Bridging the Gene-Behavior Divide through Neuroimaging
Deletion Syndromes: Velocardiofacial (22q11.2 Deletion) and
Williams (7q11.23 Deletion) Syndromes

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Abstract

Investigating the relationship between genes and the neural substrates of complex human behavior
promises to provide essential insight into the pathophysiology of mental disorders. One approach
to this inquiry is through neuroimaging of individuals with microdeletion syndromes that manifest
in specific neuropsychiatric phenotypes. Both Velocardiofacial Syndrome (VCFS) and Williams
Syndrome (WS) involve haploinsufficiency of a relatively small set of identified genes on the one
hand and association with distinct, clinically-relevant behavioral and cognitive profiles on the
other hand. In VCFS, there is a deletion in chromosomal region 22q11.2 and a resultant
predilection toward psychosis, poor arithmetic proficiency, and low performance intelligence
quotients. In WS, there is a deletion in chromosomal region 7q11.23 and a resultant predilection
toward hypersociability, non-social anxiety, impaired visuospatial construction, and often
intellectual impairment. Structural and functional neuroimaging studies have begun not only to
map these well-defined genetic alterations to systems-level brain abnormalities, but also to
identify relationships between neural phenotypes and particular genes within the critical deletion
regions. Though neuroimaging of both VCFS and WS presents specific, formidable
methodological challenges, including comparison subject selection and accounting for
neuroanatomical and vascular anomalies in patients, and many questions remain, the literature to
date on these syndromes, reviewed herein, constitutes a fruitful “bottom-up” approach to defining
gene-brain relationships.

Introduction

Parallel advancement in both genetic and neuroimaging technologies in recent years has
offered neuroscience an opportunity to elucidate the relationships between genes, neural
function, and behavior, as never before. “Top-down” approaches – using what is known
about the clinical presentation, combined with neuroimaging of neurochemical,
neuroanatomical, and neurophysiological features of the illness to infer and test for specific
genetic effects – have offered insights into the biological plausibility of the involvement of
certain genes of interest and their mechanism. However, such approaches are intrinsically

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limited in scope, and, moreover, large-scale population-based investigations, such as genome-wide association studies for a particular psychiatric illness, have lent increasing support for the principle that clinical behavioral phenotypes are rooted in many gene variants, potentially of small individual effects, which have been challenging to characterize. Thus, to dissect specific molecular contributions to human brain development and function, bottom-up approaches that study the neural and behavioral consequences of a well-described genetic variation are essential. Taking advantage of genetic accidents of nature, a number of investigators have begun to address this need by implementing in vivo neuroimaging experiments of individuals with classic microdeletion syndromes. Two of these have been best studied and will be reviewed here. Velocardiofacial Syndrome (VCFS) and William’s Syndrome (WS) – result from circumscribed, small hemideletions in chromosomal bands 22q11.2 and 7q11.23, respectively, and are remarkable for their distinctive behavioral sequelae. Though these two syndromes arise from deletion of different genes, have different clinical and neuropsychological profiles, and demonstrate distinct neuroimaging phenotypes (Campbell, et al., 2009), by virtue of their shared molecular etiology (i.e., microdeletion), they both present tremendous opportunities for understanding the genetic foundations of physiological brain function and neuropsychiatric illness. In contrast to many other studied genetic variations in humans (e.g., single nucleotide polymorphisms (SNPs)), the hemideletions in VCFS and WS represent alterations definitively targeted to the involved genes (e.g., no linkage disequilibrium confound), show clinically relevant effect sizes at the behavioral level, and confer generally unambiguous, categorical gene dose effects. The neuroimaging of these conditions, by examining structural and functional neural correlates of both the associated genetic defect and relevant behavioral measures, has begun to offer critical insight into the molecular regulation of human brain development and function at the systems level, but remains an ongoing endeavor with many important questions yet unanswered. Because neuroimaging investigations of these disorders require overcoming similar methodological challenges and testing similar fundamental hypotheses about the pathogenesis of specific neuropsychiatric phenotypes within a broader clinical syndrome, by considering the literatures of both VCFS and WS – which have made substantial but disparate advances toward these ends – this review intends to highlight ways in which these literatures inform each other and identify fertile ground for future study.

**Velocardiofacial (22q11.2 Deletion) Syndrome**

**Background**


VCFS is associated with a constellation of somatic phenotypes that include: palatal deformities (e.g., cleft palate, palatopharyngeal asymmetry), congenital heart disease (e.g., ventricular septal defect, interrupted aortic arch, tetralogy of Fallot, and truncus arteriosus), and characteristic facial morphology (Shprintzen, et al., 1978, Shprintzen, 2008). Associated vascular, ocular, skeletal, immunological and endocrinological abnormalities have also been reported (Shprintzen, 2008). Notably, there is great heterogeneity in the severity and

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particular collection of signs and symptoms in any one individual, and a number of such individuals likely escape clinical detection (Shprintzen, 2008).

Neuropsychological and psychiatric manifestations of VCFS are similarly manifold. Individuals with VCFS show a range of deficits on formal cognitive tests, including: poor performance intelligence quotients (IQ) and visuospatial, arithmetic and working memory impairments (Moss, et al., 1999, Wang, et al., 2000, Bearden, et al., 2001, Woodin, et al., 2001, Lajiness-O’Neill, et al., 2005, Simon, et al., 2005a, Simon, et al., 2005b, Bish, et al., 2007). One study has reported lower full-scale IQs in individuals with familial compared to de novo deletions (Smedt, et al., 2007). Though developmental delays are present early in life (Gerdes, et al., 1999), there is also, similar to schizophrenia, a significant decline in verbal IQ from childhood to early adulthood (Gothelf, et al., 2005). Among the vast array of psychiatric disturbances associated with this syndrome, including elevated rates of affective, anxiety, attentional, compulsive and developmental disorders (Papolos, et al., 1996, Gothelf, et al., 2004, Baker and Skuse, 2005, Fine, et al., 2005, Antshel, et al., 2006), VCFS has garnered particular attention for conferring an increased risk of schizophrenia. This is in part due to its remarkable prevalence, with up to 30% of VCFS individuals meeting full diagnostic criteria (Murphy, et al., 1999, Bassett, et al., 2005, Gothelf, et al., 2005, Gothelf, et al., 2007a) (though one study has reported greater bipolar spectrum illness than schizophrenia in a sample of 25 VCFS patients (Papolos, et al., 1996)) and even more with subsyndromal psychosis (Baker and Skuse, 2005), potentially constituting the strongest known genetic predictor of schizophrenia aside from twinship.

