PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

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X-linked lissencephaly-2 via *ARX* Gene Sequencing (Test #502)

Brief Description of Clinical Features: Lissencephaly is defined as "smooth brain" with absent gyri (agyria) or abnormally wide gyri (pachygyria) (Barkovich et al. Ann Neurol 1991; 30:139–46). X-linked lissencephaly-2 (LISX2) (OMIM 300215), also known as X-linked lissencephaly with ambiguous genitalia (XLAG), is a developmental disorder characterized by structural brain anomalies, early-onset intractable seizures, severe psychomotor retardation, craniofacial abnormalities and ambiguous genitalia (Dobyns et al. Am J Med Genet 86:331-337, 1999; Ogata et al. Am J Med Genet 94:174-176, 2000; Bonneau et al. Ann Neurol 51:340-349, 2002). Males are severely affected and often die within the first days or months of life, whereas female carriers may be unaffected or have a milder phenotype (Bonneau et al. 2002; Marsh et al. Brain 132:1563-1576, 2009). LISX2 is part of a developmental disorders spectrum including lissencephaly, hydranencephaly, Proud syndrome (OMIM # 300004), infantile spasms without brain malformations (EIEE1; OMIM 308350), and syndromic (OMIM 309510) and nonsyndromic (OMIM 300419) mental retardation (Kato et al. Hum Mutat 23:147-159, 2004; Wallerstein et al. Clin Neurol Neurosurg 110:631-634, 2008).

Genetics: X-linked lissencephaly-2 is inherited in an X-linked manner and is caused by mutations in the *ARX* gene (Kitamura et al. Nat Genet 32:359-369, 2002; Bonneau et al. 2002; Kato et al. 2004). *ARX* encodes the Aristaless-related homeobox transcription factor, which plays a crucial role in cerebral development and patterning (Bienvenu et al. Hum Molec Genet 11:981-991, 2002). A mix of missense, nonsense, splice site and small deletion, insertion and duplication mutations has been reported in the *ARX* gene (Stromme et al. Nat Genet 30: 441-445, 2002; Kitamura et al. 2002; Bonneau et al. 2002; Kato et al. 2004; Proud et al. Am J Med Genet 43:458-466, 1992). It also has been reported that patients with premature truncation or nonsense as well as missense mutations in highly conserved regions had brain malformation syndromes, including LISX2 and Proud syndrome, whereas patients with expansion of the polyalanine tract in exon 2 had epileptic encephalopathy or mental retardation without brain malformations (Kato et al. 2004).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of the 5 coding exons (exons 1-5) of the *ARX* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on each side are sequenced. As indicated, we will also perform sequencing of any single exon (Test #100) in family members of patients with known mutations and to confirm previous research results ($190 charge).
Reference Sequences: Genomic: **NC_000023.9** mRNA: **NM_139058.1** Protein: **NP_620689.1 (CCDS 14215.1)**

Indications for Test: Candidates for this test are patients with X-linked lissencephaly with ambiguous genitalia, Proud syndrome, EIEE1, syndromic and nonsyndromic mental retardation and family members of patients with known mutations.

Sensitivity of Test: Sensitivity of this test is currently unknown.

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Prices: **Sequencing of *ARX* gene** **$ 590**

CPT Codes:

Sample Ascertainment x1	83890 $ 30	DNA Isolation x1	83891 $ 40
Amplification x8	83898 $ 160	Sequencing x8	83904 $ 240
Separation x1	83894 $ 40	Interpretation/Report x1	83912 $ 80

Accreditation Info: CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12).

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