

Specimen Collected: 08-Jun-21 16:02

Primary Ciliary Dyskinesia by NGS | Received: 08-Jun-21 16:02 Report/Verified: 08-Jun-21 16:06

Procedure	Result	Units	Reference Interval
Primary Ciliary Dyskinesia Specimen	Whole Blood		
Primary Ciliary Dyskinesia Interp	Positive ^{f1 i1}		

Result Footnote

f1: Primary Ciliary Dyskinesia Interp
INDICATION FOR TESTING
Chronic bronchitis, situs inversus totalis.

RESULT

Two pathogenic variants were detected in the DNAH5 gene.

PATHOGENIC VARIANTS

Gene: DNAH5 (NM_001369.2)
Nucleic Acid Change: c.4348C>T; Heterozygous
Amino Acid Alteration: p.Gln1450Ter
Inheritance: Autosomal Recessive

Gene: DNAH5 (NM_001369.2)
Nucleic Acid Change: c.6763C>T; Heterozygous
Amino Acid Alteration: p.Arg2255Ter
Inheritance: Autosomal Recessive

INTERPRETATION

Two pathogenic variants, c.4348C>T; p.Gln1450Ter, and c.6763C>T; p.Arg2255Ter, were detected in the DNAH5 gene by massively parallel sequencing. Pathogenic variants in DNAH5 are associated with autosomal recessive primary ciliary dyskinesia 3, with or without situs inversus (MIM: 608644). This result is consistent with a diagnosis of primary ciliary dyskinesia if the two pathogenic variants occur on opposite chromosomes.

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 DNAH5 c.4348C>T; p.Gln1450Ter variant (rs771663107) is reported in the literature in the homozygous or compound heterozygous state in multiple individuals and families affected with primary ciliary dyskinesia (Faily 2009, Ferkol 2013). This variant is reported in ClinVar (Variation ID: 208992) and is only observed on one allele in the Genome Aggregation Database, indicating it is not a common polymorphism. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, this variant is considered to be pathogenic.

The DNAH5 c.6763C>T; p.Arg2255Ter variant (rs745918507) is reported in the literature in individuals affected with primary ciliary dyskinesia, including at least one individual with a different pathogenic DNAH5 variant on the opposite chromosome (Boaretto 2016, Quinlan-Jones 2019). This variant is reported in ClinVar (Variation ID: 454795) and is only observed on four alleles in the Genome Aggregation Database, indicating it is not a common polymorphism. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS

*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H-High, i-Test Information, L-Low, t-Interpretive Text, @=Performing lab

Unless otherwise indicated, testing performed at:

ARUP Laboratories

500 Chipeta Way, Salt Lake City, UT 84108

Laboratory Director: Tracy I. George, MD

ARUP Accession: 21-159-122511

Report Request ID: 15088103

Printed: 23-Jun-21 14:37

Page 1 of 4

Result Footnote

f1: Primary Ciliary Dyskinesia Interp
Genetic consultation is indicated, including a discussion of medical screening and management. Parental testing may be considered to determine whether the DNAH5 variants are on the same or opposite chromosomes (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). At-risk family members may consider targeted testing for the identified pathogenic variants (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS

Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics.
Likely benign and benign variants are not included in this report.

REFERENCES

Boaretto F et al. Diagnosis of primary ciliary dyskinesia by a targeted next-generation sequencing panel: molecular and clinical findings in Italian patients. J Mol Diagn. 2016;18(6):912-922.

This result has been reviewed and approved by [REDACTED]

Test Information

i1: Primary Ciliary Dyskinesia Interp
BACKGROUND INFORMATION: Primary Ciliary Dyskinesia Panel, Sequencing

CHARACTERISTICS: Primary ciliary dyskinesia (PCD, also known as Kartagener syndrome) is a rare inherited condition that results from an underlying defect in the structure or function of motile cilia, impacting multiple body systems. Patients with PCD typically first present with neonatal respiratory distress, chronic oto-sinopulmonary disease, and year-round wet coughing. Approximately half of patients with PCD will have a laterality defect such as situs inversus totalis or heterotaxy. PCD is also associated with infertility and ectopic pregnancy due to ciliary dysfunction.

PREVALENCE: Approximately 1 in 16,000

CAUSE: Pathogenic germline variants in genes associated with structure and function of the motile cilia

INHERITANCE: Autosomal recessive; rare X-linked recessive forms have been reported

PENETRANCE: 100 percent

GENES TESTED: ARMC4*, CCDC103*, CCDC114*, CCDC151, CCDC39, CCDC40*, CCDC65, CCNO, CFAP298*, DNAAF1, DNAAF2, DNAAF3, DNAAF4, DNAAF5*, DNAH1, DNAH11, DNAH5, DNAI1, DNAI2*, DNAL1, DRC1, GAS8, LRRC6, MCIDAS, NME8, PIH1D3, RSPH1, RSPH3, RSPH4A, RSPH9, SPAG1*, ZMYND10

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

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Page 2 of 4

Test Information

i1: Primary Ciliary Dyskinesia Interp
 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. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity of sequencing 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 diagnosis of primary ciliary dyskinesia. 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. 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:

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 exons(s) 4(Chr19:48822049-48822069)
 CCDC40(NM_001243342) exon(s) 18
 CFAP298(NM_001350335) partial exons(s) 5(Chr21:33975399-33975450)
 CFAP298(NM_001350337) partial exons(s) 6(Chr21:33974534-33974561)
 DNAAF5(NM_017802) exon(s) 1
 DNAI2(NM_001353167) exon(s) 13
 SPAG1(NM_001374321) partial exons(s) 11(Chr8:101225456-101225529)
 SPAG1(NM_003114) partial exons(s) 11(Chr8:101225456-101225529)
 SPAG1(NM_172218) partial exons(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.

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Page 3 of 4

Test Information

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

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Page 4 of 4