Structural Studies

Qualitative magnetic resonance imaging (MRI) studies, though often performed in small groups of patients, have described a number of replicated findings in VCFS. Structural brain abnormalities detected with greater frequency in patients include: midline anomalies, such as cavum septum pellucidum and cavum vergae (Vataja and Elomaa, 1998, Chow, et al., 1999, van Amelsvoort, et al., 2001, Shashi, et al., 2004, van Amelsvoort, et al., 2004) as well as hypoplastic cerebellar vermis (Mitnick, et al., 1994, Lynch, et al., 1995, Vataja and Elomaa, 1998, Chow, et al., 1999, van Amelsvoort, et al., 2001, Shashi, et al., 2004, van Amelsvoort, et al., 2004) as well as hypoplastic cerebellar vermis (Mitnick, et al., 1994, Lynch, et al., 1995, Vataja and Elomaa, 1998, Chow, et al., 1999), white matter hyperintensities on T2-weighted images (Mitnick, et al., 1994, Lynch, et al., 1995, Chow, et al., 1999, van Amelsvoort, et al., 2001, van Amelsvoort, et al., 2004), cerebellar atrophy (Lynch, et al., 1995, Chow, et al., 1999), and cerebellar atrophy or ventricular enlargement (Chow, et al., 1999). Reductions in cerebellar vermis size (Eliez, et al., 2001d) and total cerebellar volume (van Amelsvoort, et al., 2001, van Amelsvoort, et al., 2004), as well as reduced total cerebral volume (Eliez, et al., 2000, Eliez, et al., 2001c, Simon, et al., 2005c) and ventricular enlargement (Eliez, et al., 2000, Chow, et al., 2002, Simon, et al., 2005c, Campbell, et al., 2006) have been echoed by quantitative reports. Notably, all of these findings have also been reported in schizophrenia (Persaud, et al., 1997, Shenton, et al., 2001), but most studies have not attempted to disentangle how these observations differentially reflect associations with manifest psychosis or 22q11.2 microdeletion. One investigation addressing this issue applied qualitative assessments, volume of interest analyses, and voxel-based morphometry to MRI scans from VCFS patients with and without schizophrenia and learning-disabled volunteers (van Amelsvoort, et al., 2004). This study found no differences between VCFS patients with and without schizophrenia in septum pellucidum frequency, amount of white matter hyperintensities, or cerebellar atrophy. However, VCFS patients with schizophrenia showed reduced total (gray and white matter) cerebral volumes and increased cerebrospinal fluid volumes when compared with VCFS patients without schizophrenia. Similarly, Shaer and colleagues (2009a) recently reported that VCFS patients with schizophrenia show extensive suprasellar cortical thinning compared to healthy controls and VCFS patients without schizophrenia. Notably, a recent longitudinal study identified no differences in volumetric
changes over time between VCFS patients who developed schizophrenia and those that did not (Gothelf, et al., 2007b).

Another qualitative neuroimaging finding reported in VCFS is gyral pattern abnormalities — in particular, polymicrogyria, but also pachygyria (Bingham, et al., 1998, Bird and Scambler, 2000, Kawame, et al., 2000, Ghariani, et al., 2002, Ebara, et al., 2003, Koolen, et al., 2004, Sztriha, et al., 2004, Robin, et al., 2006) — which has recently received some quantitative corroboration in an MRI study of VCFS children and young adults showing reduced gyral complexity relative to healthy comparison subjects (Schaer, et al., 2006). These data raise the unresolved question of whether such gyral abnormalities are rooted in embryonic vascular developmental or primary neural migratory aberrancies. Indeed, in the case of both VCFS and WS, interpretation of disturbances of brain parenchymal structure and function must consider the potential contribution of syndrome-associated cardiovascular abnormalities. In VCFS, for instance, a range of cardiac and Circle of Willis anomalies have been described (Shprintzen, 2008), which together could lead to irregular regional cerebral perfusion and subsequent disruption of early brain maturational processes, resulting not only in abnormal gyriﬁcation (Larroche, et al., 1994), but also suboptimal neuronal integrity and subcortical development (Miller, et al., 2007). Though isolated mutations in TBX1 within the VCFS critical region lead to characteristic cardiovascular but not necessarily neuropsychiatric phenotypes in some humans (Yagi, et al., 2003), recent evidence suggests that haploinsuﬃciency of this gene can impart substantial neurobehavioral consequences (Paylor, et al., 2006), illustrating that even at the molecular level, distinguishing cardiovascular and neural etiologies is not a trivial endeavor. It is therefore notable that even though some findings discussed below have been demonstrated to be robust to cardiac disease status (Bearden, et al., 2007) or cardiac surgical history (Kates, et al., 2001), one recent investigation has reported diminished total brain volume and gyriﬁcation at the parieto-temporo-occipital junction in VCFS patients with signiﬁcant cardiac disease histories versus those without (Schaer, et al., 2009b).

With this caveat in mind, recent structural studies in VCFS have increasingly focused on identifying more regionally precise alterations in neural systems that might contribute to observed behavioral phenotypes, using both voxel-based and targeted volume-of-interest approaches, and diffusion tensor imaging, and correlating imaging results with behavioral measures. This has resulted in a number of VCFS studies identifying parietal lobe abnormalities, in line with this region’s role in performing visuospatial and arithmetic tasks, which are particularly challenging to VCFS patients. These findings include: left parietal gray matter volume reductions (Eliez, et al., 2000), parietal cortical thinning (Bearden, et al., 2007, Bearden, et al., 2009), left parietal white matter volume reductions (Kates, et al., 2001), reduced fractional anisotropy in several left parietal regions (Barnea-Goraly, et al., 2003) but greater fractional anisotropy and less radial diffusivity in the right inferior parietal lobule (Simon, et al., 2005c, Simon, et al., 2008), and reduced bilateral (though left more than right) parietal gyral complexity (Schaer, et al., 2006). To pursue these findings further, one study was able to show that in VCFS patients, worse arithmetic task performance correlated with reductions (relative to healthy individuals) in left inferior parietal lobe fractional anisotropy (Barnea-Goraly, et al., 2005), and another that slower response inhibition correlated with abnormally increased right parietal fractional anisotropy.

