Borjeson-Forssman-Lehmann Syndrome: PHF6 Gene Sequencing

**Condition Description**

Borjeson-Forssman-Lehmann syndrome (BFLS) is an X-linked intellectual disability syndrome. Characteristics of this syndrome include severe mental defect, epilepsy, hypogonadism, hypometabolism, marked obesity, swelling of subcutaneous tissue of face, narrow palpebral fissure, and large but not deformed ears. Affected individuals may have a characteristic facial appearance consisting of prominent superciliary ridges, deep-set eyes, ptosis, and large ears.

The phenotype of BFLS seems to evolve with age. Generally, babies with BFLS are floppy, with failure to thrive, big ears, and small external genitalia. In childhood, boys may display learning problems and moderate short stature, with emerging truncal obesity and gynecomastia. Head circumference is usually normal, and macrocephaly may be seen. Big ears and small genitalia remain. The toes are short and fingers tapered and malleable. In late adolescence and adult life, the classically described heavy facial appearance emerges.

Some heterozygous females display milder clinical features such as tapering fingers and shortened toes. Significant learning problems have been reported in approximately 20% of female carriers, and skewed X inactivation in approximately 95%. Carrier females have also been reported with epilepsy, characteristic facial features, obesity, amenorrhea, and hypothyroidism.

Mutations in the PHF6 gene (Xq26.3) have been associated with BFLS.

For patients with suspected BFLS, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

[Click here](#) for the OMIM summary on this condition.

**Genes**

PHF6

**Indications**

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of Borjeson-Forssman-Lehmann syndrome.
- Carrier testing in adult females with a family history of Borjeson-Forssman-Lehmann syndrome.

**Methodology**

PCR amplification of 11 exons contained in the PHF6 gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

**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 biochemical phenotype.

Analytical Sensitivity: ~99%

**Specimen Requirements**

Submit only 1 of the following specimen types:

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* 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**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

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**

- Deletion/duplication analysis of the \(PHF6\) gene by CGH array is available for those individuals in whom sequence analysis is negative (YI).
- A CGH array-based test for deletion/duplication analysis of 64 different X-linked intellectual disability genes is available (OL).
- **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 to adult females who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.