Heterotaxy and Situs Inversus Panel

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Laterality defects, such as heterotaxy and situs inversus, are developmental defects characterized by the abnormal placement of the abdominal (visceral) organs. Situs inversus totalis involves the complete transposition of all visceral organs, while heterotaxy (situs ambiguus) is used to describe any deviation from the standard placement of organs in the abdomen. Laterality defects can also impact the left-right symmetry in the heart, and many individuals with heterotaxy have congenital heart defects. These conditions are clinically and genetically heterogeneous and have been associated with pathogenic variants in a number of different genes that are involved in both early embryo development and pathways related to left-right patterning. Clinical symptoms are variable and depend on the function of the organs involved.

Featured ARUP Testing

Heterotaxy & Situs Inversus Panel, Sequencing 3002682

Method: Massively Parallel Sequencing

- Use to detect variants in genes known to cause laterality defects such as situs inversus, heterotaxy, or complex congenital heart defects.
- Regions of low coverage and reported variants are confirmed by Sanger sequencing as necessary.

Disease Overview

Symptoms/Associated Disorders

Symptoms vary depending on the organs involved and may include cyanosis or other complications of congenital heart disease, digestive problems due to intestinal malrotation, or immunologic disorders due to abnormal spleen function.

Primary ciliary dyskinesia (Kartagener syndrome) is an associated disorder caused by abnormalities of the motile cilia, which leads to sinopulmonary disease, infertility, and, in 50% of cases, situs inversus. For more information, see the Primary Ciliary Dyskinesia Panel Test Fact Sheet.

Epidemiology/Prevalence

Heterotaxy syndrome affects approximately one in 10,000 individuals and is causative of about 3% of cases of congenital heart defects.

Genetics

Etiology

Pathogenic germline variants in genes associated with left-right symmetry in early embryo development

Penetrance

Varies; some associated genes exhibit reduced penetrance

Inheritance

Varies; see Genes Tested table

Test Interpretation

Clinical Sensitivity

Variable, dependent on phenotype/condition

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a heritable laterality defect.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted gene(s)
  - Regulatory region and deep intronic variants
  - Large deletions/duplications in any of the tested genes
  - Noncoding transcripts
  - The following exons are not sequenced due to technical limitations of the assay:
    - ANKS6(NM_173551) exon(s) 1
    - ARMC4(NM_001290020) exon(s) 9
    - ARMC4(NM_001290021) exon(s) 13
    - ARMC4(NM_001312689) exon(s) 4
    - ARMC4(NM_018076) exon(s) 9
    - CCDC103(NM_001258397) exon(s) 4
    - CCDC114(NM_001364171) exon(s) 3
    - CCDC114(NM_001364171) partial exon(s) 4(Chr19:48822049-48822069)
    - CCDC40(NM_001243342) exon(s) 18
    - CFAP298(NM_001350335) partial exon(s) 5(Chr21:33975399-33975450)
    - CFAP298(NM_001350337) partial exon(s) 6(Chr21:33974534-33974561)
    - DNAAF5(NM_017802) exon(s) 1
    - DNAI2(NM_001353167) exon(s) 13
    - GATA6(NM_005257) partial exon(s) 2(Chr18:19751812-19751963)
    - PKD1L1(NM_138295) partial exon(s) 8(Chr7:47955029-47955060)
    - SPAG1(NM_001374321) partial exon(s) 11(Chr8:101225456-101225529)
    - SPAG1(NM_003114) partial exon(s) 11(Chr8:101225456-101225529)
    - SPAG1(NM_172218) partial exon(s) 11(Chr8:101225456-101225529)
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

Genes Tested

Gene Name	MIM #	Associated Disorder	Inheritance Pattern
ANKS6	615370	Nephronophthisis	AR
ARL2BP	615407	Retinitis pigmentosa with or without situs inversus	AR
ARMC4	615408	PCD	AR
CCDC103	614677	PCD	AR
CCDC114	615038	PCD	AR
CCDC151	615956	PCD	AR
CCDC39	613798	PCD	AR
CCDC40	613799	PCD	AR
CFAP298	615494	PCD	AR
CFAP53	614759	Visceral heterotaxy	AR
CRELD1	607170	Atrioventricular septal defect, partial, with heterotaxy syndrome	AD
DNAAF1	613190	PCD	AR
DNAAF2	612517	PCD	AR
DNAAF3	614566	PCD	AR
DNAAF4	608706	PCD	AR
DNAAF5	614864	PCD	AR
DNAH1	603332	PCD	AR
DNAH11	603339	PCD	AR
DNAH5	603335	PCD	AR
DNAI1	604366	PCD	AR
DNAI2	605483	PCD	AR
DNAL1	610062	PCD	AR
FOXH1	603621	Congenital heart defects (multiple types)	AD
GATA4	600576	Congenital heart defects (multiple types)	AD
GATA6	601656	Congenital heart defects (multiple types)	AD

AD, autosomal dominant; AR, autosomal recessive; PCD, primary ciliary dyskinesia; XLR, X-linked recessive

Gene Name	MIM #	Associated Disorder	Inheritance Pattern
INVS	243305	Nephronophthisis	AR
LRRC6	614930	PCD	AR
MMP21	608416	Visceral heterotaxy	AR
NKX2-5	600584	Congenital heart defects (multiple types)	AD
NME8	607421	PCD	AR
NODAL	601265	Visceral heterotaxy	AD
PIH1D3	300933	PCD	XLR
PKD1L1	609721	Visceral heterotaxy	AR
SPAG1	603395	PCD	AR
ZIC3	300265	Visceral heterotaxy, Congenital heart defects	XLR
ZMYND10	607070	PCD	AR

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Additional Resources

Teele SA, Jacobs JP, Border WL, et al. Heterotaxy syndrome: proceedings from the 10th International PCICS meeting. *World J Pediatr Congenit Heart Surg*. 2015;6(4):616-629.

Related Information

Primary Ciliary Dyskinesia Panel

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