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Velo-cardio-facial syndrome

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Purpose of review

Velo-cardio-facial syndrome has emerged from obscurity to become one of the most researched disorders this past decade. It is one of the most common genetic syndromes in humans, the most common contiguous gene syndrome in humans, the most common syndrome of cleft palate, and the most common syndrome of conotruncal heart malformations. Velo-cardio-facial syndrome has an expansive phenotype, a factor reflected in the wide range of studies that cover both clinical features and molecular genetics. In this review, we cover multiple areas of research during the past year, including psychiatric disorders, neuroimaging, and the delineation of clinical features.

Recent findings

The identification of candidate genes for heart anomalies, mental illness, and other clinical phenotypes has been reported in the past year with a focus on *TBX1* for cardiac and craniofacial phenotypes and *COMT* and *PRODH* for psychiatric disorders. The expansive phenotype of velo-cardio-facial syndrome continues to grow with new behavioral and structural anomalies reported. Treatment issues are beginning to draw attention, although most authors continue to focus on diagnostic issues.

Summary

Its high population prevalence, estimated to be as common as 1:2000 has sparked a large amount of research, as has the model the syndrome serves for identifying the causes of mental illness and learning disabilities, but it is obvious that more information is needed. Intensive scrutiny of velo-cardio-facial syndrome will undoubtedly continue for many years to come with the hope that researchers will turn more of their attention to treatment and treatment outcomes.

Keywords

22q11 deletion, *COMT*, congenital heart disease, DiGeorge sequence, immune disorder, mental disorders, *TBX1*, VCFS (velo-cardio-facial syndrome)

Abbreviations

ADD	attention deficit disorder
ADHD	attention deficit hyperactivity disorder
CHD	congenital heart disease
FISH	fluorescent in-situ hybridization testing
OCD	obsessive-compulsive disorder
VCFS	velo-cardio-facial syndrome

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Introduction

Velo-cardio-facial syndrome (VCFS) has emerged from a relatively obscure multiple anomaly syndrome to one of the most researched and well-studied disorders over the past decade. Although initially delineated and named in 1978 [1], the same disorder was described earlier by many authors and initial documentation of the same disorder appears as early as 1955 [2,3]. Relatively few publications appeared before 1992 when two events sparked interest in the syndrome, the first being the discovery of a microdeletion from the long arm of chromosome 22 at the *q11.2* band [4–6] and the second being a report of a high frequency of mental illness as a clinical feature [7]. Since 1992, there have been many publications focusing on the genetics of the syndrome, the phenotypic spectrum, and studies of cognition and mental illness. What has become clear is that VCFS is the most common microdeletion syndrome in humans, the most common syndrome of cleft palate, and the most common syndrome associated with conotruncal heart anomalies. Learning disorders are nearly ubiquitous in the syndrome, and immune disorders, speech and language impairment, and behavioral abnormalities occur in most cases. Therefore, essentially every case with VCFS will present to pediatricians with multiple problems. The recent literature reflects much of this variability of clinical presentation, although there has been little emphasis on treatment. To date, there has been a major emphasis on phenotype to genotype correlations to isolate the direct causes of the various phenotypes in VCFS, and on the continuing expansion of the phenotype. The development of fluorescent in-situ hybridization testing (FISH) for the disorder in the mid-1990s has resulted in a large number of diagnoses worldwide that has sparked increased clinical and research investigations of the disorder. There have been at least 78 journal articles published during the period of this review (slightly more than a year) that directly discuss VCFS, although there are many more articles that indirectly mention aspects of the disorder or discuss VCFS within the context of similar disorders. We will focus on VCFS as the direct subject matter of current publications.

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Diagnostic issues

The name ‘velo-cardio-facial syndrome’ was added to the genetics lexicon in 1978 [1], but not all clinicians and researchers use this term to designate the disorder caused by a deletion at *22q11.2*. Alternative names for this disorder include DiGeorge syndrome or DiGeorge sequence, conotruncal anomalies face syndrome, Cayler syndrome, *22q11* deletion syndrome, and Sedlačková syndrome [8*,9]. Although many clinicians believe that it is possible to express VCFS in the absence of a detectable deletion of *22q11.2*, recent publications have suggested that so-called ‘nondeleted’ cases are actually clinical diagnostic errors rather than absent positive FISH findings. Although some publications have continued to perpetuate the notion that several different disorders are caused by the exact same deletion from chromosome 22 [10], it is now clear that the broad phenotype of VCFS manifests many possible expressions that overlap with other conditions [8*,9,11].

Phenotypic descriptions

Although VCFS has been extensively described for more than 25 years, new phenotypic descriptions continue to be published as larger numbers of subjects are examined by larger numbers of clinician scientists. Over the past year, the publications have focused primarily on behavioral and central nervous system phenotypes with smaller numbers of articles related to heart, immunologic, and otolaryngologic manifestations.

