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Velo-Cardio-Facial Syndrome

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Abstract

Velocardiofacial syndrome (VCFS) also known as DiGeorge, conotruncal anomaly face and Cayler syndromes is caused by a microdeletion in the long arm of chromosome 22. We review the history of the syndrome from the first clinical reports almost half a century ago to the current intriguing molecular findings associating genes from the microdeletion region and the physical and neuropsychiatric phenotype of the syndrome. Velocardiofacial syndrome has a wide spectrum of more than 200 physical manifestations including palate and cardiac anomalies. Yet, the most challenging manifestations of VCFS are the learning disabilities and neuropsychiatric disorders. As VCFS is relatively common and as up to one third of the subjects with VCFS develop schizophrenia like psychotic disorder the syndrome is the most commonly known genetic risk factor to schizophrenia. Identifying the genetic, cognitive and psychiatric risk factors for VCFS-schizophrenia is under the focus of intensive research.

Keywords

Velocardiofacial syndrome; schizophrenia; chromosome 22; COMT; microdeletion

Velo-cardio-facial syndrome (VCFS) has drawn much attention since 1992 when there were simultaneous reports of a high prevalence of psychiatric illness, especially schizophrenia, as a clinical feature and the discovery of its cause, a deletion from chromosome 22 (Scambler et al., 1992). Prior to 1992, VCFS had received relatively little attention in the medical literature, but after 1992, thousands of journal articles have been published worldwide concerning VCFS. This increase in interest reflects the hypothesis that linking the known chromosome deletion in VCFS-related schizophrenia represents a human model for the genetic basis of psychosis.

The History of VCFS

The delineation of velo-cardio-facial syndrome as a specific and distinct inherited genetic disorder occurred in 1978 (R. J. Shprintzen et al., 1978) with the description of 12 cases

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including an affected mother and daughter. However, the first known cases of VCFS to appear in the medical literature were probably those published by Eva Sedlačková in 1955 (Sedlačková, 1955). and then again in 1967 (Sedlackova, 1967) who described a number of cases of children with hypernasal speech and reduced facial animation. In 1968, DiGeorge (DiGeorge, 1968) described the association of thymic aplasia, hypoparathyroidism, and congenital heart disease in children who rarely survived to adulthood so that the full range of clinical features could not be observe, most importantly the behavioral and cognitive manifestations. In addition, the affected individuals would not live long enough to reproduce therefore limiting the ability to confirm modes of inheritance. William Strong (Strong, 1968) published a well-documented report of a single family with multiple affected members that received very little attention but it was really the first publication to confirm that the genetic disorder we now call VCFS was a heritable genetic disorder that involved both physical manifestations and cognitive and behavioral disorders. VCFS was also described in the Japanese literature beginning in 1976 (Kinouchi, Mori, Ando, & Takao, 1976; Momma et al., 2001) but was called conotruncal anomaly face syndrome (CAFS). It has now been recognized that the disorders described by Shprintzen, DiGeorge, Kinouchi, and Sedlačková all represent the same disorder Hence, differences in nosology do not imply different conditions and it is now known that all of these disorders are simply different names for the same condition that has widely variable expression (Robin & Shprintzen, 2005).

Population Prevalence of VCFS

There have been a number of reports of the population prevalence or birth frequency of VCFS, ranging from approximately 1:7000 to 1:4000 based on an analysis of birth records. However, many individuals with VCFS do not present with obvious anomalies at birth. Approximately one-third of individuals with VCFS do not have congenital heart disease, and most do not have overt clefts of the palate. Other structural anomalies associated with VCFS require special procedures, such as ultrasound or MR scans to detect, and therefore often go unnoticed until a physiologic problem develops later in life. Therefore, data collected at birth of from birth records would of necessity be underestimates of population prevalence. A more realistic population prevalence in the U.S. and other developed nations where most children survive surgery for congenital heart disease has been calculated to be between 1:1600 and 1:2000 (R. J. Shprintzen, 2008).

