

X-linked Heterotaxy (HTX1) via ZIC3 Gene Sequencing (Test #932)

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). X-linked heterotaxy 1 (HTX1; OMIM 306955) is due to mutations (missense, nonsense, frameshifts) in the zinc finger transcription factor *ZIC3*. Although males are most commonly affected, there are reports in the literature of symptomatic heterozygous females (Gebbia et al. *Nature* 17:305-308, 1997; Ware et al. *Am J Hum Genet* 74:93-105, 2004; Chhin et al. *Hum Mutat* 28:563-570, 2007). Patients with isolated CHDs without any evidence for heterotaxy have also been found to harbor mutations in *ZIC3* (Megarbane et al. *Eur J Hum Genet* 8:704-708, 2000). A 1.3Mb deletion of Xq26.3 including the *ZIC3* locus has been found to segregate in an Italian family with heterotaxy (Chung et al. *Am J Hum Genet* 155A:1123-1128, 2011).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 3 coding exons of the *ZIC3* 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_000023.10 mRNA: NM_003413.3 Protein: NP_003404.1 (CCDS 14663.1)

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

Sensitivity of Test: Mutations in the *ZIC3* gene are estimated to cause >75% of familial X-linked cases of heterotaxy, ~1% of sporadic cases of heterotaxy, and ~1% of cases with isolated CHDs without laterality defects (Ware et al. *Am J Hum Genet* 74:93-105, 2004).

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 exon of the *ZIC3* Gene: \$ 540

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x7	83898	\$ 140	Sequencing x7	83904	\$ 210
Separation x1	83894	\$ 35	Interpretation/Report x1	83912	\$ 85

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

Contact: Anthony Krentz, Ph.D., anthony.krentz@preventiongenetics.com www.preventiongenetics.com