Behavioral and brain anomalies

VCFS displays a wide spectrum of developmental, neuropsychological, and psychiatric manifestations. The detection of these disorders may depend on the age and ascertainment of the samples of subjects studied. For example, although the average age of onset of psychosis in VCFS has been reported to be approximately 21 years of age, similar to that in the general population [12], studies reporting behavioral abnormalities in children have not reported longitudinal data to determine if early disorders such as attention deficit disorder (ADD)/attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) predict subsequent psychosis [13]. It has been suggested that the frequency of early onset psychosis in VCFS is not particularly high compared with the general population, although these data are far from conclusive [14].

Several investigators in previous years have hypothesized a relation between a polymorphism in the *COMT* gene that is located in the *22q11.2* critical region for VCFS and is always deleted in the syndrome. *COMT* degrades synaptic dopamines in the brain. Two polymorphisms in *COMT* have been reported; a low activity allele (*COMT158^{met}*) and a high activity allele (*COMT158^{val}*) [10] and the association of the most severe form of mental illness in adults with VCFS has been with the *COMT158^{met}* allele [15,16].

Although data to date that report the *COMT* genotype in psychotic adults with VCFS has uniformly shown such individuals to have a single copy of the *COMT158^{met}* allele, one report has suggested that the *COMT158^{val}* allele may result in more psychopathology, although the cases studied were younger children and psychosis was not diagnosed in the sample [13]. The same author found that presence of the *COMT158^{met}* allele in individuals with VCFS performed better on tests of executive functioning based on standardized neuropsychological testing [17]. Others have implicated additional genes in the deleted region as possible candidates for psychosis in addition to *COMT*, including *PRODH* [18,19] and *ARVCF* [20], which is adjacent to *COMT*, but to date, these hypotheses have not been confirmed and the major focus has remained on *COMT*. What is clear to investigators is that VCFS represents an important model for studying mental illness because a high percentage of affected individuals have psychiatric illness [21] leading to the conclusion that one or more genes in the deleted region must play an important role in the development of mental illness [22,23].

Studies of cognitive function using a variety of standardized instruments have been reported from a number of centers around the world, including the US, Israel, and Europe [24–31]. An important question that is just beginning to be addressed is the relation between cognitive impairments and mental illness [24], although most reports have been focused on developmental and learning disabilities [27,28,31] and attentional or behavioral characteristics such as ADD/ADHD and OCD [25,26,29,30]. Reports consistently show that attentional problems are the most common finding in children with VCFS, but that OCD and other behavioral disorders are also common, including generalized anxiety, phobias, and mood disorders.

A number of other studies have taken this process one-step further by combining standardized neuropsychological testing with sophisticated quantitative and/or functional imaging of the brain [32–35,36**]. In the reports studying brain anatomy and function a wide variety of areas are implicated in the behavioral and cognitive problems associated with VCFS including frontal deep white matter [32], the caudate nucleus [32], the prefrontal cortex [32,33], increased sulcal cerebrospinal fluid in the temporal and posterior brain [34], the cingulate gyrus [35], and total brain volume [32–34,36**]. One report notes a more significant decrease in brain volume and cognitive performance in subjects with VCFS who have schizophrenia versus those who do not [36**]. Other researchers have found abnormalities of the corpus callosum [37,38], polymicrogyria [39], and pachygyria [40] based on neuroimaging studies. Two quantitative magnetic resonance imaging studies found increased size of the corpus callosum, one in a small sample of 13 subjects and 13 controls [37], and a

second in a large sample of 60 VCFS subjects matched to 52 age- and gender-matched control subjects [38]. Across all measures, children with VCFS demonstrated a larger corpus callosum area, although VCFS with ADHD had smaller corpus callosum than children with VCFS without ADHD did (although still larger than controls). It was concluded that corpus callosum anomalies could be of importance in determining brain-behavior relations in VCFS. Also noted, as in previous reports, is a very high frequency of cavum septum pellucidum, a finding also common in individuals with schizophrenia [37]. Clearly, brain anomalies also cover a wide spectrum, as do other physical anomalies in VCFS.

