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).

• Pratichizzo, 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.
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. Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. 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.

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 to 10 cc of blood in a purple top (EDTA) tube
- Cost: $1000
- CPT codes: 81406
- Turn-around time: 4 weeks

**OFD1 deletion/duplication analysis**
- Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
- Cost: $1000
- CPT codes: 81405
- 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:**