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Patient Report

Patient Age/Gender: Female

Specimen Collected: 08-Jun-21 16:02

Heterotaxy and Situs Inversus by NGS | **Received: 08-Jun-21 16:02** | **Report/Verified: 08-Jun-21 16:07**

Procedure	Result	Units	Reference Interval
Heterotaxy and Situs Inversus Specimen	Whole Blood		
Heterotaxy and Situs Inversus Interp	Positive f1 i1		

Result Footnote

f1: Heterotaxy and Situs Inversus Interp

INDICATION FOR TESTING
Transposition of the great arteries, pulmonary atresia, asplenia, bronchiectasis

RESULT
One likely pathogenic variant was detected in the NODAL gene.

LIKELY PATHOGENIC VARIANT
Gene: NODAL (NM_018055.4)
Nucleic Acid Change: c.194-1G>T; Heterozygous
Inheritance: Autosomal Dominant

INTERPRETATION
One copy of a likely pathogenic variant, c.194-1G>T, was detected in the NODAL gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic variants in NODAL are associated with autosomal dominant visceral heterotaxy 5 (MIM: 270100). This result is consistent with a diagnosis of visceral heterotaxy 5. This individual's offspring have a 50 percent chance of inheriting the likely pathogenic variant.

No additional pathogenic variants were identified in the targeted genes by massively parallel sequencing. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classification: The NODAL c.194-1G>T variant (reported as c.892-1G>T, Li 2019) is reported in the literature in individuals affected with laterality defects and/or cardiovascular malformations (Li, 2019; Mohapatra, 2009). This variant is reported in ClinVar (Variation ID: 545544) and is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. This variant disrupts the canonical splice acceptor site of intron 1, which is likely to negatively impact gene function. Based on available information, this variant is considered to be likely pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified likely pathogenic variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Likely benign and benign variants are not included in this report.

REFERENCES
Li AH, et al. Genetic architecture of laterality defects revealed by whole exome sequencing. Eur J Hum Genet. 2019;27(4):563-573.

Mohapatra B, et al. Identification and functional characterization of NODAL rare variants in heterotaxy and isolated cardiovascular malformations. Hum Mol Genet. 2009;18(5):861-871.

Result Footnote

f1: Heterotaxy and Situs Inversus Interp

This result has been reviewed and approved by [redacted]

Test Information

i1: Heterotaxy and Situs Inversus Interp

BACKGROUND INFORMATION: Heterotaxy and Situs Inversus Panel, Sequencing

CHARACTERISTICS: Laterality defects such as heterotaxy and situs inversus are developmental defects characterized by the abnormal placement of the abdominal (visceral) organs.

EPIDEMIOLOGY: Heterotaxy syndrome affects approximately 1 in 10,000 individuals. This condition is causative of about 3 percent of congenital heart defects cases.

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

INHERITANCE: Varies

PENETRANCE: Varies; some associated genes exhibit reduced penetrance.

GENES TESTED: ANKS6*, ARL2BP, ARMC4*, CCDC103*, CCDC114*, CCDC151, CCDC39, CCDC40*, CFAP298*, CFAP53, CRELD1, DNAAF1, DNAAF2, DNAAF3, DNAAF4, DNAAF5*, DNAH1, DNAH11, DNAH5, DNAI1, DNAI2*, DNAL1, FOXH1, GATA4, GATA6*, INVS, LRRC6, MMP21, NKX2-5, NME8, NODAL, PIH1D3, PKD1L1*, SPAG1*, ZIC3, ZMYND10

*One or more exons are not covered by sequencing for the indicated gene; see limitations section below.

METHODOLOGY: Capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a heritable laterality defect. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants and deep intronic variants will not be identified. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level mosaic or somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
ANKS6(NM_173551) exon(s) 1
ARMC4(NM_001290020) exon(s) 9

Test Information

i1: Heterotaxy and Situs Inversus Interp

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)

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.