

Heterotaxy, Visceral 5 (HTX5) via *NODAL* Gene Sequencing (Test #931)

Brief Description of Clinical Features: Heterotaxy syndrome or *situs ambiguus* results from a failure to properly establish left-right asymmetry during embryogenesis resulting in an abnormal arrangement of thoracic and/or abdominal visceral organs, including the heart, lungs, liver, spleen, intestines, and stomach. Affected patients frequently have significant morbidity and mortality due to a wide variety of cyanotic congenital heart defects. Common defects besides cardiac malformations include asplenia or polysplenia, left-sided liver, right-sided stomach, gastrointestinal malrotation, and altered lung lobation. Classic heterotaxy (cardiac malformations and visceral laterality defects) has an estimated prevalence of 1:10,000 live births (Lin et al. *Genet Med* 2:157-172, 2000).

Genetics: Heterotaxy is a heterogeneous genetic disorder. Mutations in at least 7 genes (*NODAL*, *ZIC3*, *CFC1*, *FOXH1*, *LEFTY2*, *GDF1*, *ACVR2B*) involved in *NODAL* signaling have been proposed to cause heterotaxy and/or congenital heart defects (CHDs). These proteins play an essential role in establishing left-right patterning during organogenesis, including the heart and great vessels (reviewed by Hamada et al. *Nat Rev Genet* 3:103-113, 2002). Defects in *NODAL* signaling factors are also found in 5-10% of patients with isolated CHDs without heterotaxy, including tetralogy of Fallot, double outlet right ventricle, transposition of the great arteries, and cardiac septal defects (Roessler et al. *Am J Hum Genet* 83:18-29, 2008; Mohapatra et al. *Hum Mol Genet* 18:861-871, 2009). Heterotaxy, visceral 5 (HTX5; OMIM 270100) is inherited as an autosomal dominant disorder with variable penetrance caused by loss of function mutations in the TGFβ-related ligand *NODAL* (Gebbia et al. *Nature* 17:305-308, 1997). Missense, nonsense, in-frame insertion/deletions and splice site mutations in the *NODAL* gene have been found in patients with left-right asymmetry anomalies and CHDs, such as tetralogy of Fallot, transposition of the great arteries, and double outlet right ventricle (Gebbia et al. *Nature* 17:305-308, 1997; Roessler et al. *Am J Hum Genet* 83:18-29, 2008; Roessler et al. *Mol Genet Metab* 98:225-234, 2009; Mohapatra et al. *Hum Mol Genet* 18:861-871, 2009; De Luca et al. *Heart* 96:673-677, 2010).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 3 coding exons of the *NODAL* gene plus ~50 bp of flanking non-coding DNA on either side of each exon. We will also perform sequencing of any single exon or pair of exons for family members of patients with known mutations and to confirm previous research results (Test #100 or #200, \$190-340 charge).

Reference Sequences: Genomic: NC_000010.10 mRNA: NM_018055.4 Protein: NP_060525.3 (CCDS 7304.1)

Indications for Test: All patients with heterotaxic phenotypes are candidates for this test. Patients with isolated CHDs without abdominal laterality defects are also candidates for this test.

Sensitivity of Test: Mutations in the *NODAL* gene are estimated to cause 5-10% of all cases of heterotaxy and 4% of cases with CHDs without visceral laterality defects (Roessler et al. *Am J Hum Genet* 83:18-29, 2008; Roessler et al. *Mol Genet Metab* 98:225-234, 2009; Mohapatra et al. *Hum Mol Genet* 18:861-871, 2009).

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 3-4 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of coding exons of the *NODAL* Gene: \$ 540

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x6	83898	\$ 130	Sequencing x6	83904	\$ 215
Separation x1	83894	\$ 40	Interpretation/Report x1	83912	\$ 85

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

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