THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

# OFD Syndrome Testing: Mutation analysis of *OFD1*

## 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).

**Mutations of the *OFD1* gene have also been identified in patients with Simpson-Golabi-Behmel syndrome and X-linked Joubert syndrome.**

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:

Comprehensive sequence coverage of the coding regions and splice junctions of the *OFD1* gene is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

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

*OFD1* sequencing and deletion/duplication analysis

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| Sample specifications: | 3 to10 cc of blood in a purple top (EDTA) tube |
| Cost: | $1000 |
| CPT codes: | 81405, 81406 |
| Turn-around time: | 4 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.

***For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.***

## 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.


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