Classic Lissencephaly/Subcortical Band Heterotopia: \textit{DCX} Gene Sequencing

\textbf{Condition Description}

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

\textit{DCX} is the only gene known to be associated with \textit{DCX}-related disorders. The \textit{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 \textit{DCX} mutations on protein function is therefore not yet fully understood.

\textit{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 \textit{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 \textit{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 \textit{DCX} mutation may have somatic 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. \textit{PAFAH1B1} abnormalities generally give rise to a p>a gradient, whereas abnormalities of \textit{DCX} generally give rise to an a>p gradient (GeneReviews). This testing is for the \textit{DCX} gene only.

Please click here for the GeneReviews summary on this condition.

\textbf{Genes}

\textit{DCX}

\textbf{Indications}

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of classic lissencephaly or SBH/double cortex syndrome.
- Carrier testing in adult females with a family history of classic lissencephaly or SBH/double cortex syndrome.

\textbf{Methodology}

PCR amplification of 6 coding exons contained in the \textit{DCX} 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 dyeoxy 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 will not detect large deletions.

\textbf{Detection}

Clinical Sensitivity:
Sequence analysis of the DCX gene has been shown to identify 100% of mutations in families with more than one affected family member. Please see the condition description for detection rates in simplex families. Mutations in the promoter region, some mutations in the introns, other regulatory element mutations, and large deletions cannot be detected by this analysis.

Analytical Sensitivity: ~99%.

Results of molecular analysis should be interpreted in the context of the patient's 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) or ACD (yellow 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

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 Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

### Related Tests

- **Lissencephaly: DCX Gene Deletion/Duplication (SQ)** is available for those individuals in whom sequence analysis is negative.
- Sequence (SPAFA) and deletion/duplication (DPAFA) analysis are available for the PAFAH1B1 gene.
- **X-Linked Mental Retardation: 64-Gene Deletion/Duplication (OL)**
- **Known Mutation Analysis (KM)** is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- 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.