



MNX1 Sequencing for Currarino Syndrome

Clinical Features:

Currarino syndrome is an autosomal dominant condition defined by a triad of findings including partial sacral agenesis, presacral mass, and anorectal malformation. Common presenting clinical findings include anterior meningocele, other presacral mass (e.g. teratoma, lipoma, cyst), chronic constipation in childhood, and renal/urinary tract and/or gynecologic issues. In affected individuals, sacral agenesis typically involves sacral vertebrae S2-S5. Variable expressivity and reduced penetrance have been reported in families with *MNX1*-related Currarino syndrome, though a proportion of reportedly asymptomatic individuals are noted to have visible sacral defects on X-ray. Heterozygous mutations in *MNX1* (also known as *HLXB9*) have been identified in nearly all cases of familial Currarino syndrome and in ~30% of sporadic cases (1).

Molecular Genetics:

The *MNX1* gene is expressed during embryonic development in the basal plate of the spinal cord, hindbrain, pharynx, esophagus, stomach and pancreas (2).

Inheritance:

MNX1-related Currarino syndrome is inherited in an autosomal dominant fashion and most cases are inherited. Variable expressivity and penetrance have been reported; therefore, parents of affected individuals may be asymptomatic carriers. Recurrence risk for parents of an affected individual depends on their carrier status.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *MNX1* gene is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. **Please note that we are unable to sequence c.264-450 in exon 1 of *MNX1* for technical reasons.** Deletion/duplication analysis of the *MNX1* is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

MNX1 sequencing

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$1000
CPT codes:	81404
Turn-around time:	4 weeks

MNX1 deletion/duplication analysis

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$1000
CPT codes:	81403
Turn-around time:	4 weeks

Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory.

Results

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

References:

1. Lynch SA, Wang Y, Strachan T et al. Autosomal dominant sacral agenesis: Currarino syndrome. *J Med Genet* 2000; 37: 561-566.
2. Hagan DM, Ross AJ, Strachan T et al. Mutation analysis and embryonic expression of the *HLXB9* Currarino syndrome gene. *Am J Hum Genet* 2000; 66: 1504-1515