The VCFS Microdeletion

The hallmark molecular finding present in most VCFS patients is a hemizygous microdeletion of the 22q11.2 segment of the long arm of chromosome 22. About 85–90% of 22q11.2DS individuals have a typically deleted region (TDR) of ~3 million base pairs, which encompasses about 40 genes; 10–12% have a nested deletion of ~1.5 million base pairs and few cases have smaller deletions in or just outside the TDR (Carlson et al., 1997). While most cases are sporadic (*de novo*), in about 5%–15% of patients it is inherited as an autosomal dominant trait (Swillen et al., 1998). Similar to other syndromes caused by a microdeletion (e.g. Williams syndrome), the molecular diagnosis of VCFS is currently performed by fluorescence *in situ* hybridization (FISH) with specific molecular probes located in the deleted region.

The proposed mechanism for the creation of the deletion involves chromosomal rearrangements caused by the presence of low-copy repeats (LCR), which flank the 3.0 and 1.5 Mb TDR deletions. Interestingly, no correlation was found between the extent of the deletion and the clinical severity of the symptoms in 22q11.2DS individuals(Lindsay, 2001).

Phenotypic Findings

VCFS has an expansive phenotype of physical, metabolic, endocrine, and behavioral features. None of the findings occur with 100% frequency, and none are obligatory. Moreover, many

of the findings in VCFS are very common among other multiple anomaly syndromes thereby creating overlap of phenotypes with syndromes as etiologically diverse as fetal alcohol syndrome, Down syndrome, and Noonan syndrome. Many clinicians associate VCFS with congenital heart disease and cleft palate because individuals with VCFS make up such a large percentage of these cases. Reports have shown that VCFS constitutes a very high percentage of children with conotruncal heart anomalies, including 15% of individuals with tetralogy of Fallot, and 50% or more of children with interrupted aortic arch, type B and truncus arteriosus (Goldmuntz et al., 1998). It has also been reported that VCFS constitutes more than 8% of children with cleft palate, submucous cleft palate and occult submucous cleft palate (R. J. Shprintzen, Siegel-Sadewitz, Amato, & Goldberg, 1985). Congenital heart disease is found in approximately 71% of people with VCFS and palatal anomalies in 75% (R.J. Shprintzen & Golding-Kushner, 2008), but the most common clinical features of VCFS are actually the behavioral and cognitive and the most common structural anomaly is vascular (R.J. Shprintzen & Golding-Kushner, 2008).Vascular anomalies of some type occur in nearly all individuals with VCFS, as do cognitive or psychiatric manifestations. Vascular anomalies, such as aberrant location of vessels, missing vessels, or small vessels are difficult to detect and may therefore be recognized less frequently than obvious and symptomatic anomalies such as heart malformations. Behavioral and learning disorders will not be evident until later in life and therefore may go unrecognized for many years. At the present time, the majority of new diagnoses of VCFS come from pediatric cardiology programs or craniofacial/cleft palate centers with a far smaller number from developmental or psychiatric programs. It is therefore important for clinicians to recognize the psychiatric manifestations of this syndrome at all developmental stages.

Cognitive and Neuroanatomical Deficits

The average full-scale IQ score in individuals with VCFS is in the mid-seventies, within the borderline-intelligence range (Swillen et al., 1997). In 25% to 40% of subjects, intelligence is in the mental retardation range. When present, mental retardation is usually mild (R. J. Shprintzen, 2000; Swillen et al., 1997). The cognitive profile of subjects with VCFS is characterized by relative strengths in the areas of reading, spelling, and rote memory, and relative weaknesses in the areas of visuospatial memory and arithmetic (Simon, Bish et al., 2005), and it seems to change with development: Cross-sectional studies in children with VCFS indicated an 8–10-point higher verbal IQ (VIQ) than performance IQ (PIQ) (Campbell & Swillen, 2005). Whereas in adults, VIQ was lower than PIQ by 3.6 points (Henry et al., 2002). A recent longitudinal study confirmed that during adolescence, there is a decline in VIQ scores of individuals with VCFS (Gothelf et al., 2005)