Importantly, all of the above cited studies (and most of the VCFS studies discussed in this section, with rare exceptions (e.g., (Kates, et al., 2001, Baker, et al., 2005)), used healthy comparison subjects unmatched for IQ, introducing the possibility that some of these findings may be related to IQ generally, rather than VCFS speciﬁcally. Indeed, when a subset of IQ-matched subjects were compared in one volumetric study, the reported VCFS-associated reductions in parietal white matter were substantially weakened (Kates, et al.,
This illustrates a particular challenge to research in VCFS, and, as echoed below, WS; comparison subject selection and subsequent analyses must be able to address the issue of IQ, which is both part of the illness under study and a potential independent contributor to altered brain development and function. In VCFS patients, lower IQ may be associated with reduced frontotemporal cortical thickness (Schaer, et al., 2009a). In healthy individuals, domain-general intelligence scores show a positive correlation with total brain size (McDaniel, 2005) and distributed regional gray matter volumes (Haier, et al., 2004, Colom, et al., 2006) and fractional anisotropy (Schmithorst, et al., 2005, Yu, et al., 2008). Likewise, compared with healthy normal-IQ individuals, those with idiopathic mental retardation show more qualitative structural abnormalities, including some relevant to the VCFS imaging phenotype (e.g., enlarged lateral ventricles and thinned corpus callosum) (Spencer, et al., 2005), as well as widespread reductions in regional gray matter volumes (Spencer, et al., 2006) and fractional anisotropy (Yu, et al., 2008), underscoring the need to better characterize the specificity of reported neuroimaging results in VCFS.

In addition to parietal structural findings outlined above, several studies have identified abnormalities of the corpus callosum in VCFS, including reduced fractional anisotropy throughout this structure (Simon, et al., 2005c). Using manual segmentation methods, VCFS patients show greater corpus callosum volumes, though discrepancies in subregional analyses exist, with some investigators reporting greater isthmus volumes (Shashi, et al., 2004) and others reporting greater rostrum (but not isthmus) volumes (Machado, et al., 2007). In the latter study, reaction time on an enumeration task correlated inversely with rostrum volumes in VCFS, but not healthy, children. In the largest study of its kind to date (60 VCFS patients and 52 age-matched control subjects), VCFS patients showed larger total and subregional (all except the genu) corpus callosum volumes, which inversely correlated with teacher ratings of behavioral symptoms (Antshel, et al., 2005). However, children with VCFS and comorbid attention-deficit hyperactivity disorder showed reduced corpus callosum volumes compared to those with VCFS alone. In contrast, another study showed increased midbody corpus callosum volumes in children with VCFS and comorbid schizophrenia (Usiskin, et al., 1999). These last two studies form a particularly interesting illustration of the complexity introduced by psychiatric comorbidity in studying neurogenetic syndromes, highlighting the potential for independent or interaction effects of diagnosis, even when that diagnosis is associated with the syndrome itself.

Several studies measuring frontal lobe total or gray matter volumes in VCFS children have found either no change or absolute volume reductions that disappear or become relative enlargements when accounting for total brain volume (Eliez, et al., 2000, Kates, et al., 2001, Kates, et al., 2004, Simon, et al., 2005c). This has been interpreted as relative sparing of the frontal lobes from pathology; however, orbitofrontal cortical thinning in VCFS children (Bearden, et al., 2007, Bearden, et al., 2009, though see Schaer, et al. 2009a reporting frontal thickening in VCFS children with subsequent accelerated thinning with age), reduced frontal gyral complexity in a mixed-age VCFS group, and frontal gray matter reductions (even with total brain volume correction) in adult VCFS cohorts that include patients with schizophrenia have also been reported (van Amelsvoort, et al., 2001, Chow, et al., 2002), raising the possibility that either metric, comorbid psychosis and/or late developmental effects might play a role in detecting emergent frontal cortical pathology when present in VCFS. As discussed below, contextual genetic influences may also have a hand in abnormal frontal development in VCFS (Gothelf, et al., 2005). Furthermore, voxel-based morphometric studies in children with VCFS have found reductions of frontal white matter (van Amelsvoort, et al., 2001, Simon, et al., 2005c, Campbell, et al., 2006), though current diffusion tensor imaging evidence does not support disrupted frontal axonal organization in this syndrome (Simon, et al., 2005c). In view of these data, it is interesting to note preliminary evidence that frontostriatal relationships may be altered in VCFS, as
correlations between frontal and caudate volumes found in healthy volunteers were absent from VCFS children’s scans in one study (Kates, et al., 2004). This may be closely linked to striatal alterations however, as this same study reported increased relative caudate volumes in patients, a finding replicated in another investigation, which also showed a relationship with emotional symptoms (Campbell, et al., 2006). Enlarged caudate volumes have also been observed in two other studies that controlled for total brain volume (Sugama, 2000) and antipsychotic medication exposure (Eliez, et al., 2002). Further corroborative striatal abnormalities documented in VCFS include: greater caudate fractional anisotropy (Simon, et al., 2008), reduced internal capsule volumes (Kates, et al., 2004, Campbell, et al., 2006), and an association between schizotypy and putamen volumes in patients (Campbell, et al., 2006).

Structural differences in the temporal lobes, including gray matter thinning (Bearden, et al., 2007, Bearden, et al., 2009), reduced gray matter volume (Chow, et al., 2002), and reduced white matter volume (van Amelsvoort, et al., 2001) have also been reported in VCFS. Recent findings in the medial temporal lobes have been of particular interest because of this region’s importance in schizophrenia and association with learning, memory and social/emotional processing. Reductions in absolute, but not relative, hippocampal volumes has been reported (Eliez, et al., 2001c, Kates, et al., 2006), but two studies – one in children and one in a mixed-age sample – found hippocampal reductions in VCFS that not only survived correction for intracranial volume (Debbane, et al., 2006, Deboer, et al., 2007) but also were associated with cognitive impairment. Findings in the amygdala have been less consistent, with one study suggesting that children with VCFS have larger amygdalae and smaller amygdala-prefrontal cortex ratios (Kates, et al., 2006), and another failing to detect differences (Eliez, et al., 2001c). Finally, increased anterior and decreased posterior fusiform gyrus volumes (Glaser, et al., 2007) in VCFS children have been reported, mimicking the anterior-posterior gradient of the relative frontal-parietal findings discussed above, and posited to be related to social functional impairments by the authors. These and the above-cited types of anatomical variations in patients with neurodevelopmental disorders (Simon, et al., 2005c) bring an important methodological challenge to voxel-based analyses of patients with VCFS or WS, especially children, in that adequate registration to an unbiased common template becomes paramount.

