**FLNA-related Disorders: FLNA Gene Sequencing**

**Test Code:** SFLNA  
**Turnaround time:** 6 weeks  
**CPT Codes:** 81479 x1

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### Condition Description

Intellectual disability (ID) is a nonprogressive cognitive impairment affecting 1-3% of the Western population. It is estimated that up to 50% of moderate-severe cases have genetic causes and approximately 10% are due to X-linked intellectual disability disorders (XLID). XLID can be syndromic or nonsyndromic and is observed in all ethnic groups. More than 100 XLID syndromes have been described in the literature to date. Fragile X is the most common XLID syndrome (~1 in 4000 males) while others can be quite rare with only a few patients reported in the literature. Males can have moderate to severe intellectual disability depending on the syndrome, and carrier females can also be affected, but typically have milder clinical symptoms.

**Periventricular Nodular Heterotopia**

Mutations in the *FLNA* gene (Xq28) can cause X-Linked Periventricular Nodular Heterotopia (PVNH), a neurologic disorder. It is characterized by seizures and the appearance of nodules lining the margins of the lateral cerebral ventricles. These nodules are formed as a failure in neuronal migration into the cerebral cortex. Volume is normal in the neocortex of affected individuals even though proper migration fails in a subpopulation of neurons. Extraneural features include cardiac valvular anomalies, predisposition to premature stroke, small joint hyperextensibility, gut dysmotility, and persistent ductus arteriosus. PVNH is most often seen in females; however, mutations have been identified in some males.

**Otopalatalodigital Spectrum Disorders**

The Otopalatalodigital Spectrum Disorders include otopalatalodigital syndrome type I (OPD1), otopalatalodigital syndrome type II (OPD2), frontometaphyseal dysplasia (FMD), and Melnick-Needles syndrome (MNS). All are characterized by skeletal dysplasia. Affected males can range from mild manifestations in OPD1 to more severe phenotypes in FMD and OPD2. MNS is prenatally lethal in males. Affected females can have variable expressivity.

Males with OPD1 have skeletal dysplasia (digital anomalies, limitation of joint movement, mild bowing of the limbs); characteristic facial features, deafness, cleft palate, and oligohyodontia. They have normal intelligence. Females with OPD1 can be similarly affected to males with OPD1. Males with OPD2 have skeletal dysplasia (thoracic hypoplasia, limb bowing, digital anomalies, and delayed closure of the fontanel); characteristic facial features that are more pronounced; cardiac defects; genitourinary defects; central nervous system anomalies; and developmental delay. Females with OPD2 usually have a subclinical phenotype. Males with FMD present with skeletal dysplasia (distal phalangeal hypoplasia, progressive contractures of the hand, joint limitation, scoliosis, and limb bowing); characteristic facial features; oligohyodontia; hearing loss; underdevelopment of the musculature; extraskeletal anomalies; and cleft palate. They are of normal intelligence. Females with FMD can present similarly to the males with FMD. Females with MNS present with skeletal dysplasia (short stature, thoracic hypoplasia, limb bowing, joint subluxation, and scoliosis); characteristic facial features; hearing loss; and hydronephrosis. They are of normal intelligence.

Mutations in the *FLNA* gene cause the four Otopalatalodigital Spectrum Disorders.

*FLNA* encodes filamin A, a binding protein that regulates reorganization of the actin cytoskeleton. It does this by interacting with transmembrane receptor complexes, integrins, and second messengers.

**References:**

- Gene Reviews
  - OMIM #300017: FLNA gene
  - OMIM #300049: PVNH
  - OMIM #304120: OPD2
  - OMIM #309350: MNS
  - OMIM #311300: OPD1
  - OMIM #305620: FMD

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### Genes

**FLNA**

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of FLNA-Related disorders.
- Carrier testing in adults with a family history of FLNA-Related disorders.

### 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

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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**

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 will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Analytical Sensitivity: ~99%

**Specimen Requirements**

*Submit only 1 of the following specimen types*

**Type: DNA, Isolated**

Specimen Requirements:
- Microtainer
- 8µg
- Isolation using the Perkin Elmer™Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:
- Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

**Type: Whole Blood (EDTA)**

Specimen Requirements:
- EDTA (Purple Top)
  - Infants and Young Children (2 years of age to 10 years old): 3-5 ml
  - Older Children & Adults: 5-10 ml
  - Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
- Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

**Type: Saliva**

Specimen Requirements:
- Oragene™ Saliva Collection Kit
  - Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
- Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

**Related Tests**

- Deletion/duplication analysis of the FLNA 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.
- X-Linked Intellectual Disability panels are available for 30, 60, and 90+ genes.