Cognitive and neuroimaging studies of children with VCFS conducted in the last decade have provided information on the specific cognitive deficits and their possible underlying neural circuits (Schaer & Eliez, 2007; Simon, Bish et al., 2005). The frontostriatal and frontoparietal neural networks seem to be particularly affected. Children perform worse than would be expected by their cognitive level on tasks requiring shifts of attention, cognitive flexibility, and working memory (frontal cortex and caudate nucleus) (Sobin et al., 2004; Woodin et al., 2001) and on tasks involving visuospatial and numerical abilities (posterior parietal cortex) (Kates et al., 2004). Compatible findings have been reported in neuroimaging studies showing morphological changes in the frontral cortex (Eliez, Barnea-Goraly, Schmitt, Liu, & Reiss, 2002; Simon, Bearden, Mc-Ginn, & Zackai, 2005), and reduced parietal grey matter and white matter volumes, even after controlling for their reduced cortical volumes (Campbell et al., 2006a; Eliez, Schmitt, White, & Reiss, 2000a; Kates et al., 2001b). In addition, children with VCFS had abnormal activation of the parietal cortex on functional MRI during performance of mathematical (Eliez et al., 2001) and response-inhibition tasks. In a preliminary study, our team showed that adolescents with VCSF performed equally well to controls on the Go/NoGo

response inhibition task, but to do so, they had to activate more superior and inferior parietal regions (Gothelf, Hoeft et al., 2007).

Of note are reports suggesting that some neuroanatomical characteristics of children and adolescents with 22q11.2DS, before the onset of psychosis, are different than that of idiopathic schizophrenia. For example, unlike patients with idiopathic schizophrenia, frontal volumes in children and adolescents with 22q11.2DS are proportionally enlarged and posterior cortical regions including parietal, occipital, and cerebellar volumes are proportionally reduced in youth with 22q11.2DS.(Campbell et al., 2006b; Eliez, Schmitt, White, & Reiss, 2000b; Kates et al., 2001a; Simon, Ding et al., 2005) In addition white matter cortical volume reductions seem to be more prominent in VCFS than GM volume reductions. (Campbell et al., 2006b; Eliez et al., 2000b; Kates et al., 2001a; Simon, Ding et al., 2005; van Amelsvoort et al., 2004) (Gothelf, Penniman, Gu, Eliez, & Reiss, 2007)

Psychiatric Disorders in Childhood and Adolescence

The common psychiatric disorders reported in high proportion of children and adolescents with VCFS include attention-deficit/hyperactivity disorder (ADHD, 35% to 46%), oppositional defiant disorder (16%–43%), specific and social phobias (23%–61%), generalized anxiety disorder (17%–29%), separation anxiety disorder (16%–21%), and obsessive-compulsive disorder (4%–33%) and major depressive disorder and dysthymia (10%–20%)(Antshel, Fremont et al., 2006; Arnold, Siegel-Bartelt, Cytrynbaum, Teshima, & Schachar, 2001; Feinstein, Eliez, Blasey, & Reiss, 2002a; Gothelf et al., 2004). These psychiatric disorders were also found to be common in cognitively matched children and adolescents (K. D. Baker & Skuse, 2005; Feinstein, Eliez, Blasey, & Reiss, 2002b). It is not surprising that developmental disabilities in children are accompanied by high rates of behavioral problems and psychiatric disorders. This is because children with developmental disabilities share common risk factors, such as social isolation and rejection, impairments in social and daily living skills, low self-esteem, and overprotection by parents. Psychiatric disorders are also common in children with other neurogenetic syndromes. For example, ADHD which is present in about half of children with VCFS is present in 25% to 60% in children with other neurogenetic syndromes including fragile X, Williams, Prader-Willi and Turner syndromes (Leyfer, Woodruff-Borden, Klein-Tasman, Fricke, & Mervis, 2006; Russell et al., 2006; Sullivan et al., 2006; Wigren & Hansen, 2005). Thus ADHD is probably a nonspecific common pathway for a variety of risk factors affecting brain development and function. In addition, the clinical characteristics of ADHD seem too broad and heterogeneous for qualifying as a behavioral phenotype of any clinical condition.

