CFC1, FOXH1, NODAL and ZIC3 Heterotaxy Syndrome

Heterotaxy syndrome is a multiple congenital anomaly syndrome characterized by complex cardiovascular malformations and visceral situs anomalies. Autosomal recessive, autosomal dominant, and X-linked inheritance occur, although heterotaxy is most commonly sporadic. The ZIC3 gene is a zinc finger transcription factor that causes the X-linked form of heterotaxy. The ZIC3 gene contains 4 exons and is located at chromosome Xq26.2. ZIC3 mutations have been identified in approximately 75% of families with X-linked heterotaxy and in 1% of sporadic patients with congenital heart disease (1,2). ZIC3 mutations have also been identified in females with cardiovascular malformations.

NODAL encodes a TGFβ ligand that is critical for establishing left-right asymmetry during early development. The NODAL gene contains 3 exons and is located at chromosome 10q22.1. CFC1 encodes a co-factor required for NODAL signaling through the TGFβ pathway to generate left-right asymmetry. The CFC1 gene contains 6 exons and is located at chromosome 2q21.1. FOXH1 encodes a forkhead transcription factor. The forkhead protein domain binds DNA and the C-terminal domain interacts with phosphorylated Smad proteins to mediate TGFβ signaling. The FOXH1 gene contains 3 exons and is located at chromosome 8q24.3. Mutations in NODAL cause heterotaxy or heterotaxy spectrum cardiovascular malformations in up to 10% of sporadic cases (2-4). In addition to heterotaxy, mutations in these 3 laterality genes have been identified in isolated cardiovascular malformations including transposition of the great arteries (TGA), double outlet right ventricle (DORV), unbalanced atrioventricular canal defects, conotruncal defects such as tetralogy of Fallot (TOF) and septal defects in 5-10% of isolated cases (2,4,5). Mutations in these genes exhibit autosomal dominant inheritance with reduced penetrance and variable expressivity. Missense variants have been identified that appear to act as susceptibility alleles (4,6,7). Mutations are identified in one or more of these genes in a higher percent of familial cases (6). Mutations in NODAL pathway genes also account for approximately 1% of holoprosencephaly cases (4).

Indication
To identify the molecular basis of heterotaxy syndrome or related cardiovascular malformations including TGA, DORV, TOF, and atrioventricular canal defects; determination of recurrence risk, especially in cases of X-linked heterotaxy.
Methodology:

All coding exons as well as the exon/intron boundaries and a portion of untranslated regions of the gene(s) are amplified by PCR. Genomic DNA sequences from both forward and reverse directions are obtained by automatic fluorescent detection using an ABI PRISM® 3730 DNA Analyzer. Sequence variants different from National Center for Biotechnology Information GenBank references are further evaluated for genetic significance. If a mutation is identified, a known familial mutation analysis will be available for additional family members.

Sensitivity & Accuracy:

Greater than 99% of the mutations are detectable by sequence based methods. Sequencing does not detect deletions or duplications.

References:

Peripheral blood in EDTA tube
Adult: 5-10mL
Child: 3-5mL
Infant: 1-3mL
For other specimen types, please contact Amy Garrison at 513-803-3317

Panel 4 to 6 weeks
Full Mutation Analysis (Individual genes) 2-4 weeks
Known Mutation Analysis (Individual genes) 1-2 weeks

Full Gene Sequencing:
CFCI Sequencing  81479
FOXHI Sequencing  81479
NODAL Sequencing  81479
ZIC3 Sequencing  81479
Additional Family Members  81403