Genetics of Childhood Disorders: XXV. Velocardiofacial Syndrome

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Velocardiofacial syndrome (VCFS) is a genetic syndrome with a range of psychiatric symptoms. Identification of the gene(s) involved in its expression should lead to an improved understanding of both normal CNS development and how specific mutations contribute to psychiatric disorders. VCFS was first defined by Robert Shprintzen more than 20 years ago. Only in recent years, with the increased interest in molecular biology in psychiatry, has it received wider recognition.

VCFS has an estimated prevalence of 1 in 4,000, making it the second most common genetic syndrome after Down syndrome. It is caused by a microdeletion in the long arm of chromosome 22. Several disorders, such as DiGeorge syndrome, some cases of Pierre-Rubin syndrome, and other rarer syndromes, are caused by a seemingly identical microdeletion. Identification of the gene(s) that are affected by the deletion will be required before it is known whether the same or different genes contribute to the expression of these disorders. Together with VCFS, they are collectively referred to as the 22q11 deletion syndromes (22qDS).

Ninety percent of patients with 22qDS have a deletion of approximately 3 million base pairs, while 7% have smaller deletions of 1.5 million bases. Similar to other syndromes caused by a microdeletion, the molecular diagnosis of 22qDS is usually made by fluorescence in situ hybridization (FISH) (Ward et al., 1999). In FISH, a fluorescently labeled sequence of a few thousand nucleotides is constructed in the laboratory. This sequence is used as a probe that will bind to the complementary sequence of bases on chromosome 22. As there are two copies of each chromosome, two hybridization signals will appear on the FISH examination in the normal individual. In those cases in which a deletion is present, fluorescence will be detected on only one chromosome (Fig. 1). Ninety-five percent of 22qDS can be detected with this technique. The rest fail to be detected because they are caused by unique deletions or unbalanced translocations.

There are several major clinical characteristics of 22qDS. *Congenital heart disease* is present in 74% of patients with 22qDS. The most common are tetralogy of Fallot, interrupted aortic arch, and ventricular septal defect. Screening of patients with cardiac anomalies ascertained at cardiac clinics determined that the deletion is present in 3% to 15% of them. The prevalence of the deletion among cardiac patients is highest for