Another psychiatric entity reported to be common in VCFS is autistic spectrum disorders. Autistic spectrum disorders were reported in 14% to 45% and a ‘full blown’ autistic disorder was found in 5% to 11% of children and adolescents with VCFS(Antshel, Aneja et al., 2006; Fine et al., 2005; Vorstman et al., 2006). However, as with ADHD, the rates of autistic disorder are not higher in VCFS than in other neurogenetic disorders. In fact, for some syndromes such as fragile X, tuberose sclerosis, Angelman, and Smith-Lemlie-Opitz the rates of autism are higher than in VCFS and in the range of 25% to 65%(Zafeiriou, Ververi, & Vargiami, 2007). Many children with developmental disabilities manifest deficits in social skills. However, in our view social skills deficit should be considered a symptom of autism only when the social skills exhibited are far below what is expected from the cognitive level of the individual. The DSM criteria do not provide such norms and consequently clinicians tend to pathologize behaviors that are actually normal, within the context of the developmental level of the child.

Psychiatric Disorders in Late Adolescence and Adulthood

As mentioned, the increased rate of most psychiatric disorders in children with VCFS is similar to that in children with other developmental disabilities(K. Baker, Baldeweg, Sivagnanasundaram, Scambler, & Skuse, 2005; Feinstein et al., 2002a). However, by late adolescence and early adulthood, this picture seems to change as up to one-third of the patients with VCFS develop psychotic disorders mostly resembling schizophrenia and schizoaffective disorder(Bassett et al., 2003; Gothelf et al., 2005; Murphy, Jones, & Owen, 1999). Psychotic disorders are far more common in adolescents and young adults with VCFS than in matched IQ subjects without the syndrome. In a longitudinal five-year follow-up of children and adolescents with VCFS we found that by the second evaluation, 32% of the patients with VCFS had acquired psychotic disorders as opposed to only 4% of the controls (Gothelf et al., 2005). Not only is schizophrenia more common in VCFS but also VCFS was found to be more common in schizophrenia patients screened for the 22q11.2 deletion. The rates of the deletion in adults with schizophrenia was found to be 0.3% to 2% (Arinami et al., 2001; Karayiorgou et al., 1995) which is higher than the estimated 1 in 5000 live births prevalence of the syndrome in the general population(Botto et al., 2003). Rates are even higher in patients with childhood-onset schizophrenia (5.7%) (Sporn et al., 2004), and in patients with schizophrenia and additional major manifestations of VCFS, namely, cardiac and palate anomalies, typical facies, hypocalcemia, and learning disabilities (from 20% for one manifestation to 53% for two) (Bassett et al., 1998; Gothelf et al., 1997).

A recent study using whole-genome scan found that rare *de novo* copy number mutations were significantly associated with schizophrenia in the general population and were collectively about 8 times more frequent in sporadic, but not familial, cases of schizophrenia than in the unaffected controls (Xu et al., 2008). Interestingly, copy number variations (deletions) in 22q11.2 were the most prominent. They were found in 1.8% of schizophrenia patients and accounted for 17.6% of all *de novo* mutations found in these patients (Xu et al., 2008). The strong bidirectional association between schizophrenia and 22q11.2 deletion make VCFS the most common known genetic risk factor for schizophrenia.

