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OFD1 testing

Clinical Features:

Oral-facial-digital syndrome, type 1

Patients with oral-facial-digital syndrome, type 1 (OFD1) [OMIM #311200] have oral (lobed tongue, cleft palate, hamartomas or lipomas of tongue or dental abnormalities), facial (cleft lip, hypertelorism, telecanthus, hypoplastic alae nasi, or micrognathia) and digital (brachydactyly, syndactyly, radial/ulnar deviation or polydactyly) abnormalities. As many as 40% of individuals have structural brain abnormalities including agenesis of the corpus callosum and Dandy-Walker malformation. Approximately 50% of individuals have mental retardation, usually mild. Less than 50% of individuals have polycystic kidney disease (1).

Simpson-Golabi-Behmel syndrome, type 2

Two families have been described with a severe form of Simpson-Golabi-Behmel syndrome (SGBS2) [OMIM #300209]. Males in these families have renal cysts, dysmorphic features, macrocephaly, developmental delay and respiratory problems. Most males died very early in life. Females appear unaffected (2, 3).

X-linked Joubert syndrome

Patients with Joubert syndrome (JS) [OMIM #300804] have a specific hindbrain formation described on brain MRI as the “molar tooth sign”. Other features of the classic form of this condition include hypotonia, cerebellar ataxia, dysregulated breathing patterns, and developmental delay. Retinal, renal, or liver abnormalities, colobomas and orofacial or digital signs have been described in patients within the JS spectrum (4).

OFD1 testing is reasonable for:

- females with adult-onset polycystic kidney disease without evidence of involvement of male relatives
- females with at least 2 of the following: lingual anomalies, facial milia, oral frenula, brain malformations
- males with macrocephaly, delays, severe respiratory problems, and family history consistent with XL inheritance
- males with molar tooth sign and family history consistent with XL inheritance

Molecular Genetics:

Mutations of the *OFD1* [OMIM #300170] gene have been identified in patients with OFD1 (5), SGBS2 (2), and XLJS (4).

- Prattichizzo, et al. (2008) detected *OFD1* mutations in 81 of 100 (81%) patients with characteristic facial features of OFD1 (6). Recently, intragenic deletions of one or more exons of *OFD1* have been reported in approximately 5% of patients with a clinical diagnosis of OFD1 (7).
- Budny, et al. (2006) described one family with SGBS2 males and unaffected females with a truncating mutation in *OFD1 (2)*. Another family with SGBS2 was mapped to the region surrounding *OFD1 (8)*.
- Coene, et al. (2009) described one family and an isolated male with JS and two different truncating mutations in *OFD1 (4)*.

OFD1 has 23 coding exons. Nonsense, missense, frameshift and splicing mutations have been identified in the *OFD1* gene. There are no clear genotype-phenotype correlations to date with regards to *OFD1* mutations and the three different disorders.

Inheritance and Prevalence:

OFD1 mutations are inherited in an X-linked pattern. Recurrence risk for offspring of affected individuals is 50%. OFD1 occurs in 1 in 50,000 live births, and most affected individuals are female. Males have been described, though most are abnormal fetuses delivered by females with OFD1. Approximately 75% of cases have no family history of the condition [1]. Both SGBS2 and XLJS have been described in only a couple families. Males appear to be primarily affected in these conditions and females appear to be unaffected carriers.

Additional Resources:

AboutFace International
Phone: 800-665-FACE
Email: info@aboutfaceinternational.org
www.aboutfaceinternational.org

Test methods:

We offer mutation analysis of all coding exons and intron/exon boundaries of *OFD1* by direct sequencing of amplification products in both the forward and reverse directions. We also offer oligonucleotide array-CGH analysis to identify deletions/duplications involving the coding region of the *OFD1* gene. Deletions/duplications of less than 2 kb may not be detected by this methodology. Array-CGH will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Patients with negative results or variants of unknown significance can enroll in Dr. Brunella Franco's research study at the Telethon Institute of Genetics and Medicine in Italy. Please contact Dr. Franco (franco@tigem.it) to obtain more information about participation, if desired.

Please, send a completed Oral-Facial-Digital Syndrome, Type 1 Clinical Checklist and patient consent form with each sample.

OFD1 sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1700
CPT codes:	81406
Turn-around time:	4-6 weeks

OFD1 deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405
Turn-around time:	4 weeks

Testing for a known mutation in additional family members by sequence analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$390
CPT codes:	81403
Turn-around time:	3-4 weeks

Prenatal testing for a known mutation by sequence analysis

Sample specifications:	2 T25 flasks of cultured cells from amniocentesis or CVS or 10 mL of amniotic fluid
Cost:	$540
CPT codes:	81403
Turn-around time:	1-2 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

References:

1. Toriello H, Franco B. Oral-Facial-Digital Syndrome Type 1. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 2002.
2. Budny B, Chen W, Omran H et al. A novel X-linked recessive mental retardation syndrome comprising macrocephaly and ciliary dysfunction is allelic to oral-facial-digital type I syndrome. Hum Genet 2006: 120: 171-178.
3. Terespolsky D, Farrell SA, Siegel-Bartelt J et al. Infantile lethal variant of Simpson-Golabi-Behmel syndrome associated with hydrops fetalis. Am J Med Genet 1995: 59: 329-333.
4. Coene KL, Roepman R, Doherty D et al. OFD1 is mutated in X-linked Joubert syndrome and interacts with LCA5-encoded lebercilin. Am J Hum Genet 2009: 85: 465-481.
5. Ferrante MI, Giorgio G, Feather SA et al. Identification of the gene for oral-facial-digital type I syndrome. Am J Hum Genet 2001: 68: 569-576.

6. Prattichizzo C, Macca M, Novelli V et al. Mutational spectrum of the oral-facial-digital type I syndrome: a study on a large collection of patients. Hum Mutat 2008: 29: 1237-1246.
7. Thauvin-Robinet C, Franco B, Saugier-Veber P et al. Genomic deletions of OFD1 account for 23% of oral-facial-digital type 1 syndrome after negative DNA sequencing. Hum Mutat 2009: 30: E320-329.
8. Brzustowicz LM, Farrell S, Khan MB et al. Mapping of a new SGBS locus to chromosome Xp22 in a family with a severe form of Simpson-Golabi-Behmel syndrome. Am J Hum Genet 1999: 65: 779-783.