

Genetic Testing for Velocardiofacial Syndrome / DiGeorge Syndrome: FISH for the Common 22q11.2 Deletion TBX1 Sequence Analysis

Disorder also known as: Velocardiofacial syndrome (VCFS), DiGeorge syndrome (DGS)

Clinical Features:

Velocardiofacial syndrome (VCFS) and DiGeorge syndrome (DGS) are well-characterized syndromes with multi-system involvement, dysmorphic facial features, and cognitive disabilities. A range of systemic findings may include congenital heart defects, which are present in 75% of individuals¹ (conotruncal malformations, interrupted aortic arch, ventricular/atrial septal defects and teratology of fallot), palatal defects seen in 69% of individuals (velopharyngeal incompetence (VPI), submucosal cleft palate and cleft palate), and immune deficiencies secondary to thymic hypoplasia seen in up to 77% of individuals.² Typical facial features include a long face, small almond shaped eyes, a wide bridged nose, and malformations of the ear. Learning disabilities, including delayed speech and developmental milestones, are present in 70-90% of individuals.³ Additional findings may include hypocalcemia (most severe during the neonatal period), feeding problems, psychiatric illness, seizures, renal abnormalities, short stature, hypotonia, scoliosis, and tapered fingers. Atypical features include autoimmune diseases (thrombocytopenia, juvenile rheumatoid arthritis, and vitiligo), hearing loss, and growth hormone deficiencies.

Inheritance Pattern/Genetics:

Autosomal Dominant

Test Methods:

Ninety five percent of patients with VCFS/DGS have a defined 1.5-3Mb deletion in the 22q11.2 region including TBX1 and 24-30 additional genes, and most can be detected by FISH analysis. GeneDx offers FISH analysis with the TUPLE probe. Alternatively, whole genome array CGH (GenomeDx) analysis is available (see the GenomeDx information sheet for additional details: http://www.genedx.com/site/cytogenetic_testing). Both of these tests are reliable and sensitive assays for detecting a VCFS/DGS deletion.⁸

For those VCFS/DGS patients without the classic deletion, GeneDx performs bi-directional sequence analysis of the coding region and splice sites of the TBX1 gene (exons 1-9). If a sequence change is identified, it is confirmed with a second analysis using sequencing, heteroduplex or restriction fragment analysis or another appropriate method. In appropriate cases, if TBX1 sequencing is negative and FISH testing using the TUPLE1 (HIRA) probe is

negative, GenomeDx whole genome array CGH is also available to detect atypical deletions and duplications in the 22q11.2 region.

Test Sensitivity:

Although reports of TBX1 variants are rare, multiple variants in the gene have been published in two studies.^{4,5} In one study, TBX1 variants were identified by sequencing in 3 of 13 patients with clinical features of VCFS/DGS who did not have the common 22q11.2 deletion⁴. Another publication included 38 non-deleted patients with clinical features of 22q11.2 deletion syndrome, two of whom had a variant identified in the TBX1 gene.⁵ Two additional familial variants were reported in single case studies.^{6,7}

References:

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