A number of structural findings among the plethora enumerated above require replication and further study. Similarly, several other reports, including reduced gray matter and increased fractional anisotropy in the posterior cingulate (Simon, et al., 2005c) and reduced thalamic volumes (Bish, et al., 2004), require further investigation. Nonetheless and despite the heterogeneity inherent in this disorder, in sum, emerging structural data increasingly support a profile of temporal-parietal-cerebellar hypotrophy and midline maldevelopment in VCFS (see table 1 for a brief summary of replicated findings).

**Functional Studies**

Few functional MRI (fMRI) studies of VCFS have been reported, and as in the structural studies above, most have been limited by small sample sizes. Nonetheless, these investigations have suggested abnormalities in circuits important for mathematical, executive, and social-emotional functions, in a manner consistent with the neuropsychological and structural findings in this illness. Two studies have identified parietal lobe dysfunction in different cognitive contexts: one used an arithmetic task to show worse accuracy and concomitant increased activation in the inferior parietal lobule in adolescents with VCFS (Eliez, et al., 2001b), and another used a non-spatial n-back working memory task to show reduced inferior parietal (and frontal operculum) activation in VCFS children (Kates, et al., 2007). Two additional studies have used face-viewing paradigms to show in VCFS less activation to emotional (versus neutral) faces in the insula and premotor cortex.
regions (though more activation in occipital cortex) (van Amelsvoort, et al., 2006) and reduced fusiform gyrus activation in response to neutral faces compared to houses, an effect that was stronger in patients with psychosis, as well as reduced repetition adaptation effects in this region when viewing neutral faces (Andersson, et al., 2008). Thus, though there are still insufficient data to provide a definitive or comprehensive characterization of the functional imaging phenotypes of this disorder, fMRI investigations to date support the hypothesis of disrupted parietal circuitry, which is evident even across different cognitive paradigms and is presaged by the convergent above-reviewed morphometric evidence. The reported findings further raise the possibility of face-processing dysfunction, potentially in line with more subtle changes in fusiform shape (Glaser, et al., 2007); however, additional work to address the regional and domain (e.g., attentional or IQ effects) specificity of these findings, as well as direct examination of relationships between related structural and functional measures, will help develop current understanding of the neural correlates of VCFS.

Specific Genes and Neural Phenotypes

A number of genes in the VCFS critical region on chromosome 22 are expressed in the developing and adult central nervous system, and potentially contribute to VCFS neuropsychiatric phenotypes (Maynard, et al., 2003, Arinami, 2006). Two of these – COMT (catechol-O-methyltransferase; important in cortical synaptic dopamine catabolism) and PRODH (proline dehydrogenase; important in proline catabolism) – have featured prominently in the schizophrenia literature because variations in these genes have been associated both with risk of illness and schizophrenia neurophysiological phenotypes in humans (Egan, et al., 2001, Glatt, et al., 2003, Paylor, et al., 2006, Kempf, et al., 2008, Williams, et al., 2008). It is notable that TBX1 (T-box 1 transcription factor) and GNB1L (guanine nucleotide-binding protein beta subunit-like protein 1) have also recently shown association with schizophrenia and behavioral endophenotypes in mouse models (Paylor, et al., 2006, Williams, et al., 2008). Given the remarkably high incidence of comorbid diagnoses of VCFS and schizophrenia, these associations are important clues about both the genesis of schizophrenic symptoms in VCFS and the neurogenetic mechanism of non VCFS-related schizophrenia.

COMT genotype (Val158Met), the variant that has been most investigated, predicts the course of schizophrenia-related phenotypes in VCFS, such that having the remaining gene copy contain the Met (low enzymatic activity) allele is associated with greater prefrontal dysfunction (Baker, et al., 2005) as well as cognitive, clinical (i.e. psychosis), and prefrontal cortical volume decline over time (Gothelf, et al., 2005). A subsequent study confirmed worse prefrontal function but not more frequent schizophrenia in VCFS Met carriers (Bassett, et al., 2007). In a recent corroborative experiment that studied fifty-six VCFS patients, COMT low enzymatic activity allele carriers showed a trend for impaired prepulse inhibition and a significant interaction with hyperprolinemia for impaired smooth-pursuit eye movements (both impaired prepulse inhibition and smooth-pursuit eye movements have previously been used as endophenotypic measures for schizophrenia) (Vorstman, et al., 2008). These results are in line with rodent data supporting extensive functional interactions between PRODH and COMT genes relevant to frontal dopaminergic signaling (Paterlini, et al., 2005), emphasizing the complexity of neural disturbances in VCFS, in that they likely arise not only from the sum deletion of multiple genes, but also from resulting epistatic interactions. The fact that the high enzymatic activity allele is associated with illness risk and phenotypes in individuals that do not have VCFS (Egan, et al., 2001, Glatt, et al., 2003) further highlights the dependence of individual gene effects on the accompanying genetic context. In VCFS, the low activity allele would exacerbate the lower baseline COMT function arising from possession of only a single copy of this gene. Given non-linear effects
of cortical dopamine on cognitive function and prefrontal physiology, such that too little or
too much synaptic dopaminergic tone may be detrimental (Goldman-Rakic, et al., 2004),
these seemingly opposing gene effects may be reconcilable and further underscore the
unique contribution of microdeletion syndrome investigations to the wider genetic literature.
From these initial results implicating COMT in the development of psychosis and its neural
correlates in VCFS, it is clear that examination of individual variation in hemizygous genes
in relation to neuroimaging measures offers tremendous potential in understanding the
molecular and physiological underpinnings of neuropsychiatric phenotypes in microdeletion
syndromes. Additional investigation of interactions between VCFS deleted genes and other
structural and functional neurophenotypes in this disorder is therefore needed.

