The HudsonAlpha CLINICAL SERVICES LAB

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CLIA #: 01D2086581 • CAP #: 8051488

FINAL REPORT

DEMOGRAPHICS

Patient Name: John Doe
Date of Birth: 01-01-1960
Race/Ethnicity: White
Sex: Male
Sample Collection Date: 01-02-2022
Sample Received Date: 01-03-2022
Specimen Type: Blood

Test Request Date: 01-03-2022
Accession Number: ABCDEFG
Provider Accession Number: 1837123
Test Ordered: Targeted Variant Sequencing
Ordering Physician: Dr. Gene
Date of Report: 01-28-2022
Report To: Dr. Gene

CLINICAL INDICATIONS

Prior testing of the patient's mother detected a heterozygous *TTN* c.92317C>T (p.Arg30773*) variant. We were requested to perform targeted sequencing for this familial variant in this individual. The patient's mother was tested as a positive control.

RESULTS

Gene (Transcript)	Genomic Coordinates	Variant	Result	Classification[1]
TTN (NM_001267550.2)	chr2:g.178549309G>A (GRCh38)	c.92317C>T (p.Arg30773*)	Heterozygous	Pathogenic

INTERPRETATION

The patient is heterozygous for a potentially clinically significant variant in *TTN*. Pathogenic variants in this gene are associated with dilated cardiomyopathy 1G (OMIM 604145). Dilated cardiomyopathy 1G arises from the presence of a single pathogenic variant in *TTN* (autosomal dominant inheritance).

The c.92317C>T variant in the *TTN* gene has been previously reported[2,3] and is present in ClinVar[4]. The c.92317C>T is a nonsense variant, which is predicted to result in loss of function in the *TTN* gene where loss of function is a known mechanism of dilated cardiomyopathy 1G (PVS1). The c.92317C>T variant occurs in a known mutational hot-spot within the A band[2] (PM1). The Genome Aggregation Database (gnomAD) reports that the c.92317C>T variant was observed in 1/152150 alleles for genome data[5]; consistent with the expected frequency of a pathogenic variant in dilated cardiomyopathy 1G (PM2). In summary, this collective evidence supports c.92317C>T as a pathogenic variant for dilated cardiomyopathy 1G.

Test results should be interpreted in the context of the individual's clinical presentation and family history. Genetic counseling is recommended to discuss the implications of the results. Genetic testing is available for at-risk relatives.

METHODOLOGY AND LIMITATIONS

This report describes the results of dideoxy (Sanger) sequence analysis only at the genomic loci stated in this report. Other regions of the gene and genome were not analyzed. Genomic coordinates refer to GRCh38. This test is designed to evaluate single nucleotide variants and small insertions or deletions within the human genome. This test is limited in its ability to detect mosaicism and chimerism; this test may not detect variants with less than 20% variant allele proportion. This technology is limited in its ability to accurately identify variants occurring in regions with high sequence identity to other regions of the genome (e.g. paralogous genes and pseudogenes). False positive, negative or misleading results may occur for reasons that include genetic variants, blood transfusions, bone marrow transplantation, erroneous representation of family relationship, or contamination of a specimen. The chance of a false negative or a false positive result due to laboratory error cannot be completely excluded.

Sanger sequencing testing was performed by the HudsonAlpha Clinical Services Lab, LLC. This test was developed, and the associated orthologous methods and performance characteristics were determined, by the HudsonAlpha Clinical Services Lab, LLC. It has not been cleared or approved by the U.S. Food and Drug

Administration. To date, the U.S. Food and Drug Administration has determined that such clearance or approval is not necessary. These tests are used for clinical purposes, and therefore validation was done as required under the requirements of the Clinical Laboratory Improvement Act of 1988 as a Laboratory Developed Test (LDT). These test results should not be regarded as investigational or for research.

The classification of variant pathogenicity was determined using guidelines from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology[1]. Please note that variant classification and/or interpretation may change over time if and when more information becomes available.

REFERENCES

[1]Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-24.

[2]Goli R, Li J, Brandimarto J, et al. Genetic and Phenotypic Landscape of Peripartum Cardiomyopathy. Circulation. 2021;143(19):1852-1862.

[3]Choi SH, Weng LC, Roselli C, et al. Association Between Titin Loss-of-Function Variants and Early-Onset Atrial Fibrillation. JAMA. 2018;320(22):2354-2364.

[4]https://www.ncbi.nlm.nih.gov/clinvar/variation/202424

[5]Karczewski KJ, Francioli LC, Tiao G, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020;581(7809):434-443.

LAB DIRECTOR SIGNATURE

Ghunwa Nakouzi, Ph.D, FACMG, Laboratory Director _____ Date _____

David Bick, M.D., FACMG, Associate Laboratory Director _____ Date _____