs. CTL & 22qDS w/out SZ) (T. van Amelsvoort et al., 2004)	Children: ↓ (Boddaert et al., 2006) & young adults (Chiang et al., 2007; Reiss, Eliez, Schmitt, Straus et al., 2000)	↑ (Cutting et al., 2002; Greenwood et al., 2005) (B. D. Moore, 3rd et al., 2000; Steen et al., 2001)
Ventricles	↑ (Eliez, Blasey, Freund et al., 2001; Reiss et al., 1995) (A. D. Lee et al., 2007)	↑ vs. CTL & 22qDS w/out SZ (T. van Amelsvoort et al., 2004) ↑ Adults w/SZ: (Chow et al., 2002)		
Frontal Lobe	= (Kates et al., 2002) or ↓ GM in children/adolescents (Gothelf, Furfaro et al., 2007)	↓ WM after IQ correction / vs. IQ matched CTL (Campbell et al., 2006; T. van Amelsvoort et al., 2001) ↑ Children (Eliez 2000, Kates 2001, 2004; Simon 2005) ↓ Adults w/SZ (Chow et al., 2002)	↑ Orbitofrontal region (Chiang et al., 2007; Reiss et al., 2004) ↓ (Meyer-Lindenberg A, 2004)	↑ WM (Cutting et al., 2002; Greenwood et al., 2005)
Parietal Lobe	= WM (Kates et al., 2002) ↑ GM in children/adolescents (Gothelf, Furfaro et al., 2007)	↓ Children: (Bearden et al., 2007; Eliez et al., 2000; Kates et al., 2001; Simon, Ding et al., 2005)	↓ Children: GM (Boddaert et al., 2006) / young adults (Eckert, Galaburda, Mills et al., 2006; Meyer-Lindenberg A, 2004; Reiss, Eliez, Schmitt, Straus et al., 2000)	↑ WM (Cutting et al., 2002)
Temporal Lobe	↓ (Gothelf, Furfaro et al., 2007; Kates et al., 2002) Adolescents/young adults: = (Reiss, Lee, & Freund, 1994)	Children: = (Eliez, Blasey, Schmitt et al., 2001) Adults: ↓ (Chow et al., 2002; T. van Amelsvoort et al., 2001)	= (Reiss, Eliez, Schmitt, Straus et al., 2000) or ↑ (P. M. Thompson et al., 2005)	
Occipital Lobe	= (Kates et al., 2002) or ↓ (A. D. Lee et al., 2007)	Children: = (Eliez et al., 2000) or ↓ (Bearden et al., 2007; Kates et al., 2001; Simon, Ding et al., 2005) Adults w/SZ: (Chow et al., 2002)	↓ (Boddaert et al., 2006; Eckert, Galaburda, Mills et al., 2006; Meyer-Lindenberg A, 2004; Reiss et al., 2004)	
Subcortical Structures Hippocampus	Children: (Kates et al., 2002; Reiss et al., 1994) Adults: = for pM and fM (Jakala et al., 1997)	↓ Children: (Eliez, Blasey, Schmitt et al., 2001) (Debbane, Schaer, Farhoumand, Glaser, & Eliez, 2006; Kates et al., 2006)	= size but altered shape in HP midportion (Meyer-Lindenberg et al., 2005)	
Amygdala	Children = (Reiss et al., 1994) Or ↓ in children/adolescents (Gothelf, Furfaro et al., 2007)	= (Debbane et al., 2006; Eliez, Blasey, Schmitt et al., 2001) or ↑ (Kates et al., 2006)	↑ (Chiang et al., 2007)	
Basal Ganglia Caudate	↑ (Eliez, Blasey, Freund et al., 2001; Reiss et al., 1995) (Gothelf,	↑ (Eliez, Barnea-Goraly, Schmitt, Liu, & Reiss, 2002; Kates et al.,	↓ (Chiang et al., 2007)	

Brain Structure(s)	Fragile X	22q11.2DS	Williams Syndrome	NF1
Thalamus	Furfaro et al., 2007) ↑ (Eliez, Blasey, Freund et al., 2001; Reiss et al., 1995) (Gothelf, Furfaro et al., 2007)	2004) (Campbell et al., 2006) ↓ Esp. posterior (Bish, Nguyen, Ding, Ferrante, & Simon, 2004)	↓ (Reiss et al., 2004) (Chiang et al., 2007)	
Corpus Callosum		↑ Rostrum/isthmus (Machado et al., 2007; Shashi et al., 2004), vs. CTL & 22q+ADHD (Antshel et al., 2005)	Posterior (Luders et al. ↓ 2007; (Tomaiuolo et al., 2002) Splenium, isthmus (Schmitt, Eliez, ↓ Warsofsky, Bellugi, & Reiss, 2001a)	↑ (Dubovsky et al., 2001; Margariti et al., 2007) (Kayl et al., 2000; B. D. Moore, 3rd et al., 2000)
Cerebellum	Vermis ↓ (Mazzocco et al., 1997; Reiss, Aylward et al., 1991; Reiss, Freund et al., 1991) (Mostofsky et al., 1998)	↓ Vermis: Children (Bish et al., 2006; Eliez, Schmitt et al., 2001), Adults (T. van Amelsvoort et al., 2004)	↑ Vermis (Chiang et al., 2007; Reiss, Eliez, Schmitt, Straus et al., 2000; Schmitt et al., 2001b)	
White matter microstructure (via diffusion tensor imaging)	↓ FA in frontostriatal & parietal sensorimotor circuits (Barnea-Goraly, Eliez et al., 2003)	↓ FA in frontal, parietal, temporal regions (Barnea-Goraly, Menon et al., 2003; Simon, Ding et al., 2005)	Deviation in posterior fiber tract course, ↓ lateralization of fiber coherence (Marenco et al., 2007); ↑ FA in right superior longitudinal fasciculus (Hoefl et al., 2007)	↑ ADC values, particularly in UBOs (Alkan et al., 2005; Tognini et al., 2005); ↑ ADC values, particularly in globus pallidus (Eastwood et al., 2001)

* Gray Matter +White Matter CTL=Control; SZ=schizophrenia; WM=white matter; GM=gray matter FA = Fractional Anisotropy; ADC=Apparent Diffusion Coefficient pM=premutation; fM=full mutation