Early Psychiatric Symptoms Predicting the Emergence of Pscyhotic Disorders

There are early psychiatric signs, years before the emergence of the full-blown psychotic disorder that seem to predict the later development of schizophrenia in VCFS. Subthreshold psychotic symptoms are very common in VCFS occurring in one- third to one-half of children with the syndrome(K. D. Baker & Skuse, 2005; Debbane, Glaser, David, Feinstein, & Eliez, 2006; Feinstein et al., 2002b). In a longitudinal follow-up of children and adolescents with VCFS into young adulthood, the presence during childhood of sub threshold psychotic symptoms was identified as a major risk factor for later development of psychotic disorders (Gothelf et al., 2007). Internalizing symptoms, anxiety and depression, in childhood also significantly predicted the onset of psychotic disorders at follow-up during adolescence. The strongest predictor among the anxiety disorders was OCD; all four subjects who had OCD at baseline exhibited psychotic disorders in early adulthood. Interestingly, although ADHD is recognized as the most common psychiatric disorder in VCFS (40% to 50% of subjects), its presence did not seem to place the children at greater risk for later development of a psychotic disorder(Gothelf, Michaelovsky et al., 2007). Together, these studies suggest a prolonged gradual evolution of the psychotic disorders in VCFS. Longitudinal studies of non-VCFS schizophrenia reported a similar long-drawn out process, wherein neurological, cognitive and behavioral manifestations are already present from early childhood (Poulton et al., 2000).

Candidate Genes for the Neuropsychiatric Morbidity in VCFS

It is believed that the pathology of VCFS is caused by haploinsufficiency (insufficient amount of the gene product due to the presence of only one allele instead of two) of one or more genes

contained in the chromosomal region of 22q11.2. Lack of appropriate amount of these proteins may impact the developmental stages that determine neurodevelopment and affect functioning of the mature brain.

As mentioned before, the deletion region contains over thirty genes many of which are possible candidates for mediating the pathogenesis of 22q11.2DS. These include genes involved in regulation of transcription, cell cycle and signaling, neuronal transmission pathways, and ionic channels (Maynard, Haskell, Lieberman, & LaMantia, 2002).

TBX1—Studies in mouse models of VCFS revealed a crucial role for the transcription factor *TBX1* in the normal cardiac and pharyngeal development(Lindsay et al., 2001b; Merscher et al., 2001). But haploinsufficiency of *TBX1* alone does not explain all the symptoms of VCFS, particularly the neuro-developmental and neuropsychiatric manifestations, because *TBX1* is not prominently expressed in the adult brain (Maynard et al., 2003).

It is possible that the VCFS neuropsychiatric phenotype is related to other genes in the 22q11.2 region relevant to brain neurodevelopment and neural transmission. The effect of these genes may be mediated through genetic variations, like specific mutations or common polymorphisms, which modify the biological activity of receptors, transporters, enzymes etc., that play a role in the physiological pathways associated with the neuropsychiatric processes. Few of the prominent candidate genes are reviewed below.

COMT—The catechol-*O*-methyltransferase (*COMT*) gene, coding for the COMT enzyme, is one of the prominent candidate genes for susceptibility to mental disorders. The COMT enzyme is responsible for catecholamine inactivation including brain neurotransmitters such as dopamine and norepinephrine. The ^{158}Met variant of the membrane-bound enzyme (MB-COMT) has substantially lower enzymatic activity in the brain compared to the ^{158}Val allele (Chen et al., 2004). Thus these variants are often referred to as *COMT* high and low activity alleles. The ^{158}Val/Met variations in the *COMT* gene have been intensively investigated in relation to prefrontal cortex processes and cognitive functions (Egan et al., 2001; Tunbridge, Harrison, & Weinberger, 2006) and predisposition to psychiatric disorders (Azzam & Mathews, 2003; Glatt, Faraone, & Tsuang, 2003). VCFS individuals with only one *COMT* low activity allele are expected to have the lowest possible COMT activity compared to normal population and thus, the lowest rate of dopamine inactivation in the brain.

