

***PAFAH1B1*-associated Lissencephaly/Subcortical Band Heterotopia: *PAFAH1B1* Gene Sequencing**

Test Code: SPAFA

Turnaround time: 4 weeks

CPT Codes: 81479 x1

Condition Description

PAFAH1B1-associated lissencephaly/subcortical band heterotopia (SBH) includes Miller-Dieker syndrome (MDS) and isolated lissencephaly sequence (ILS). During embryogenesis, reduced levels of neuronal migration cause the cortical malformations, lissencephaly and SBH. Lissencephaly refers to a "smooth brain" with absent gyri or abnormally wide gyri. SBH refers to a band of heterotopic gray matter located beneath the cortex but separated from it by a thin layer of normal white matter. MDS is characterized by lissencephaly, distinctive facial features, and severe neurological abnormalities. ILS is characterized by lissencephaly, which leads to developmental delay, intellectual disability, and seizures.

Mutation of the *PAFAH1B1* (17p13.3) gene, previously known as the *LIS1* gene, cause *PAFAH1B1*-associated lissencephaly/subcortical band heterotopia. MDS is caused by deletions that include both the *PAFAH1B1* and the *YWHAE* genes. ILS is caused by mutation of the *PAFAH1B1* gene with ~68% of mutations being detected by deletion/duplication analysis and ~32% being detected by sequencing analysis.

Please note that lissencephaly and SBH are graded by anterior-posterior gradient and severity. When the lissencephaly or SBH is more severe posteriorly, it is referred to as a posterior to anterior (p>a) gradient. When more severe anteriorly, it is referred to as an anterior to posterior (a>p) gradient. *PAFAH1B1* abnormalities generally give rise to a p>a gradient, whereas abnormalities of *DCX* generally give rise to an a>p gradient (GeneReviews). This testing is for the *PAFAH1B1* gene only.

For patients with suspected *PAFAH1B1*-associated lissencephaly/subcortical band heterotopia, deletion/duplication analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by deletion/duplication analysis, full gene sequencing is appropriate.

References:

- GeneReviews
- [OMIM #601545](#): *PAFAH1B1* gene
- [OMIM #607432](#): Lissencephaly 1

Deletion/Duplication testing should be ordered as the first tier test.

Genes

LIS1, [PAFAH1B1](#)

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of *PAFAH1B1*-Associated Lissencephaly/Subcortical Band Heterotopia in an individual in whom deletion/duplication analysis was negative.
- Carrier testing in adults with a family history of autosomal recessive *PAFAH1B1*-Associated Lissencephaly/Subcortical Band Heterotopia in whom deletion/duplication analysis was negative.

Methodology

PCR amplification of 10 exons contained in the *PAFAH1B1* 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: ~32%. 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: 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.

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: DNA, Isolated**Specimen Requirements:**

Microtainer

8µg

Isolation using the Perkin Elmer™ Chemagen™ 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.

Related Tests

- Deletion/duplication analysis of the *PFAFH1B1* gene is available and is required before sequencing analysis.
- Both sequencing (SO) and deletion/duplication (SQ) analysis of the *DCX* gene is available.
- 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.