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

**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. Extracerebral features include cardiac valve 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.

**Otopalatodigital Spectrum Disorders**

The Otopalatodigital Spectrum Disorders include otopalatodigital syndrome type I (OPD1), otopalatodigital 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 oligohypodontia. 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 fontanels); 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; oligohypodontia; 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 Otopalatodigital 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

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OMIM #300049: PVNH  
OMIM #304120: OPD2  
OMIM #309350: MNS  
OMIM #311300: OPD1  
OMIM #305620: FMD  

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 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

* 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.

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.