Summary of VCFS Neuroimaging

Neuroimaging studies have revealed a network of abnormalities that attempt to link genetic,
neuronal and behavioral aspects of VCFS in the service of better understanding how
22q11.2 hemideletion confers such a unique and complex neuropsychiatric phenotype.
Replicated structural anomalies coupled with abnormal neurophysiology co-localized to the
parietal cortex appear to align well with arithmetic deficits in this syndrome. Additionally,
susceptibility to psychosis may manifest at the neuronal systems level in multiple structural
findings common to VCFS and schizophrenia, such as striatal abnormalities, and specific
genetic (e.g. COMT) influences on cortical development, though clear pathways from genes
to neural circuits to psychosis in VCFS remain elusive. A particular challenge is to bring
replicated structural findings (e.g., reduced cerebellar volume) into a functional context via
multimodal and longitudinal imaging and to employ further investigation into the neural
correlates of variations in intact gene copies within the 22q11.2 region.

Williams Syndrome

Background

Relative to VCFS, Williams syndrome (WS) is a more infrequent disorder (prevalence of
1:7500–1:20,000 live births) that is caused by a hemizygous deletion of ~1.6 megabases
(Mb) typically containing approximately 28 genes on chromosomal location 7q11.23
(Stromme, et al., 2002, Osborne and Mervis, 2007, Schubert, 2009), which occurs regardless
of parental origin of the affected chromosome (Schubert, 2009). The hemideleted region is
flanked by low-copy-repeat sequences (LCR), and the deletions arise as a consequence of
unequal crossing over and misalignment that occurs during meiosis due to the substantial
similarity of the flanking LCR blocks (Shaw and Lupski, 2004, Osborne and Mervis, 2007,
Schubert, 2009). In addition to the classic WS deletion, recently discovered duplications in
the WS region also arise through unequal recombination between 7q11.23 (Somerville, et al.,
2005, Osborne and Mervis, 2007, Schubert, 2009), and extremely rare cases of
deletions that include part of the WS locus but are smaller or larger than the typical WS
deletion have also been reported (Frangiskakis, et al., 1996, Morris, et al., 2003),
demonstrating variable outcomes of this genomic region’s inherent vulnerability to

Relative to healthy individuals, chromosome transmitting parents of WS probands show a
six-fold increase in paracentric inversion of the WS locus (Osborne, et al., 2001, Bayes, et
al., 2003). Like the deletions, such inversions also result from a misalignment between the
inverted homologous LCR blocks, again demonstrating the vulnerability of this genomic
region to variation (Osborne, et al., 2001, Bayes, et al., 2003, Scherer, et al., 2005, Schubert,
2009). However, though they appear to predispose toward the WS deletion in offspring,
these inversions are not accompanied by typical WS symptoms (Scherer, et al., 2005, Tam,
et al., 2008).
The large majority of individuals with the typical WS deletion have a number of characteristic somatic abnormalities, including, distinct facial appearance, short stature, weakness of connective tissues, motor coordination problems, as well as cardiovascular abnormalities, such as supravalvular aortic stenosis (SVAS) (Williams, et al., 1961, Beuren, et al., 1962, Partsch, et al., 1999, Committee on Genetics, 2001, Osborne and Mervis, 2007). Orthopedic, endocrine, and gastrointestinal dysfunctions are also prevalent in WS (Committee on Genetics, 2001).


**Structural Studies**

On average, individuals with WS show several widespread neurostructural changes, including reduced brain size and overall curvature of the brain as well as increased gyral complexity – abnormalities that likely represent aberrant cortical maturation and are reflected in anomalous formation of the central sulcus and sylvian fissure (Jernigan and Bellugi, 1990, Galaburda, et al., 2001, Schmitt, et al., 2001a, Schmitt, et al., 2002, Jackowski and Schultz, 2005, Thompson, et al., 2005, Eckert, et al., 2006a, Gaser, et al., 2006). Though cellular alterations in several specimens of postmortem WS visual (Galaburda, et al., 2002) and parietal cortices (Holinger, et al., 2002) have been reported, more work is required to better characterize the underlying cellular pathological correlates of the generalized neuroanatomical abnormalities observed with in vivo structural imaging.
Similar to research in VCFS outlined above, recent neuroimaging studies in WS have increasingly focused on identifying neuroanatomical alterations associated with this disorder’s unique cognitive and behavioral features. Recent findings have largely converged on two key neural systems, parietal nodes along the dorsal stream and limbic regions, which appear to be particularly affected by the WS deletion and closely related to distinct behavioral phenotypes.

In light of the fact that the visual system is composed of dual processing streams emerging from the primary visual cortex - a dorsal “where” processing stream projecting into the parietal cortex and a ventral “what” processing stream projecting into the temporal lobe (Ungerleider and Mishkin, 1982) - neuropsychological data demonstrating poor performance in WS on tests such as block design and pattern construction, but relatively spared face processing (Mervis, et al., 1999, Mervis, et al., 2000, Mervis and Morris, 2007) implicate specific abnormalities of the dorsal stream. Because of the parietal lobes’ importance in regulating visuospatial cognition and attention (Brody and Pribram, 1978, Posner, 1987, Farah, 1989, Hubbard, et al., 2005, Cavanna and Trimble, 2006, Gottlieb, 2007, Burgess, 2008, Medendorp, et al., 2008, Buetti and Walsh, 2009, Sack, 2009), aberrant parietal anatomy in WS is a promising candidate neurogenetic phenotype for the marked visuospatial construction deficit in WS. Consistent with this notion, using a variety of approaches, independent studies have repeatedly found parietal region structural abnormalities, including reduced gray matter volume (Meyer-Lindenberg, et al., 2004, Reiss, et al., 2004, Eckert, et al., 2005, Boddaert, et al., 2006), reduced sulcal depth (intraparietal/occipitoparietal sulcus;) (Kippenhan, et al., 2005), and alterations of white matter integrity and connectivity (Marenco, et al., 2007). Findings of parietal abnormalities in WS have been remarkably consistent across different methodological approaches. For example, a strong relationship exists between sulcal depth and adjacent gray matter volume reductions in the intraparietal sulcal region (IPS) (Kippenhan, et al., 2005), where white matter tract changes were subsequently identified (Marenco, et al., 2007). In particular, using DTI, Hoeft et al demonstrated significant association between measures of higher fractional anisotropy in the superior longitudinal fasciculus and deficits in visuospatial construction in WS (Hoeft, et al., 2007).

