OFD1 (Cxorf5) Gene Analysis in Oral-Facial-Digital Syndrome Type 1

Clinical Features:

At least nine distinct forms of Oral-Facial-Digital syndromes have been described. The X-linked dominant Oral- Facial-Digital syndrome type 1 (OFD1) is the most common and has an estimated prevalence of 1/50,000 – 1/250,000. OFD1 is characterized by malformations of the oral cavity, face and digits in heterozygous females and lethality in hemizygous (46, XY) males. The only affected male reported to survive after birth had Klinefelter syndrome (47, XXY). Approximately 75% of females with OFD1 have no family history. Oral abnormalities include: clefting of the hard or soft palate, median or pseudocleft of the upper lip, tongue hamartomas or lipomas, tongue clefts, hypodontia and other dental abnormalities. Facial dysmorphic features include: hypertelorism, frontal bossing, broad nasal bridge, micrognathia, facial milia and hypoplasia of the alae nasi. Digital abnormalities affect the hands more often than the feet and include: brachydactyly, syndactyly, fifth-finger clinodactyly, pre- and postaxial polydactyly. Adult-onset polycystic kidney disease (PKD) leading to renal failure is a distinct feature of OFD type 1, and can often be the presenting feature in females with a mild phenotype. Central nervous system involvement includes brain malformations such as agenesis of the corpus callosum, hydrocephaly, porencephaly, cerebellar abnormalities and intracerebral cysts. Additionally, individuals with OFD1 have varying degrees of mental retardation.

Inheritance Pattern/Genetics:

X-Linked dominant, with lethality in 46,XY males

Test Methods:

Bi-directional sequence analysis of the OFD1 gene is offered in two tiers, as evidence suggests a higher frequency of variants in select exons. Tier 1 includes sequencing of exons 3, 8-9, 13 and 16, and is expected to identify the majority of OFD1 variants. Tier 2 analysis encompasses the remaining exons of the OFD1 gene. In females who test negative for a variant by sequencing, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion/duplication of one or more exons of this gene. Any variant is confirmed by repeat analysis using sequencing, restriction fragment analysis, qPCR or another appropriate method.

Test Sensitivity:

DNA sequencing is estimated to identify a pathogenic OFD1 variant, the only known gene associated with Oral-Facial-Digital syndrome type 1, in approximately 50-80% of patients with this diagnosis.[1-3] In a study of 25 individuals from 16 families with classical OFD type 1, Thauvin-Robinet et al. (2006) showed that 67% had small intragenic variants that would be

detectable by sequencing methods.[2] In a more recent study, 26 of 131 (20%) patients were negative for OFD1 gene sequencing. Of these 26 patients, 6 (23%) individuals were found to harbor a partial gene deletion of OFD1, accounting for 5% of OFD type 1 patients.[3] The sequencing approach used by GeneDx will identify >99% of existing small, intragenic variants in the OFD1 gene. Array CGH analysis (ExonArrayDx) is expected to detect a complete OFD1 gene deletion, as well as most partial gene deletions that involve one or more exons.

All types of variants have been identified, including frameshift, nonsense, missense, and splice site variants. The majority of variants (42-65.5%) are within exons 3, 8, 9, 13, and 16 of the OFD1 gene.[2,5] Most of the variants lead to premature protein truncation and therefore are predicted to result in a loss of function mechanism.[4] Additionally, heterozygous deletions of the OFD1 have been described, including six partial deletions (exon 5, exons 1-8, exons 1-14, exons 10-11, exons 13-23, and exon 17).[3] One study examined possible genotype-phenotype correlations and found that renal cysts are more commonly seen in patients with slice site variants, mental retardation was observed more frequently in patients with variants in exons 3, 8, 9, 13 and 16, and dental abnormalities were associated more often with variants in the coiled-coil domains of OFD1.[2]

References:

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