Prenatal FISH Analysis in 22q11.2 Deletion Syndrome (DiGeorge Syndrome; Velocardiofacial Syndrome)

Clinical Features:
22q11.2 deletion syndrome has a prevalence of about one in 1/2000–3000 in the general population. It is a well-characterized syndrome with variable multisystem involvement, dysmorphic facial features, and cognitive disabilities. Findings include congenital heart defects, which are present in 75% of individuals[1] (conotruncal malformations, including tetralogy of fallot, interrupted aortic arch, and ventricular/atrial septal defects), palatal defects (~69%) (velopharyngeal incompetence), submucosal cleft palate and cleft palate), and immune deficiencies secondary to thymic hypoplasia (up to 77%). Typical facial features include a long face, small almond shaped eyes, small lower set 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[2]. 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.

The presence of one or more of the following prenatal ultrasound findings may be indicative of 22q11.2 deletion syndrome: cardiac anomalies (see above), cleft palate, polyhydramnios, renal, or skeletal anomalies (pre- and postaxial polydactyly) and absence of the thymic shadow.

Inheritance Pattern/Genetics:
Autosomal Dominant, most cases de novo.

The majority (greater than 95%) of patients with 22q11.2 Deletion Syndrome have a genomic microdeletion (of approximately 1.5-3 Mb) on chromosome band 22q11.2, typically detected by fluorescence in situ hybridization (FISH) using the TUPLE1 (HIRA) probe. The remaining patients (less than 5%) have a smaller, atypical 22q11.2 deletion (not detectable by TUPLE1 FISH), a chromosomal rearrangement involving 22q11.2, or variants in the TBX1 gene.

Test Methods:
FISH analysis is based on the hybridization of a fluorescently labeled probe to metaphase spreads and interphase nuclei prepared from cell cultures derived from amniotic fluid, chorionic villus sample, or products of conception (POC). FISH probes have a specific sequence that is complementary to a particular region of the genome. The presence, absence, amplification, or translocation of the targeted region is analyzed with a fluorescent microscope. GeneDx offers FISH analysis with the TUPLE probe for detecting a VCFS/DGS deletion.

Test Sensitivity:

Greater than 95% of patients with Deletion Syndrome have a defined 1.5-3Mb deletion in the 22q11.2 region including TBX1 and 24-30 genes, and most can be detected by FISH analysis.

References:

1. McDonald-McGinn, D. et al. (2001) Genet Med. 3(1): 23-29
2. Solot, C. et al. (2000) J Commun Disord. 33:187-204.