Though not yet studied with longitudinal methods, parieto-occipital gray matter reductions in WS have been observed both cross-sectionally in children (aged 5–15 years) (Boddaert, et al., 2006) and in adults (Meyer-Lindenberg, et al., 2004, Reiss, et al., 2004, Eckert, et al., 2005), further strengthening the reliability of this finding and suggesting a persistence of this abnormality across development, in accord with the timecourse of the visuospatial construction deficit itself. Future research examining the developmental trajectories of the WS brain in concert with the developmental trajectories of WS behavioral and cognitive features will help to establish gene-neurodevelopment interactions.

As discussed above, in studying neurodevelopmental disorders that are often accompanied by intellectual disability, controlling for IQ confounds is an essential consideration. It is therefore notable that reduced gray matter volume and abnormal sulcal morphology of the IPS, along with co-localized altered white matter connectivity, have been observed in WS individuals both with and without mental retardation (Meyer-Lindenberg, et al., 2004, Reiss, et al., 2004, Eckert, et al., 2005, Kippenhan, et al., 2005, Van Essen, et al., 2006, Hoeft, et al., 2007, Marenco, et al., 2007). However, to what degree and how these and other neural abnormalities in WS may be related to general IQ effects remain important mechanistic and methodological questions that must be addressed. These considerations notwithstanding, together, the above findings suggest that manifold but linked abnormalities in the parietal region are likely neural correlates of the visuospatial construction deficit in WS.
It is well established that limbic pathways are important for the modulation of social and emotional behavior (Cammer, 1971, Sperry, et al., 1979, Kyle, 1988, Murray, 1991, Singer, 2007, Adolphs, 2009, Behrens, et al., 2009). Because of the unique hypersociability and social fearlessness, coupled with high prevalence of specific non-social phobia in WS (Dykens, 2003, Leyfer, et al., 2006), anatomical alterations in limbic structures have been hypothesized and subsequently demonstrated in a number of recent neuroimaging reports. The orbitofrontal cortex (OFC), a component of fronto-amygdala circuitry important for social inhibition (Rolls, et al., 1994) and for making social value judgments (Stone, et al., 1998, Adolphs, 2003), is structurally anomalous in WS, both with regard to gray matter volume reductions (Meyer-Lindenberg, et al., 2004, Eckert, et al., 2005, though, see Reiss, et al., 2004) and altered cortical folding patterns (Van Essen, et al., 2006). While IQ differences across study populations may play a role in some of these discrepant findings, Eckert, et al (2006b) demonstrated that the type of image processing performed in these normalized whole brain analyses affects the OFC differences. Unlike the majority of studies showing reduced gray matter volume in the IPS and OFC of WS individuals, findings in the amygdala (which is both functionally and structurally linked to the OFC) tend to point to either no change (Meyer-Lindenberg, et al., 2004) or an increase in gray matter volume (Reiss, et al., 2004, Chiang, et al., 2007). A recent study suggests that gray matter increases in this region predict approachability ratings of faces (Martens, et al., 2009). Additionally, reduced parahippocampal volume (Reiss, et al., 2004), as well as anterior to posterior changes in hippocampal shape, coupled with reduced activation, blood flow, and metabolic integrity of the hippocampus (Meyer-Lindenberg, et al., 2005b) have been reported. Furthermore, reduced insular volumes coupled with reduced blood flow in the anterior insula in WS have been recently described (Jabbi, et al., 2008).

In addition to parietal and limbic findings, abnormalities in other regions such as the dorsal forebrain (Galaburda, et al., 2001), corpus callosum (Schmitt, et al., 2001a, Schmitt, et al., 2001c, b, Tomaiuolo, et al., 2002, Luder, et al., 2007, Gothelf, et al., 2008), and cerebellum (Schmitt, et al., 2001c, Chiang, et al., 2007) have also been reported and merit additional study. In light of evidence showing abnormal gyrification (Larroche, et al., 1994) and other neurodevelopmental alterations (Miller, et al., 2007) being linked to cardiovascular abnormalities in VCFS, whether reported structural abnormalities in WS are to some extent impacted by congenital cardiovascular conditions is a topic that also requires further investigation. Taken together, however, accumulating evidence of gross morphological alterations such as reduced brain size and overall curvature and increased gyral complexity, in conjunction with reductions in parietal and limbic regional volumes, points to likely structural foundations for functional alterations (outlined below) in the WS brain and provides a particularly valuable bridge between the cognitive and behavioral phenotypes of this disorder and the underlying neurogenetic etiology (see table 2 for a brief summary of replicated findings).

Functional Studies

As in structural studies of WS, functional studies have focused on delineating neural features associated with visuospatial construction deficits and social/emotional cognition. Several functional neuroimaging studies of WS have identified abnormalities in the IPS as well as in amygdala and orbitofrontal and prefrontal cortices, respectively associated with these two behavioral signatures of WS (Meyer-Lindenberg, et al., 2004, Meyer-Lindenberg, et al., 2005a, Hoeft, et al., 2007, Haas, et al., 2009).

In a series of fMRI studies designed to test the visual processing system in a hierarchical “bottom-up” fashion in normal-IQ individuals with WS, retinotopic mapping revealed that the functional extent and locale of primary visual cortex (V1), the first cortical node for processing of visual information, is intact (Olsen, et al., 2009), as is the responsivity of the
ventral visual processing stream (Meyer-Lindenberg, et al., 2004). However, during both attention-to-location and visuospatial construction tasks, activation of the dorsal stream is decreased in WS (Meyer-Lindenberg, et al., 2004). Moreover, with structural equation modeling, information flow from an early dorsal stream IPS region (where gray matter volume was reduced) to higher-level parietal visual processing regions was found to be specifically disrupted (Meyer-Lindenberg, et al., 2004). In a related study (Sarpal, et al., 2008), participants were shown pictures of houses and faces to identify the parahippocampal place area (PPA) and the fusiform face area (FFA). While both ventral stream regions were normally activated in WS, the functional connectivity of the PPA with dorsal stream parietal cortex and of the FFA with amygdalofrontal regions was disrupted. Collectively, this body of work, as well as a finding of reduced parietal response during global visual processing (Mobbs, et al., 2007a), confirms that specific dorsal stream abnormalities are at least one proximate cause of the visuospatial construction deficits in WS.