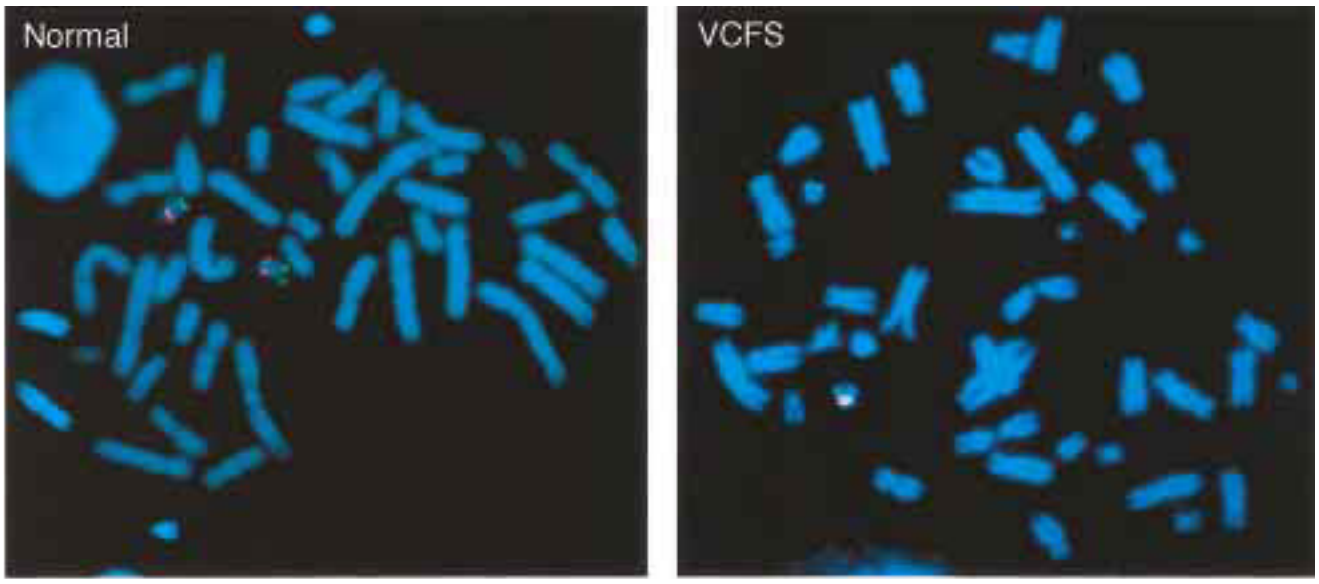

Fig. 1 A typical fluorescence in situ hybridization (FISH) picture of a normal and a velocardiofacial syndrome (VCFS) patient. The greenish signals lie outside the deleted VCFS region on chromosome 22. They are present on the two homologous chromosomes in both the normal and the VCFS patients. The red marker hybridizes to a sequence within the VCFS region. It is present on both chromosomes of the normal karyotype and is absent from the deleted chromosome of the VCFS patient. The figure was kindly provided by Dr. Ayala Aviram-Goldring, Danele Gertner Institute of Genetics, Sheba Medical Center, Tel Hashomer, Israel.

those with interrupted aortic arch and tetralogy of Fallot. An *abnormal facies* is also characteristic of patients with 22qDS. Typically, alae nasae is hypoplastic, leading to a bulbous nasal tip and prominent nasal root. The narrow face is long and narrow with flat cheeks, narrow palpebral fissures, a small mouth, receding chin, and small cupped ears. *Palatal abnormalities* are present in 83% of patients. They range from velopharyngeal incompetence to cleft lip and palate. *Hypocalcemia and T-cell immunodeficiency* are typical of the DiGeorge syndrome phenotype and are caused by hypoplastic parathyroid and thymus glands, respectively. *Other features* of 22qDS include tortuous retinal vessels, growth retardation, increased rate of juvenile rheumatoid arthritis, and urinary system anomalies.

The earliest reports on VCFS patients involved young children. As the patients grew to school age, it became apparent that they suffered from continuing behavioral problems. They were often shy and socially withdrawn, with blunted affect, but also impulsive, disinhibited, and prone to temper tantrums. Psychotic and affective symptoms often emerged in adolescence or early adulthood.

About one forth of VCFS patients develop psychotic symptoms, and a diagnosis of schizophrenia is often made in adolescence. Indeed, the prevalence of schizophrenia in VCFS patients is 25 times that of the general population. In addition, both schizophrenic and nonschizophrenic VCFS patients scored higher on a scale measuring schizotypal personality. The schizophrenia associated with VCFS has a chronic and disabling course and is associated with poor response to classical neuroleptics. Although treatment with atypical neuroleptics has not been systematically studied, few VCFS patients have responded well to clozapine for the treatment of their psychotic symptoms.

Most studies have found a significant increased prevalence of schizophrenia in VCFS. Similar increases in the rate of schizophrenia have been described with other genetic syndromes, such as homocystinuria, acute intermittent porphyria, and the sphingolipidoses and leukodystrophies. Several studies have looked at groups of schizophrenic patients and found an increased rate of VCFS. One team detected 22qD in 2 of 100 adult schizophrenic patients, a rate about 200 times greater than in the general population. Our group has reported a 22qD prevalence of 20% in a sample of schizophrenic patients with at least one prominent physical manifestation of VCFS, such as cardiac anomaly, cleft palate, or the typical facies. A study by Bassett's group found a prevalence of 60% in schizophrenic patients who had at least two physical manifestations of VCFS. Recently, the Child Psychiatry Branch of the NIMH reported a 6% rate of 22qD in a cohort of 47 patients with very-early-onset schizophrenia.

Half of VCFS children are hypotonic. In addition, most have delays in gross motor development, such as crawling and walking independently, as well as fine motor development. Though the psychotic and affective symptoms of VCFS are largely nonspecific, the cognitive deficits can be more specifically delineated. Intelligence has been intensively studied in affected preschool children, adolescents, and adults. The average total IQ score in these studies falls in the borderline intelligence range of 71 to 78. From 25% to 40% of patients were mildly retarded. Moderate to severe mental retardation was rarely found.

