Classic Lissencephaly/Subcortical Band Heterotopia: DCX Gene Deletion/Duplication

Condition Description

DCX-related disorders include the neuronal migration disorders classic lissencephaly (also known as lissencephaly type 1) in males and subcortical band heterotopia (SBH) primarily in females. The subcortical lamina heterotopia found in heterozygous females is also referred to as “double cortex” (DC) syndrome.

Males with classic lissencephaly typically have:

- developmental delay
- infantile-onset intractable seizures
- severe intellectual disability
- growth failure

In individuals with SBH/double cortex syndrome, cognitive abilities range from normal to learning disabilities and/or severe intellectual disability. Behavior problems may be observed. In SBH/double cortex syndrome, the severity of symptoms correlates with the degree of the underlying brain malformation.

The diagnosis of DCX-related disorders is suspected on MRI findings and confirmed by molecular genetic testing. The lissencephaly observed in DCX-related disorders is termed classic lissencephaly as it is characterized by absent gyria (agyria) or reduced gyration (pachygyria) with thickened cortex. DCX-associated SBH/double cortex syndrome occurs predominantly in the frontal-parietal lobes.

DCX is the only gene known to be associated with DCX-related disorders. The DCX gene (Xq22.3-q23) encodes the neuronal migration protein doublecortin (DCX), which is a microtubule-binding protein. Abnormal DCX products may affect proper microtubule formation and perturb the mitotic machinery, although not all abnormal products appear to do so to the same extent. The effect of DCX mutations on protein function is therefore not yet fully understood.

DCX-mutations can be identified in all multiplex families with SBH/double cortex syndrome and in families with SBH/double cortex syndrome in females and lissencephaly in males. Mutation detection frequency in male simplex cases of SBH/double cortex syndrome is 29% and in simplex cases of lissencephaly approximately 12% because the presentation of DCX-related lissencephaly and other lissencephalies can be similar. Mutation detection frequency in female simplex cases is approximately 80%, but can range from 38% to 90%, presumably because of inclusion of females with SBH/double cortex syndrome resulting from mosaic DCX mutations present only in neural tissue, females with SBH/double cortex syndrome from other genetic causes, and lack of deletion testing. Deletions have been found in approximately 10% of affected females. The proportion of cases caused by de novo mutations is unknown. Approximately 10% of unaffected mothers of children with a DCX mutation may have somatic mosaicism or germline mosaicism.

For patients with suspected classic lissencephaly or SBH/double cortex syndrome, 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.

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 DCX gene only.

Please click here for the GeneReviews summary on this condition.

Genes

DCX

Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of classic lissencephaly or SBH/double cortex syndrome in an individual in whom sequencing analysis was negative.
- Carrier testing in adult females with a family history of classic lissencephaly or SBH/double cortex syndrome in whom sequencing 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.

Detection

Disclaimer: This information is confidential and subject to change without notice. It may not be reproduced in whole or part unless authorized in writing by an authorized EGL representative.
Deletions have been found in approximately 10% of affected females. 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**

#### Type: DNA, Isolated

**Specimen Requirements:**
- Microtainer
- Isolation using the Perkin Elmer™ 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.

#### 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.

### Special Instructions

Please submit copies of diagnostic biochemical test results along 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

- Lissencephaly: DCX Gene Sequencing (SO) is required before deletion/duplication analysis.
- Sequence (SPAFA) and deletion/duplication (DPAFA) analysis are available for the PAFAH1B1 gene.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.