

The University of Chicago Genetic Services Laboratories



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Molecular Testing for Lissencephaly

Clinical Features:

Lissencephaly and subcortical band heterotopia (SBH) are brain malformations caused by deficient neuronal migration.

- Lissencephaly—"smooth brain" with absent (agyria) or abnormally wide gyri (pachygyria)
- SBH—"double cortex"; band of heterotopic gray matter below the cortex separated by a thin zone of normal white matter
- Miller-Dieker syndrome—lissencephaly, characteristic facial features and severe neurologic abnormalities
- X-linked lissencephaly with abnormal genitalia (XLAG)—lissencephaly and moderately increased thickness of the cortex, absence of the corpus callosum, infantile spasms, hypothalamic dysfunction including deficient temperature regulation, and ambiguous genitalia in males.

Lissencephaly and SBH are classified by anterior-posterior gradient and severity. This classification may help determine the best order for genetic testing.

Dr. William Dobyns at the University of Chicago is available to review MRI scans and give recommendations regarding genetic testing. Please contact Mary King at 773-702-8247 to arrange this, if desired.

Molecular Genetics:

The genetic causes of lissencephaly are complex, and may result from abnormalities in one of two autosomal genes (*LIS1*, *TUBA1A*) or abnormalities in one of two X-linked genes (*ARX*, *DCX*).

- *LIS1* [OMIM#601545] abnormalities cause the most severe form of lissencephaly and are generally associated with a p>a gradient [1]. *LIS1* mutations are present in approximately 30% of patients with *LIS1*-related lissencephaly and rarely in patients with SBH. Microdeletions involving 17p13.3 are present in 100% of patients with MDS and approximately 50% of patients with lissencephaly. Intragenic deletions of one or more exons of *LIS1* are present in approximately 15% of patients with *LIS1*-related lissencephaly [2].
- *DCX* [OMIM#300121] abnormalities result in severe lissencephaly or SBH in boys, but a less severe SBH in girls [3]. *DCX* abnormalities are generally associated with an a>p gradient. In males, *DCX* mutations are present in approximately 30% with SBH and approximately 10% with lissencephaly. In females, *DCX* mutations are present in approximately 80% with SBH, especially those with diffuse bands or bilateral frontal only bands. Intragenic deletions of the *DCX* gene are present in approximately 10% of female patients with SBH in whom no mutations were identified by *DCX* sequencing [4,5].
- *TUBA1A* [OMIM#602529] mutations have been identified in patients with gyral malformations and are generally associated with a p>a gradient (similar to *LIS1*-associated lissencephaly). Of patients with cortical dysgeneses in whom *DCX*, *LIS1*, and *ARX* mutation analysis is normal, approximately 30-40% have mutations in the *TUBA1A* gene [6].
- *ARX* [OMIM#300382] mutations cause various phenotypes including XLAG, X-linked infantile spasms, and non-syndromic X-linked mental retardation [7-9].

DCX/LIS1 deletion/duplication analysis, along with sequencing of DCX, LIS1 and TUBA1A, detects abnormalities in 90-95% of patients with lissencephaly and SBH.

Test methods:

We offer full gene sequencing for all coding exons and the intron/exon boundaries of *ARX*, *DCX* and *LIS1* and *TUBA1A*. We also offer deletion/duplication analysis of the *DCX/LIS1* genes by MLPA to identify deletions/duplications of one or more exons. MLPA will identify 17p13.3 microdeletions, full gene and intragenic deletions/duplications involving *LIS1* or *DCX*. CGH array or FISH analysis may not detect intragenic deletions/duplications within these genes. The sensitivity of our deletion/duplication assay may be reduced when DNA is extracted by an outside laboratory. For best results, please provide a fresh blood sample for this testing.

Lissencephaly panel (*LIS1*, *TUBA1A* and *DCX* sequencing and *LIS1/DCX* deletion/duplication analysis)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$3675
CPT codes:	83891, 83898 x8, 83904 x15, 83900, 83901, 83912
Turn-around time:	8 weeks

DCX mutation analysis (sequencing and deletion/duplication analysis)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$1575
CPT codes:	83891, 83898 x2, 83904 x5, 83900, 83901 x2, 83912
Turn-around time:	4 – 6 weeks

DCX sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$1250
CPT codes:	83891, 83898 x3, 83904 x5, 83912
Turn-around time:	4 – 6 weeks

LIS1 mutation analysis (sequencing and deletion/duplication analysis)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$2000
CPT codes:	83891, 83898 x3, 83904 x7, 83900, 83901 x2, 83912
Turn-around time:	4 – 6 weeks

LIS1 sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$1675
CPT codes:	83891, 83898 x4, 83904 x7, 83912
Turn-around time:	4 – 6 weeks

LIS1/DCX deletion/duplicaton analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$350
CPT codes:	83891, 83900, 83912
Turn-around time:	4 weeks

TUBA1A sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$925
CPT codes:	83898 x3, 83904 x4
Turn-around time:	4 – 6 weeks

ARX sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$1000
CPT codes:	83891, 83898 x2, 83904 x4, 83912
Turn-around time:	4 – 6 weeks

Targeted analysis for a known sequence change in additional family members

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: \$390-\$450
CPT codes: please contact us for specific CPT codes
Turn-around time: 2 – 3 weeks

Prenatal testing for a known mutation

Sample specifications: 2 T25 flasks of cultured cells from amniocentesis or CVS
Cost: \$590-\$650
CPT codes: please contact us for specific CPT codes
Turn-around time: 1 – 2 weeks

Laboratory Faculty and Staff:

Soma Das, Ph.D. Director ABMG Certified Molecular Geneticist	Eden Haverfield, Ph.D. Assistant Director ABMG Eligible Molecular Geneticist
Melissa Dempsey, M.S. Assistant Director, Clinical Services and Education ABGC Certified Genetic Counselor	Chris Tan, M.S. ABGC Eligible Genetic Counselor
William B. Dobyns, M.D. Clinical Advisor ABMG Certified Clinical Geneticist	Darrel J. Waggoner, M.D. Clinical Advisor ABMG Certified Clinical Geneticist

References

1. Lo Negro et al. Point mutations and an intragenic deletion in *LIS1*, the lissencephaly causative gene in isolated lissencephaly sequence and Miller-Dieker syndrome (1997) *Hum Mol Genet* 6:157-64.
2. Dobyns WB, Das S. *LIS1*-Associated Lissencephaly/Subcortical Band Heterotopia (in preparation) *GeneReviews*. www.genetests.com
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4. Uyanik G, et al. DCX-Related Disorders (2007) *GeneReviews*. www.genetests.com
5. Matsumoto N, et al. (1999) Mutation Analysis of the *DCX* gene and genotype/phenotype correlation in subcortical band heterotopia. *European Journal of Human Genetics* 9(1): 5-12.
6. Poirier et al. (2007) Large spectrum of lissencephaly and pachygyria phenotypes resulting from de novo missense mutations in tubulin alpha 1A (*TUBA1A*). *Hum Mutat* 28:1055-64.
7. Strømme et al. (2002) Mutations in the human ortholog of *Aristaless* cause X-linked mental retardation and epilepsy. *Nat Genet* 30:441-5.
8. Kitamura et al. (2002) Mutation of *ARX* causes abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans. *Nat Genet* 32:359-69.
9. Bivenu et al. (2002) *ARX*, a novel Prd-class-homeobox gene highly expressed in the telencephalon, is mutated in X-linked mental retardation. *Hum Mol Genet*11: 981-91.

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