

Client: Example Client ABC123  
123 Test Drive  
Salt Lake City, UT 84108  
UNITED STATES

Physician: Doctor, Example

**Patient: Patient, Example**

**DOB:** Unknown  
**Gender:** Unknown  
**Patient Identifiers:** 01234567890ABCD, 012345  
**Visit Number (FIN):** 01234567890ABCD  
**Collection Date:** 00/00/0000 00:00

**Heterotaxy & Situs Inversus Panel, Sequencing**

ARUP test code 3002682

Heterotaxy and Situs Inversus Specimen      whole Blood

Heterotaxy and Situs Inversus Interp      Positive

**H=High, L=Low, \*=Abnormal, C=Critical**

Unless otherwise indicated, testing performed at:

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

Please refer to the background information included in this report for a list of the genes analyzed, methodology, 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 the 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 NODAL variant (Familial Targeted Sequencing, ARUP test code 3005867).

**COMMENTS**

Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics. Likely benign and benign variants are not reported. Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:  
NONE

**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.

This result has been reviewed and approved by [REDACTED]

**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\*,

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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  
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.

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VERIFIED/REPORTED DATES				
Procedure	Accession	Collected	Received	Verified/Reported
Heterotaxy and Situs Inversus Specimen	22-301-105115	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Heterotaxy and Situs Inversus Interp	22-301-105115	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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