FLNA-related Disorders: FLNA Gene Deletion/Duplication

Test Code: DFLNA
Turnaround time: 2 weeks
CPT Codes: 81228 x1

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 valvular anomalies, predisposition to premature stoke, 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
  - 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 in an individual in whom sequence analysis was negative.
- Carrier testing in adults with a family history of FLNA-Related disorders in whom sequence analysis was negative.

Methodology

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient’s phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

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Detection

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

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

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

- Sequence analysis of the FLNA gene is available and is required before deletion/duplication analysis.
- 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.