Cardiovascular Diseases Genetic Testing Program

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.

Molecular Genetics Laboratory

Shipping Instructions

Please enclose a test requisition form with sample. All information must be complete before sample can be processed. Samples may be shipped at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship to:

Molecular Genetics Lab
Cincinnati Children's Hospital
3333 Burnet Ave. NRB 1042
Cincinnati, OH 45229

Phone: 513-636-4474
Fax: 513-636-4373

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:

1. Ware SM, Peng J, Zhu L, Fernbach S, Colicos S, Casey B, Towbin J, Belmont JW. Identification and functional analysis of ZIC3 mutations in Heterotaxy and related congenital heart defects. American Journal of Human Genetics. 2004;74:93-105.
2. Sutherland MJ, Ware SM. Disorders of left-right asymmetry: Heterotaxy and situs inversus. American Journal of Human Genetics Part C Seminars in Medical Genetics. 2009;151C:307-317.
3. Mohapatra B, Casey B, Li H, Ho-Dawson T, Smith L, Fernbach SD, Molinari L, Niesh SR, Jefferies JL, Craigen WJ, Towbin JA, Belmont JW, Ware SM. Identification and functional characterization of NODAL rare variants in Heterotaxy and isolated cardiovascular malformations. Human Molecular Genetics. 2009;18:861-871.
4. Roessler E, Ouspenskaia MV, Karkera JD, Velez JI, Kantipong A, Lacbawan F, Bowers P, Belmont JW, Towbin JA, Goldmuntz E, Feldman B, Muenke M. Reduced NODAL signaling strength via mutation of several pathway members including FOXH1 is linked to human heart defects and holoprosencephaly. American Journal of Human Genetics. 2008;83:18-29.
5. Goldmuntz E, Bamford R, Karkera JD, dela Cruz J, Roessler E, Muenke M. CFC1 mutations in patients with transposition of the great arteries and double-outlet right ventricle. American Journal of Human Genetics. 2002;70:776-780.
6. De Luca A, Sarkozy A, Consoli F, Ferese R, Guida V, Dentici ML, Mingarelli R, Bellacchio E, Tuo G, Limongelli G, Digilio MC, Marino B, Dallapiccola B. Familial transposition of the great arteries caused by multiple mutations in laterality genes. Heart. 2010;96:673-677.
7. Selamet Tierney ES, Marans Z, Rutkin MB, Chung WK. Variants of the CFC1 gene in patients with laterality defects associated with congenital cardiac disease. Cardiology in the Young. 2007;17:268-274.
8. Bedard JE, Haaning AM, Ware SM. Identification of a novel zic3 isoform and mutation screening in patients with heterotaxy and congenital heart disease. PLoS One. 2011;6:e23755.

Specimen:

Peripheral blood in EDTA tube
Adult: 3-5mL
Child: 3-5mL
Infant: 1-3mL
For other specimen types, please contact us at 513-636-4474

Turnaround Time:

Full Panel Analysis 4-6 weeks
Known Mutation Analysis 1-2 weeks

CPT Codes:

Full Gene Sequencing	81405
Additional Family Members	81403

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3333 Burnet Ave. | Cincinnati, OH 45229
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