Heart anomalies

Early in the syndromic delineation of VCFS, publications documenting heart anomalies constituted a larger percentage of the total literature. Today, VCFS is one of the most frequently recognized syndromes associated with congenital heart disease (CHD) and in most centers all babies with tetralogy of Fallot, interrupted aortic arch type B, truncus arteriosus, and other structural heart anomalies combined with right-sided aortic arch are screened for VCFS with FISH. In short, there are fewer surprises and discoveries related to VCFS in relation to CHD. However, small numbers of publications continue to appear. Some of these articles are reports of single cases or series of cases describing clinical findings [41–43]. More interesting is a report of how the diagnosis of VCFS affects heart surgery outcomes [44]. Comparing infants with VCFS and CHD to those with Down syndrome, other genetic syndromes, and nonsyndromic cases of CHD, the highest mortality rate was seen in children with VCFS. Heart anomalies have also played a role in prenatal diagnosis [45]. The increased application of high-level ultrasonic examinations of the fetus will undoubtedly increase the number of prenatal detections of VCFS, necessitating obstetricians to know the phenotypic spectrum of VCFS so that FISH can be applied when appropriate.

Immune disorders

Immune deficiency is not among the most common anomalies in VCFS, but the problem is one of the most difficult to contend with for affected individuals and their families. Reports on immunologic and associated endocrine disorders have covered the age spectrum, from the neonatal period to adult life. A series of five infant cases with rash, lymphadenopathy, and T cell abnormalities were described, including two who died [46]. The patients developed the rash, lymphadenopathy, and oligoclonal T cells in a stochastic fashion. All patients had oligoclonal expansions in more than 50% of T-cell receptor B variable (TCRBV) families. The implication for proper management of such cases was stressed in relation to making the primary diagnosis, especially because two of the children did not have CHD.

At the other end of the age spectrum is a report of a 32-year-old man with hypoparathyroidism who was not diagnosed until that age [47]. He had many of the clinical features of VCFS, but of interest, his hypocalcemia and hypoparathyroidism were not evident until after puberty. Late detections of this type raise interesting questions about the prevalence of VCFS in the general population, as well as the natural history of the disorder. Another study of immune response in VCFS including adult subjects suggested that T cell counts in adults with VCFS are often robust even in the presence of earlier deficiencies [48]. It was hypothesized that reduced thymic production can result in compensation by peripheral proliferation [48]. This observation is consistent with the clinical observation of a generally improving immune response in individuals with VCFS over time.

The issue of live viral vaccines in VCFS is one that is often asked by parents of children with VCFS. Two recent publications have addressed this issue [49,50]. In a study of 14 children with 'DiGeorge syndrome' who were given the measles, mumps, and rubella (MMR) vaccine, no adverse reactions were noted and there was a positive antibody response to the vaccines in the subjects [49]. The study did not report if the subjects were FISH positive for *22q11.2* deletion, but 12 of the 14 cases were said to have typical craniofacial findings and developmental delay. An editorial [50] strikes a somewhat more cautious note on the administration of live viral vaccines suggesting that there are immunodeficient cases of 'DiGeorge' that might be at risk.

Cutting-edge treatments for immunodeficiency have also been addressed recently [51,52]. Thymic transplant was reported in six cases [51], one with *22q11.2* deletion and another apparently clinically diagnosed with VCFS, but reported to be negative by FISH testing for the deletion. Therefore, only one of the subjects actually had VCFS. The one patient with the deletion did not have CHD. Although one of the cases subsequently died, the patient with the deletion survived and was nearly 3 years post transplant at the time of publication. Immune function was improved, but there is obviously no control data to determine if values would have been different without the transplant. In another report, a single case of 'DiGeorge syndrome' was treated for cytomegalovirus infection using cord stem cell transplantation with dramatic improvement. The report did not mention if the patient had *22q11* deletion.

Other phenotypic findings

A number of other reports have documented a series of anomalies in reports of single or multiple cases. Esophageal atresia and tracheoesophageal fistula [53], single central incisor [54], Brown syndrome [55], ocular anomalies [55–57], Graves disease [58,59], seizures [60], bronchomalacia [61], and vascular anomalies of the neck [62] were

all described although most of these findings are not new [52,55–62]. The presence of a single central incisor is of interest because of previous associations of VCFS with holoprosencephaly and the presence of esophageal atresia or tracheoesophageal fistula points out the phenotypic overlap of VCFS with other conditions such as VATER, VACTERL, and Opitz syndrome.

Population studies

The incidence and prevalence of VCFS have been cited in many studies, ranging from 1:2000 [8*] to 1:6000 [23]. The reasons for these discrepancies may be related to methods of ascertainment, but are also probably affected by the ability to recognize the syndrome. Because the major entry point to diagnosis is CHD and at least 25% of individuals with VCFS do not have heart anomalies, many estimates are probably artificially low. In a population study based in Western Götaland, Sweden [63], a population prevalence of 13.2 per 100 000 (or 1:7575) was calculated based on all cases under 16 years of age diagnosed with VCFS by FISH compared with the total number of births in the region below the same age. However, the study did not account for the possibility that many cases were not recognized and referred for FISH, thus undoubtedly resulting in underdetection. All referrals for the FISH studies came from tertiary specialists, such as cardiologists, pediatric neurologists, child psychiatrists, immunologists, audiologists, and speech pathologists. It is notable that geneticists were not among the referral sources.

