

Oral-Facial-Digital Syndrome Type 1, Simpson-Golabi-Behmel Syndrome Type 2 and X-Linked Recessive Joubert Syndrome-10 via *OFDI* Gene Sequencing (Test #296)

Brief Description of Clinical Features: Oral-Facial-Digital syndrome type 1 (OFD1; OMIM 311200) is a developmental disorder with variable expressivity characterized by oral anomalies (lobed tongue, cleft palate, gingival frenulae, dental abnormalities); facial anomalies (ocular hypertelorism, hypoplasia of the alae nasi, upper lip median cleft, micrognathia); digital anomalies (brachydactyly, syndactyly, clinodactyly; preaxial or postaxial polydactyly, duplicated hallux); brain anomalies (intracerebral cysts, corpus callosum agenesis, cerebellar agenesis with or without Dandy-Walker malformation) and polycystic kidneys. In addition, about 50% of patients diagnosed with OFD1 have learning disabilities (Gorlin and Psaume. *J Pediatr* 61: 520–530, 1962; Feather et al. *Hum Mol Genet* 6:1163-1167, 1997; Ferrante et al. *Am J Hum Genet* 68:569-576, 2001). OFD1 is embryonic male-lethal X-linked dominant condition caused by mutations in the *OFDI* gene (Feather et al. 1997; Ferrante et al. 2001).

Simpson-Golabi-Behmel syndrome type 2 (SGBS2; OMIM 300209) and Joubert syndrome-10 (JBTS10; OMIM 300804) are both X-linked recessive conditions caused by mutations in the *OFDI* gene (Budny et al. *Hum Genet* 120:171-178, 2006; Coene et al. *Am J Hum Genet* 85:465-481, 2009). SGBS2 is characterized by facial anomalies (macrocephaly, high-arched palate, low-set ears); digital anomalies (broad thumbs, short fingers); developmental delay, and respiratory problems. All SGBS2 reported patients were males who died at an early age (Budny et al. 2006). X-linked recessive Joubert syndrome-10 is characterized by a specific cerebellar and brainstem malformation known as the “molar tooth sign”, hypotonia, cerebral ataxia, postaxial polydactyly, retinitis pigmentosa, and developmental delay accompanied by mental retardation (Coene et al. 2009).

Genetics: *OFDI* encodes oral-facial-digital syndrome 1 protein (OFD1) which is localized to centrosomes and basal bodies of ciliated cells suggesting a role in cilia motility and function (Ferrante et al. *Hum Molec Genet* 18:289-303, 2009; Coene et al. 2009). A mix of missense, nonsense, frameshift and splicing mutations as well as gross deletions have been reported in *OFDI* (Ferrante et al. 2001; Rakkolainen et al. *J Med Genet* 39:292-296, 2002; Morisawa et al. *Hum Genet* 115: 97-103, 2004; Budny et al. 2006; Coene et al. 2009). Severity of the phenotype correlates with the reduction in protein length (Thauvin-Robinet et al. *J Med Genet* 43:54-61, 2006). Coene et al. predicted that all mutations before residue 631 are lethal for males and cause OFD I syndrome in females, while males with JBS10 who may live beyond the age of 30 years have mutations located in the coiled-coil domain nearest to the C terminus (Coene et al. 2009).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all the 23 coding exons (exon 1-23) of the *OFDI* gene plus ~50 bp of flanking non-coding DNA on each side. As indicated, we will also perform sequencing of any single exon (test #100) for family members of patients with known mutations and to confirm previous research results (\$190 charge).

Reference Sequences: Genomic: **NC_000023.10** mRNA: **NM_003611.2** Protein: **NP_003602.1 (CCDS 14157.1)**

Indications for Test: Candidates for this test are patients with symptoms consistent with X-linked OFD1, SGBS2 and X-linked recessive Joubert syndrome-10 and family members of patients who have known *OFDI* mutations.

Sensitivity of Test: DNA sequencing analysis detects up to ~80% of *OFDI* mutations (Prattichizzo et al. *Hum Mutat* 29:1237-1246, 2008), while gross genomic deletions account the remaining ~20% (Thauvin-Robinet et al. *Hum Mutat* 30:E320-329, 2009).

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Prices:	Sequencing of the <i>OFDI</i> gene	\$1,320
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x27	83898 \$ 420	Sequencing x27 83904 \$ 640
Separation x1	83894 \$ 70	Interpretation/Report x1 83912 \$ 120

Accreditation: CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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