The VCFS individuals who carry only one copy of the low activity ^{158}Met allele should experience dopamine overload. Thus, it is possible that the neurobiological pathway mediating *COMT* variants effect on psychopathology is through its modulation of dopamine-related PFC cognitive processes.

In view of the vast body of evidence suggesting a role of the *COMT* ^{158}Val/Met variations in prefrontal cortex related cognitive functions (Egan et al., 2001; Tunbridge et al., 2006) a longitudinal study of VCFS adolescents was carried by Gothelf et al. (2005) and showed that the ^{158}Met allele was a risk factor for decline in prefrontal cortical volume and verbal abilities, as well as for the consequent development of psychotic symptoms during adolescence. This study indicated that *COMT* genotype makes a significant contribution to brain development and neuropsychiatric outcome in adolescent subjects with VCFS. Our group found an association between the *COMT* ^{158}Val/Met polymorphism and ADHD, OCD and schizophrenia/schizoaffective (S/SZaff) disorders in subjects with VCFS. The fact that the ^{158}Met allele was shown to confer an increased genetic risk to develop these disorders suggested that hyper-dopaminergic neurotransmission, as expected in individuals with a single low activity allele, may be involved in the pathogenesis of these psychiatric disorders in VCFS individuals. In a following study we identified a haplotype composed of three SNPs (including

the ^{158}Val/Met), previously implicated in functional variation, to be associated with ADHD and OCD in VCFS individuals. (Michaelovsky et al., 2008). Interestingly, the same haplotype was recently found to be associated with efficient prefrontal performance in the general population (Meyer-Lindenberg et al., 2006). Similarly, adolescents with VCFS carrying the ^{158}Met allele showed more marked auditory mismatch negativity (MMN) amplitude reduction and poorer neuropsychological performance (Baker et al., 2005). Among 33 VCFS patients with schizophrenia the ^{158}Met allele was associated with worse performance on three frontal cognitive tests (theory of mind, Trails B and olfactory identification), communication and social functioning measures (Bassett, Caluseriu, Weksberg, Young, & Chow, 2007) In contrast, other studies found that ^{158}Met hemizygous individuals performed better on a composite measure of executive function (Bearden et al., 2004)and performed better on measures of prefrontal cognitive processing compared to ^{158}Val carriers (Shashi et al., 2006). In other studies no significant differences between ^{158}Met and ^{158}Val carriers cognitive functioning (Glaser et al., 2006), neurocognitive performance (van Amelsvoort et al., 2008) and no significant allele or allele by gender effects on frontally-mediated neuropsychological function were found (Kates et al., 2006b). Interestingly, significant differences between carriers of the two alleles were found in brain anatomy parameters such as size of frontal lobes and grey/white matter density in the cerebellum, brainstem, and parahippocampal gyrus (van Amelsvoort et al., 2008) and allele by gender interaction effect on the volumes of the dorsal and orbital prefrontal cortices (Kates et al., 2006b). In conclusion, there are some indications that VCFS *COMT Met* carriers are at cognitive and psychiatric risk. However, this is yet to be replicated. As some VCFS *COMT Val* carriers also develop schizophrenia, other genes from the deletion region are probably involved in the development of VCFS neuropsychiatric phenotype.

