Cardiovascular Diseases Genetic Testing Program

Heterotaxy Panels

Heterotaxy is a multiple congenital anomaly syndrome characterized by complex cardiovascular malformations and visceral situs anomalies. Primary ciliary dyskinesia (PCD) is one cause of heterotaxy, with 6.3% of PCD patients being affected. The majority of cases of heterotaxy are sporadic, however autosomal recessive, autosomal dominant, and X-linked inheritance have been described. Recent epidemiologic studies indicate heterotaxy is the most highly heritable cardiovascular malformation. Genetic testing for heterotaxy provides important management and recurrence risk information.

In general, heterotaxy seen in the presence of PCD is an autosomal recessive condition, whereas isolated heterotaxy is thought to have complex or autosomal dominant inheritance with reduced penetrance and variable expressivity. X-linked heterotaxy can also occur and is known to be associated with mutations in the *ZIC3* gene. Mutations in *ZIC3* are thought to account for 75% of familial cases of X-linked heterotaxy, and 1% of sporadic heterotaxy (both in males and females).

In addition to single gene causes, heterotaxy has also been reported in cases of other ciliopathies, aneuploidies, chromosomal rearrangements and microdeletions.

Indication

The **Heterotaxy V2 panel** is a comprehensive 17 gene panel for patients with heterotaxy with or without congenital heart disease. See the complete gene list below.

The **Heterotaxy V1 reflex panel** is a 13 gene panel for patients with a suspected heterotaxy-related disorder when the **Heterotaxy V1 panel** (*CFC1*, *FOXH1*, *NODAL*, and *ZIC3*) did not find any mutations.

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:

Heterotaxy V2 Panel and Heterotaxy V1 reflex Panel: Next Generation Sequencing: All coding exons, as well as their flanking regions, of the genes listed in the panel are enriched from the patient's genomic DNA and sequenced using a solid-state sequencing-by-synthesis process. DNA sequences are assembled and compared to the published genomic reference sequences in Genome Reference Consortium Build 37. Dideoxy DNA sequencing is used to provide data for bases with insufficient coverage and to confirm the reported variants from next-generation sequencing. This assay does not detect variants in the promoter regions, deep intronic regions, or other regulatory elements, and does not detect large deletions or mosaicisms. Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen).

Heterotaxy V1 Panel: 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:

The analytic sensitivity of this test is 99.9% and the analytic specificity is 100%.

Selected references:

Sutherland MJ, Ware SM. Disorders of left-right asymmetry: Heterotaxy and situs inversus. *American Journal of Medical Genetics C Seminar Medical Genetics*. 2009;151C:307-317.

Oyen N, Poulsen G, Boyd HA, Wohlfahrt J, Jensen PK, Melbye M. Recurrence of congenital heart defects in families. *Circulation*. 2009;120:295-301.

Chhin B, Hatayama M, Bozon D, Ogawa M, Schon P, Tohmonda T, Sassolas F, Aruga J, Valard AG, Chen SC, Bouvagnet P. Elucidation of penetrance variability of a *ZIC3* mutation in a family with complex heart defects and functional analysis of *ZIC3* mutations in the first zinc finger domain. *Human Mutation*. 2007;28:563-570.

Tariq M, Belmont JW, Lalani S, Smolarek T, Ware SM. *SHROOM3* is a novel candidate for heterotaxy identified by whole exome sequencing. *Genome Biology*. 2011;12:R91.

Specimen:

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

Turnaround Time:

Heterotaxy V1 Panel Analysis 4-6 weeks
Heterotaxy V1 Reflex Panel Analysis 8-10 weeks
Heterotaxy V2 Panel Analysis 8-10 weeks
Known Mutation Analysis 1-2 weeks

CPT Codes:

Heterotaxy V1 Panel Analysis: 81479 x4
Heterotaxy V1 Reflex Panel Analysis: 81479 x13
Heterotaxy V2 Panel Analysis: 81479 x17
Known Mutation Analysis: 81479

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HIDL Heterotaxy Panel Gene List

Gene	Phenotype	Heterotaxy V1 panel (Sanger)	Heterotaxy V2 panel (NGS)	Heterotaxy reflex panel (NGS)
ACVR2B	Heterotaxy type 4		x	x
BCL9L	Recessive visceral heterotaxy (heterotaxy 6)		x	x
CCDC11	Heterotaxy syndrome / Situs inversus totalis		x	x
CFC1	Heterotaxy type 2; d-Transposition of the great arteries type 2	x	x	
CRELD1	Partial atrioventricular septal defect, with heterotaxy syndrome		x	x
DNAH11	Primary ciliary dyskinesia		x	x
DNAH5	Primary ciliary dyskinesia		x	x
FOXH1	Ventricular septal defects, Tetralogy of Fallot	x	x	
GATA6	Atrial septal defect type 9, Atrioventricular septal defect type 5, Tetralogy of Fallot		x	x
GDF1	Heterotaxy and conotruncal heart defect		x	x
GJA1	Atrioventricular septal defect type 3; Oculodentodigital dysplasia, autosomal recessive; Craniometaphyseal dysplasia, autosomal recessive		x	x
LEFTY2	Heterotaxy		x	x
NAT10	Heterotaxy with ciliary aplasia		x	x
NKX2-5	Isolated nonsyndromic congenital heart defects		x	x
NODAL	Heterotaxy type 5	x	x	
SHROOM3	Heterotaxy		x	x
ZIC3	Heterotaxy 1, X-linked	x	x	

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