In Israel, a cohort of 634 individuals with schizophrenia was screened for *22q11.2* deletions [64]. Positive findings for the deletion were found for 1% of the sample (six cases). The authors note that this frequency is at least 40 times higher than the frequency of the syndrome in the general population, thus confirming the increased risk of mental illness in VCFS. In a similar study among Afrikaners in South Africa, a 2% frequency of VCFS was found among a sample of 85 schizophrenics [65].

In their screening of a sample of cases with conotruncal heart anomalies in Germany [66], investigators searched for somatic mutations among individuals with VCFS and those without, obtaining heart tissues and thymus for analysis. It is noted that of 23 patients with conotruncal anomalies who were having surgery, nine had VCFS.

Following a different tact, a sample of patients from Athens, Greece was screened with FISH if they had phenotypes the investigators considered consistent with VCFS [67]. Seventeen of 139 patients were positive for the deletion (12.2%). These data suggest a lack of familiarity with the overall ‘gestalt’ of the VCFS phenotype.

In a more limited sample, but a more genetically homogeneous one, investigators performed a careful phenotypic

analysis of 17 individuals from two large kindreds [68]. They found that only 46% of the affected individuals had CHD. There are several ways these data may be interpreted. Perhaps both families had epigenetic factors that predisposed them from developing CHD. Conversely, it may be that this pure ascertainment from related individuals may actually represent a truer picture of the frequency of CHD. Diagnosis in all family members was more easily made and therefore milder cases did not escape detection.

Genomics

The large majority of individuals with VCFS have a deletion of three million base pairs containing dozens of genes. The challenge has been to determine how much of the extensive phenotype can be traced back to one or more of these genes. Many investigators now believe that deletion of the gene *TBX1* is responsible for the cardiac and vascular findings and perhaps other anomalies traced to the neural crest [69–72]. Other genes have also been implicated in the anomalies found in VCFS, including *DGCR8* [73] and *HIRA* [74]. It has also been reported that a regulatory effect that accounts for malformations in VCFS is the inactivation of TGF β signaling in the neural crest stem cells [75]. The mechanism of spontaneous rearrangements at *22q11.2*, originally described several years ago, was confirmed in another study demonstrating a recombination error in stage 1 of meiosis [76]. The unique arrangement of *22q11.2* that makes it a hot spot for rearrangement has been traced as an evolutionary change in the structure of human DNA as described in a 2003 study by Babcock and colleagues from the Albert Einstein College of Medicine. The ‘hot’ nature of the region is further illustrated by a report of first cousins who both had de-novo deletions at *22q11.2* [77].

The question of phenotypic expression in relation to the size of the deletion was also raised in a report analyzing deletion size in familial cases [78]. Analysis of 10 families with more than one generation of individuals with VCFS showed that 70% had the smaller 1.5 Mb deletion, whereas the large majority of individuals with VCFS (approximately 90%) have the more common 3 Mb deletion. The potential for milder effect resulting in increased likelihood of reproduction is raised by these data, even with the small sample size of the study.

Miscellaneous studies

With the major focus on the genetics of VCFS, other factors that might contribute to the outcome of child development and temperament were explored within a family context [79]. Improved emotional stability and reduced irritability in children with VCFS was seen when parents showed warmth rather than anger towards their children. Although the root causes of personality traits in children are complex, this report may help to turn an appropriate

focus on family dynamics, especially when one child has a significant developmental disorder.

In a survey of pediatricians and teachers in Northern and Central California, researchers found that knowledge and recognition of VCFS among the sample was poorer than that for fragile X and Down syndrome [80^{*}]. Because both teachers and pediatricians make important decisions about the management of children with VCFS, this study points out the need for additional access to information for these individuals.

Conclusion

VCFS is a common genetic disorder that is seen in all aspects of pediatric practice from general primary care to tertiary specialties. Its high population prevalence, estimated to be as common as 1:2000 has sparked a large amount of research, as has the model the syndrome serves for identifying the causes of mental illness and learning disabilities, but it is obvious that more information is needed [80^{*}]. Intensive scrutiny of VCFS will undoubtedly continue for many years to come with the hope that researchers will turn more of their attention to treatment and treatment outcomes.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 801).

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- This survey study is of critical importance because it points out where we need to do a better job if we are to improve the lot of people with VCFS. Organizations like The Velo-Cardio-Facial Syndrome Educational Foundation should take note and some degree of satisfaction in reading the article because it reinforces their goal of public and professional education.