PRODH—The *PRODH* gene encodes proline oxidase (POX), a mitochondrial enzyme that catalyses the conversion of proline to different metabolites including glutamate. Increased plasma proline was reported in VCFS individuals (Goodman, Rutberg, Lin, Pulver, & Thomas, 2000) and animal models gave evidence that *PRODH* dysfunction increases proline level and leads to altered brain function as shown by reduced PPI (Gogos et al., 1999). Many studies implicated *PRODH* variant as susceptibility factors for schizophrenia (Jacquet et al., 2005; Jacquet et al., 2002; Li et al., 2004) although others could not replicate these findings (Williams et al., 2003). Evidence for functional interaction between *PRODH* and *COMT* comes from experiments in PRODH deficient mice having low COMT activity showing increased neurotransmitter release at glutamatergic synapses as well as deficits in associative learning and response to psychomimetic drugs (Paterlini et al., 2005a). Raux et al.(Raux et al., 2007) showed an inverse correlation between plasma proline level and IQ and that hyperprolinemic VCFS patients bearing the *COMT* ^{158}Met low activity allele are at risk for psychosis. An epistasis between the *COMT* and *PRODH* genes was found in a study of the brain anatomy of schizophrenia patients: in patients with the ^{158}Val allele and one or two mutated *PRODH* alleles an increase of the white matter density in the left inferior frontal lobe was observed (Zinkstok et al., 2008). Interaction between proline level and *COMT* ^{158}Val/Met in VCFS was demonstrated by a significant reduction of smooth pursuit eye movement (SPEM) in children with high proline levels and bearing the low activity ^{158}Met allele (Vorstman et al., 2008). The above studies are consisted with the hypothesis that the phenotypic expression in VCFS in terms of cognition and comorbidity can be affected by each gene alone and by interaction between genes that affect the same pathway (e.g., dopaminergic, glutamatergic).

ZDHHC8 is another candidate gene from the deleted region which may be relevant to the VCFS phenotype because it affected PPI in female knockout mice (Mukai et al., 2004) and showed significant association with schizophrenia (Liu et al., 2002).

DGCR8—A recent study investigated the biogenesis of microRNAs (miRNAs) in 22q11 deleted mice and identified a subset of brain miRNAs affected by the microdeletion (Stark et al., 2008). They demonstrated that the abnormal miRNA biogenesis is caused by the haploinsufficiency of the DGCR8 gene, which encodes an RNA-binding moiety. In addition, DGCR8 deficient mice show behavioral and neuronal deficits associated with the VCFS (Stark et al., 2008).

In addition, genes from the deleted region may interact with genes elsewhere in the genome as was suggested for TBX1. Interactions of Tbx1 and modifiers genes: Fgf8, Fgf10, Cbx2, Pitx2 caused abnormal pharyngeal arch development and as a result craniofacial and cardiovascular anomalies in mouse models (Aggarwal & Morrow, 2008).

Animal Models of 22q11.2 Deletion

The 22q11.2 deletion was also modeled in laboratory animals (Arguello & Gogos, 2006). Knockout mice deleted in chromosome 16, in a region homologous to part of the human 22q11, were constructed by Lindsay et al., 1999. Heterozygously deleted mice were found to have cardiovascular defects similar to those in VCFS patients (Lindsay et al., 1999) and to show deficits in sensorimotor gating, learning and memory similar to patients with schizophrenia (Paylor et al., 2006).

A single-gene knockout mouse strain for PRODH showed several neurochemical and behavioral features relevant to schizophrenia (Gogos et al., 1999) and served to demonstrate the interaction between the PRODH and COMT genes at the biochemical/molecular level as well as the neurobehavioral phenotype (Paterlini et al., 2005b). Mouse models of candidate genes from the deleted region including TBX1 (Lindsay et al., 2001b) ; COMT (Gogos et al., 1998); ZDHHC8 (Mukai et al., 2004) were investigated for their potential contribution to the VCFS phenotype.

In conclusion, the recent innovative publications on the association of copy number variations (i.e. deletions/insertions) with genetic susceptibility to autism (Sebat et al., 2007) and schizophrenia (Xu et al., 2008) have rekindled the interest in VCFS. The study of the molecular mechanisms causing the clinical manifestations of VCFS offers a unique opportunity to concentrate on a specific region in the genome that contains a limited number of genes, and to assess their relevance to physical abnormalities as well as neuropsychiatric disorders.

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