As with the WS visuospatial constructive impairment, the neurofunctional underpinnings of the unique WS personality and attendant social and non-social affect processing have been at least in part elucidated by functional neuroimaging. In a normal-IQ WS cohort, relative to matched normal controls, Meyer-Lindenberg et al. (2005a) demonstrated reduced amygdala reactivity to threatening and fearful socially-relevant stimuli (faces), but when the threatening stimuli were non-social, the opposite finding emerged: amygdala response was abnormally increased. These data are in good agreement, on the one hand, with the diminished fear of strangers and consequent social disinhibition, and, on the other hand, with the high prevalence of non-social phobias and anxiety in WS (Bellugi, et al., 1999, Mervis and Klein-Tasman, 2000, Dykens, 2003, Klein-Tasman and Mervis, 2003, Leyfer, et al., 2006). The former finding has been recently replicated (Paul, et al., 2009) and extended in low IQ WS individuals studied with fMRI and ERP (Haas, et al., 2009). Furthermore, the increased tendency to approach strangers was shown to predict abnormal left amygdala response to social fear in WS (Haas, et al., In Press). Together, these findings support a functional role for the amygdala in the WS behavioral phenotype.

Harboring strong anatomical links to the amygdala, the OFC has shown functional abnormalities in WS as well, complementing morphological evidence reviewed above (Meyer-Lindenberg et al. 2004). Using the described social/non-social affective fMRI paradigm and structural equation modeling, Meyer-Lindenberg et al. (2005a) demonstrated associated disruption of OFC-amygdala functional connectivity. Because the OFC-amygdala pathway is particularly implicated in motivational valuation of social stimuli (Adolphs, 2003) and in regulating social inhibition (Rolls, et al., 1994), these data present a likely neurogenetic correlate of hypersociability and disinhibited approach to strangers in WS. Importantly, during a response inhibition task without a social or emotional component, WS individuals show reduced activity in the striatum and dorsolateral prefrontal and dorsal anterior cingulate, coupled with significantly reduced reaction time but not accuracy, suggesting the potential contribution of regions beyond the amygdala-OFC circuit to behavioral disinhibition in WS (Mobbs, et al., 2007b).

In sum, functional studies show convergent evidence of dorsal stream regional abnormalities, especially the IPS, that likely underlie the visuospatial construction deficit in WS. Limbic regions, particularly OFC-amygdala circuitry, known to be functionally involved in socially relevant affective cognition, also demonstrate functional compromise in WS. Together, these findings identify specific and dissociable neurophysiological underpinnings of the characteristic behavioral phenotypes of WS and set the stage for studying which genes within the WS locus might be responsible for these distinctive neural abnormalities (Meyer-Lindenberg, et al., 2006).
Specific Genes and Neural Phenotypes

As a result of hemizygosity, many of the ~28 genes in the WS deletion region show reduced expression in lymphoblasts and/or fibroblasts (Merla et al., 2006); however, an understanding of the specific cellular sequelae of these changes, which could explain the alterations in neural systems described above, remains limited. This is in contrast to the more straightforward characterization of WS-associated cardiovascular abnormalities resulting from hemideletion of the elastin (ELN) gene (Fazio, et al., 1991, Curran, et al., 1993, Morris, et al., 1993, Tassabehji, et al., 1997, Morris, 1998, Osborne and Mervis, 2007, Schubert, 2009). Thus, identifying which of the genes in the WS deletion locus are associated with which cognitive or behavioral abnormalities remains elusive and is complicated by the possible involvement of multiple genetic factors in the modulation of complex behavior such as social function and higher-order cognition. The study of individuals with smaller deletions within the 7q11.23 region offers the promise of further insights into which genes are important in the WS behavioral and neural phenotypes (Meyer-Lindenberg, et al., 2006, Osborne and Mervis, 2007). While neuroimaging studies of these rare individuals have been lacking, several behavioral studies have paved the way. For instance, the fact that visuospatial construction difficulties occur in a kindred with a small deletion affecting only ELN and the LIM domain kinase 1 gene (LIMK1) (Frangiskakis, et al., 1996, Morris, et al., 2003) offers strong evidence that the latter gene is involved in this aspect of the WS cognitive profile; however, findings from two partial LIMK1 deletion cases showing spared memory and visuo-spatial functioning (but impaired handwriting) has raised the possibility that LIMK1 hemizygosity alone may not always be sufficient to produce pronounced visuo-spatial deficits in every individual (Tassabehji, et al., 1999, Gray, et al., 2006, Smith, et al., 2009), in accord with hypotheses from Eckert and colleagues proposing that combined haploinsufficiency of LIMK1 and TFII-I, implicated in posterior dorsal stream structural maldevelopment, may lead to the emergence of visual-motor problems found in WS (Eckert, et al., 2006b). Additionally, the partial deletion of two members of the TFII-I transcription family of genes, GTF2IRD1 and GTF2I, was linked to craniofacial abnormalities (Tassabehji, et al., 2005) and intellectual impairment and/or visuospatial difficulties, respectively (Morris, et al., 2003, Osborne and Mervis, 2007).

Recent work in genetically modified mice has provided additional information that may guide neuroimaging studies aimed at linking individual genes in the WS locus with specific neural and behavioral abnormalities. Emerging evidence from such murine studies has suggested distinct roles for LIMK1, CLIP2, and GTF2IRD1. Interestingly, both LIMK1, important for cofilin phosphorylation, actin dynamics, and regulation of the cytoskeleton (Meng, et al., 2002), and CLIP2, which codes for a microtubule-binding protein (Hoogenraad, et al., 2000, Hoogenraad, et al., 2002), are important for neuronal maturation and migration during development, and knockout mouse models of both genes show hippocampal abnormalities. Specifically, LIMK1 knockout affects hippocampal spine morphology and long-term potentiation as well as fear responses and spatial learning (Meng, et al., 2002). Similar to LIMK1’s influence on hippocampal integrity, CLIP2 knockout results in changes in hippocampus-related behaviors and electrophysiology (Hoogenraad, et al., 2002). Thus, the observed neural consequences of both murine models are consistent with observations of structural and functional changes in the hippocampi of individuals with WS (Meyer-Lindenberg, et al., 2005b). Finally, mice with heterozygous or homozygous disruption of GTF2IRD1 exhibit decreased fear and aggression and increased social behaviors as well as significantly increased levels of serotonin metabolites in several brain regions implicated in WS, including the amygdala, frontal cortex and parietal cortex (Young, et al., 2008). Thus, these results more firmly link LIMK1, CLIP2, and GTF2IRD1 to the genesis of the distinctive neuronal and behavioral features of WS, though corroborative in vivo human data is needed.
While such single-gene manipulations in mouse models have offered insights about gene-brain mechanisms, an understanding of the complex interplay among multiple genes in the WS critical region is needed. Li et al. (2009) took advantage of the fact that this region on human chromosome 7 is largely syntenic with a segment of genes on mouse chromosome 5G2 (albeit inverted), to functionally dissect the deletion as a whole (Li, et al., 2009). They created two half-deletions of the conserved syntenic region, with the proximal deletion mice lacking GTF2I to LIMK1, distal deletion mice lacking LIMK1 to FKBP6, and the double heterozygotes carrying the complete human deletion. Mice with the proximal deletion showed increased sociability and acoustic startle response, whereas mice with the distal deletion showed cognitive defects. Approaches such as this may serve to identify gene interactions and neurogenetic mechanisms that contribute crucial aspects of the human disorder (Li, et al., 2009).