The Performance IQ score was consistently and significantly lower (by approximately 10 points) than the Verbal IQ. Information, comprehension, and coding subsets were relatively strong, whereas visual-spatial perception and problem-solving were weak. The language skills were both delayed and impaired in all VCFS patients, with the impairment being more pronounced in the expressive than the receptive domain. Although developmental language disorders are regarded as harbingers of later disabilities in reading, the latter remained intact in VCFS. Most subjects with VCFS have a history of special education needs. Taken together, the Verbal–Performance IQ split and the reading–mathematics splits are compatible with a nonverbal learning disability.

The disruption to some cognitive skills and not others indicates that VCFS may serve as a model for developmental psychopathology. Similar to what has been found in schizophrenia, patients with VCFS show aberrant early development marked by psychomotor delays; coordination deficits; specific deficits in cognition, language, learning and attention; and social withdrawal. These features strongly suggest a disruption in normal CNS development. Additional support for this model derives from imaging studies. The brain imaging findings in schizophrenics, such as enlarged lateral ventricles and decreased gray matter volume, have also been found in the few magnetic resonance imaging studies of VCFS patients, with and without schizophrenia.

What do we know about the developmental pathogenesis of VCFS or 22qDS? The embryonic neural crest cells are highly migratory cells that give rise to the mesenchyme of the third and fourth pharyngeal arches which later differentiate into specific organs and structures of the head, neck, and aortic arch. The cardiac anomalies, cleft palate, facial dysmorphism, and maldevelopment of the thymus and parathyroid gland found in 22qDS indicate that the syndrome is probably the result of an embryonic defect in the migration of neural crest cells.

The gene or genes that cause 22qDS are not yet known, although extensive efforts are under way to detect them. The disorder does not appear to be a contiguous gene deletion syndrome. One example of a contiguous gene deletion syndrome is Williams syndrome, which is caused by a microdeletion on chromosome 7. At least 16 genes lie in the large region deleted in Williams, and the mutations of several of these are thought to explain the varied symptoms seen with the disorder. Thus the deletion of a gene termed *elastin* is believed to be responsible for the connective tissue abnormalities, while the deletions of several other genes in the same region are thought to be responsible for the cognitive symptoms.

The phenotype of 22qDS is highly variable, and there is no correlation between the pattern or severity of the phenotype and the extent of the deletion. It is also unclear whether a mutation within a single gene could cause similar symptoms, although to date only deletions have been found in patients with the VCFS/DiGeorge phenotype. It is possible that the deletion causes a disruption to the expression of a transcription factor or other protein that is required for the expression of genes outside the 22qD region. The absence of these downstream proteins would be responsible for the pathophysiology of the disorder.

Several interesting genes are located within the 22qD region. One is the gene encoding for catechol-*O*-methyltransferase (COMT), an enzyme that degrades dopamine. Several polymorphisms exist within the gene, and at least one of these is associated with lower biochemical activity of COMT. A study reported that all VCFS patients with rapid-cycling bipolar affective disorder had the low-activity COMT allele in the nondeleted chromosome. However, subsequent studies found no association between the COMT alleles and schizophrenia with or without VCFS.

Because VCFS and schizophrenia share common neurodevelopmental abnormalities, it is possible that the VCFS deleted gene(s) play a role in the pathophysiology of these abnormalities in schizophrenia as well. Genes encoding for migratory factors that are expressed in the brain are strong candidates that could also explain the cytoarchitectural abnormalities in the brains of schizophrenic patients. There are several such genes in the 22qD region. These include the goosecoid-like (*GSCL*) gene which encodes for a homeobox protein; *ARVCF,* which is involved in the formation of adherens junctions between cells; the clathrin heavy chain-like gene that recycles the presynaptic membrane of vesicles after release of neurotransmitters; and *UFD1L,* which is involved in the degradation of proteins. No point mutations, however, have yet been detected in any of these candidate genes.

Association studies are a popular technique for identifying genes that contribute to the expression of a number of psychiatric disorders. Most association studies have focused on genes involved in the dopaminergic and serotonergic systems. Although these systems are probably involved at some point in the pathophysiology of these disorders, it is not certain whether they play a role in their etiology. Candidate genes in VCFS also include ones involved in the early growth and development of the brain, such as genes that regulate the migration of neurons. This line of investigation may help us to understand the underlying molecular basis of VCFS and perhaps other developmental disorders.

WEB SITES OF INTEREST

http://www.vcfsef.org
http://www.geneclinics.org/profiles/22q11deletion/index.html

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