Oral-Facial-Digital Syndrome: *OFD1* Gene Sequencing

**Condition Description**

Mutations in the *OFD1* gene (Xp22.3-p22.2) can result in one of three X-linked conditions: orofaciiodigital syndrome 1, Simpson-Golabi-Beheem syndrome type 2 or Joubert syndrome 10.

**Orofaciodigital Syndrome Type 1**

Orofaciodigital syndrome type 1 (OFD1) is characterized by malformations of the face, oral cavity, and digits. Additional characteristics include thickened alveolar ridges and abnormal dentition. In up to 40% of cases, the central nervous system may be involved. About half of individuals with OFD1 will have some degree of intellectual disability, which is usually mild. Clinical features may overlap those reported in other forms of orofaciiodigital syndrome, but type 1 can be distinguished by the X-linked inheritance pattern and polycystic kidney disease. It is lethal in males. 80% of mutations can be detected through sequence analysis and 5% of mutations can be found through deletion/duplication analysis. 75% of cases occur *de novo*.

**Simpson-Golabi-Beheem Syndrome Type 2**

Mutations in the *OFD1* gene have been reported in families with Simpson-Golabi-Beheem syndrome type 2. The liveborn males were hydropic at birth and had a combination of craniofacial anomalies that included macrocephaly, low-set posteriorly angulated ears, hypertelorism, short, broad nose with antverted nares, large mouth with a thin vermilion upper border, prominent philtrum, and high-arched or cleft palate. Other features included short neck, redundant skin, hypoplastic nails, skeletal defects, gastrointestinal and genitourinary anomalies and neurological impairment.

**Joubert Syndrome 10**

Joubert syndrome is characterized by a specific hindbrain formation, hypotonia, cerebellar ataxia, dysregulated breathing patterns, and developmental delay. Mutations in multiple genes can cause Joubert syndrome; X-linked Joubert syndrome is caused by mutations in the *OFD1* gene. Other features of Joubert syndrome 10 include recurrent infections, postaxial polydactyly and juvenile-onset retinitis pigmentosa. Obligate female carriers are unaffected.

For patients with suspected Oral-Facial-Digital syndrome, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

**References:**

- OMIM #311200: Orofaciodigital Syndrome I.
- OMIM #300170: Chromosome X Open Reading Frame 5.
- GeneReviews

**Genes**

*OFD1*

**Indications**

This test is indicated for:

- Carrier testing in adults with a family history of Oral-Facial-Digital syndrome.

**Methodology**

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Detection**

Next Generation Sequencing: Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory
element mutations cannot be detected by this analysis. Large deletions/duplications will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype. Analytical Sensitivity: ~99%.

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Deletion/duplication analysis of the **OFD1** gene by CGH array is available for those individuals in whom sequence analysis is negative.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.