In sum, the specific role of individual genes in the critical WS deletion region remains to be fully understood. Although not without challenges, linking the genetic, neuronal, and behavioral features of WS through neuroimaging offers a unique opportunity to uncover how genes are translated in the brain to produce complex human behaviors and contribute to related neuropsychiatric disorders. Similarly to the insights achieved from studying effects of COMT allelic variation on brain and behavior in healthy individuals as well as in the remaining allele in VCFS individuals (as discussed above) research into the neurogenetics of WS behavioral phenotypes such as anxiety and abnormal social approach would likely benefit from examining the neurofunctional and structural implications of allelic variation in WS locus genes, such as LIMK1, CLIP2 and GTF2IRD2, in healthy and WS individuals. As efforts to better characterize these molecular mechanisms progress, dedicated study of how variation in relevant genes regulate neuronal and behavioral phenotypes in WS throughout development will also be invaluable.

Summary of WS Neuroimaging

Targeted neuroimaging of WS has begun to yield progress in elucidating the biological underpinnings of this disorder’s characteristic neuropsychological, social cognitive, and anxiety phenotypes. A parieto-occipital abnormality evident by both structural and functional measures has been found to underlie visuospatial construction deficits in WS. Emerging evidence implicates the amygdala, OFC and related limbic pathways in the atypical social and emotional behavioral profiles in this disorder. In addition, animal models targeting specific subsets of genes in the WS deleted region are emerging as vital research tools in understanding the genotype-phenotype relationship in this syndrome. Further research is needed to examine the role of specific genes deleted in WS and catalog developmental influences of complex genotype-phenotype relationships in the emergence of syndrome-associated behavioral abnormalities.

Discussion

Both VCFS and WS, as neurodevelopmental genetic disorders arising from well-delineated hemideletions and resulting in distinctive behavioral sequelae, pose unique opportunities to use neuroimaging to study the neural mechanisms by which genes contribute to complex cognitive and behavioral phenotypes in a bottom-up fashion. This approach, in taking advantage of an intermediate brain phenotypes tactic (Gottesman and Shields, 1972) and capitalizing on restricted genetic anomalies with large effects, promises to help bridge the still vast knowledge gap between genes and psychiatric illness in a way that complements genome-wide as well as more specifically-targeted top-down research efforts studying common variants of small effects (Risch and Merikangas, 1996, Iles, 2008). In particular, neuroimaging of these two syndromes has been successful in identifying their structural sequelae – such as volumetric reductions in the temporal and parietal cortices and posterior...
fossa in VCFS and in parieto-occipital and orbitofrontal regions in WS – as well as functional correlates – such as activation abnormalities in the inferior parietal lobule during arithmetic and working memory tasks in VCFS and in the intraparietal sulcus and orbitofrontal cortex during visuospatial and social cognition respectively, in WS. Importantly, many of these findings relate to relevant behavioral measures in VCFS and WS patients and fit well with current conceptions of the neural systems underlying these behavioral functions in health.

However, common methodological barriers to fully understanding these and other findings must continue to be a focus of future study; both VCFS and WS patients are difficult to recruit in large numbers and are prone to cardiovascular anomalies, morphological abnormalities, comorbid psychiatric conditions, and mental retardation, among other complications, which may bias neuroimaging measurements if not systematically accounted for. Nonetheless, in considering the literatures of VCFS and WS together, it is notable that shared confounds with general mechanisms of action in the central nervous system, such as general intelligence deficits or possible general ischemic conditions during neurodevelopment from significant cardiovascular abnormalities, are unlikely to entirely explain the distinct neuroimaging profiles described above for each disorder. However, by the same token, shared phenotypes, such as total cerebral volume reductions, may be more likely confounded by these variables, though direct testing of these hypotheses is needed.

Future advances in delineating single-gene effects within the critical chromosomal regions of these syndromes will undoubtedly provide enormous steps forward, as presaged by initial work reviewed above examining hemizygous COMT polymorphisms in VCFS. Additionally, given the clinical heterogeneity in these syndromes, it is likely that there is a complex interaction between genes in the deleted regions of both VCFS and WS as well as interaction elsewhere in the genome, in where individual variation could play an influential role in the emergence of abnormal mental functioning (Meechan, et al., 2009). Indeed, a broader set of genes may be needed to produce the complex neuropsychiatric abnormalities in VCFS and WS, which likely result from highly integrative neuropsychological, neurophysiological and neurochemical mechanisms.

Critically, because in both disorders it is still poorly understood at what stage or stages of development such single- or multiple-gene effects occur, initial inroads toward understanding the longitudinal aspects of the observed neural abnormalities in VCFS must be buttressed by additional study, and it is imperative to develop similar longitudinal investigations in WS. A particular challenge to researchers studying these syndromes is investigating possible genetic interactions occurring either very early in development or at specific epochs over the lifespan that might underlie the emergence of pathological behavior in both VCFS and WS. Moreover, developmentally-dependent pleiotropy in certain genes within the deleted regions of both disorders could give rise to both somatic and neuronal syndromal phenotypes.

In conclusion, neuroimaging work aimed both at overcoming methodological barriers and better describing potential contributions of genetic effects – ranging from single-gene influences to developmentally-dependent epistasis – remains an important province of future microdeletion investigations. With these possibilities in mind, neuroimaging studies of VCFS and WS to date exemplify a powerful bottom-up approach to the inherent difficulties in, and the extraordinary promise of, elucidating specific genetic influences on normal and abnormal behavior.
Acknowledgments

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### Table 1

Replicated Structural Neuroimaging Findings in Velocardiofacial Syndrome

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