Focal Dermal Hypoplasia: **PORCN** Gene Deletion/Duplication

**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.

Focal dermal hypoplasia is a multisystem disorder that involves the skin, skeletal system, eyes, and face. At birth, the skin manifestations present include atrophic and hypoplastic areas of skin; cutis aplasia; fat nodules in the dermis manifesting as soft, yellow-pink cutaneous nodules; and pigmentary changes. Later, verrucoid papillomas of the skin and mucous membranes may appear. The nails can be ridged, dysplastic, or hypoplastic. Hair can be sparse or absent. Skeletal findings can include oligodactyly and/or syndactyly in one or both hands and feet and split hand/foot malformations. The central digits are most often involved. A skeletal survey may help detect the presence of osteopathia striata and/or costovertebral segmentation abnormalities. The developmental abnormalities of the eyes are usually evident at birth. Depending on the severity of the abnormality, vision can range from normal to blindness. Specific eye abnormalities reported include anophthalmia/microphthalmia, microcornea, iris and chorioretinal coloboma, lacrimal duct abnormalities, and cataracts. Craniofacial findings include facial asymmetry, pointed chin, small underfolded pinnae and notched alae nasi. These features typically develop as the individual ages. Additional features include cleft lip and/or palate, dental abnormalities, gastrointestinal anomalies, such as abdominal wall defects or diaphragmatic hernia, and renal abnormalities. Development is typically normal; however, some individuals with focal dermal hypoplasia have intellectual disability.

Focal dermal hypoplasia is caused by mutations in the **PORCN** gene (Xp11.23). Affected females are heterozygous for a mutation in the **PORCN** gene or have somatic mosaicism for a **PORCN** mutation and account for 90% of cases. Affected males have somatic mosaicism for **PORCN** mutations and account for 10% of cases. It is thought that non-mosaic hemizygous males are not viable. Affected males typically have a less severe phenotype than females. Female mutations in the **PORCN** gene are approximately 95% de novo.

**References:**

- GeneReviews
- OMIM #300651: **PORCN** gene
- OMIM #305600: Focal dermal hypoplasia

**Genes**

**PORCN**

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of Focal Dermal Hypoplasia in an individual in whom sequence analysis was negative.
- Carrier testing in adults with a family history of Focal Dermal Hypoplasia 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.

**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 PORCN 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.