MAYO CLINIC

1-800-533-1710

Telomere Disorders Gene Panel

TELDP

PATIENT NAME				ORDER NUMBER
TESTRNV, IMPLEMENTATION				**M702000286**
PATIENT ID X100407768	DATE OF BIRTH 02/19/1968	AGE 54 Y	SEX Male	REQUESTED BY ATLAS TEST
COLLECTED 2/2/2023, 8:33 AM	RECEIVED 2/7/2023, 3:06 PM	REPORTED 2/24/2023, 4:47 PM		
The collected, received, and reported dates and times on the report are in the time zone of the performing location. 7028846 MCL RochesterCampus Rochester MN 55901				CLIENT ORDER NUMBER X100407768 CLIENT MRN 321

TEST DESCRIPTION

Evaluation of 18 genes associated with telomere biology disorders

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
TERT (NM_198253.2)	c.430G>A p.Val144Met (p.V144M) Chr5(GRCh37):g.1294571C>T	Heterozygous	Pathogenic

The following heterozygous PATHOGENIC variant was detected:
TERT (NM_198253.2), chr5(GRCh37):g.1294571C>T, c.430G>A, p.Val144Met (p.V144M)

No additional reportable variants were detected within all other tested genes. See the Genes Analyzed section for a complete list of genes evaluated by this assay.

INTERPRETATION

TERT c.430G>A (p.Val144Met), PATHOGENIC
The heterozygous c.430G>A (p.Val144Met) missense variant in the TERT gene (MIM:187270) is classified as pathogenic. The TERT gene encodes a component of the telomerase enzyme, which is responsible for maintenance of telomeres, protective structures found at the ends of chromosomes. Pathogenic variants in this gene have been associated with autosomal dominant and autosomal recessive forms of dyskeratosis congenita, autosomal dominant aplastic anemia, autosomal dominant telomere-related bone marrow failure, and autosomal dominant telomere-related pulmonary fibrosis. This variant has been previously reported in association with telomere-related pulmonary fibrosis, and functional studies demonstrate that this variant results in defective trafficking, which prevents localization of the protein to telomeres (1-6). In one study, the p.Val144Met variant accounted for 22.4% of cases in a cohort of patients with lung disease and TERT gene variants (2). This variant is absent from large control databases (7,8). Taken together, this evidence supports a pathogenic classification for this TERT gene variant. The finding of a pathogenic TERT variant is supportive of a diagnosis of telomere related pulmonary fibrosis for this individual but should be correlated with clinical findings. Appropriate screening and/or management strategies should be considered.

This result should be interpreted in the context of clinical findings, family history, and other laboratory testing.

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Consultation with a genetics professional is recommended for interpretation of this result and to determine whether reproductive risk assessment and familial testing may be of benefit to this family. Genetic testing for family members is available by ordering FMTT / Familial Mutation, Targeted Testing for the specific variant(s) detected. Please contact the laboratory at 1-800-533-1710 or the online test catalog at www.mayocliniclabs.com for information about FMTT.

REFERENCES:

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3) Garcia CK. Idiopathic pulmonary fibrosis: update on genetic discoveries. Proc Am Thorac Soc. 2011;8(2):158-162. doi:10.1513/pats.201008-056MS (PMID 21543794)
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5) Zhong FL, Batista LF, Freund A, Pech MF, Venteicher AS, Artandi SE. TPP1 OB-fold domain controls telomere maintenance by recruiting telomerase to chromosome ends. Cell. 2012;150(3):481-494. doi:10.1016/j.cell.2012.07.012 (PMID 22863003)
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7) dbSNP: www.ncbi.nlm.nih.gov/snp; Sherry ST, Ward M and Sirotkin K. dbSNP-Database for Single Nucleotide Polymorphisms and Other Classes of Minor Genetic Variation. Genome Res. 1999;9:677-679 (PMID 10447503)
8) gnomAD Browser: gnomad.broadinstitute.org/; Karczewski K, Francioli LC, MacArthur DG, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020; 581(7809):434-443 (PMID 32461654)

METHOD

Next generation sequencing (NGS) and/or Sanger sequencing was performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known pathogenic variants. NGS and/or a polymerase chain reaction (PCR)-based quantitative method was performed to test for the presence of deletions and duplications in the genes analyzed. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for indels less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. See the Genes Analyzed field for a list of genes tested.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria.

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See www.mayocliniclabs.com (TEST ID TELDP) for details regarding genes with regions not routinely covered.

GENES ANALYZED

ACD, CTC1, DKC1, LIG4, NAF1, NHP2, NOP10, PARN, POT1, RPA1, RTEL1, STN1, TERC, TERT, TINF2, USB1, WRAP53 and ZCCHC8

DISCLAIMER

Clinical Correlations
An online research opportunity called GenomeConnect (genomeconnect.org), a project of ClinGen, is available for the recipient of this genetic test. This patient registry collects de-identified genetic and health information to advance the knowledge of genetic variants. Mayo Clinic is a collaborator of ClinGen. This may not be applicable for all tests.

If testing was performed because of a clinically significant family history it is often useful to first test an affected family member. Detection of a reportable variant(s) in an affected family member would allow for more informative testing of at risk individuals.

To discuss the availability of further testing options or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted at 1-800-533-1710.

Technical Limitations
Next generation sequencing may not detect all types of genomic variants. In rare cases, false negative or false positive results may occur. The depth of coverage may be variable for some target regions, but assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria.

Additionally, low level mosaic variants may not be detected.

This test is not designed to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Please refer to the Targeted Genes and Methodology Details for the Telomere Disorders Gene Panel in the Special Instructions section of the Test Catalog for the most up to date list of genes included in this test.

Reclassification of Variants Policy

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See www.mayocliniclabs.com (TEST ID TELDP) for information regarding the laboratory's policy for reclassification of variants.

Variant Evaluation
Variant curation is performed using published ACMG-AMP recommendations as a guideline. Other gene-specific guidelines may also be considered. Variants classified as benign or likely benign are not reported.

Results from in silico evaluation tools may change over time and should be interpreted with caution and professional clinical judgment.

TEST CLASSIFICATION
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

RELEASED BY

Ann Marie Moyer, M.D., Ph.D.

Code : MCR Laboratory : Mayo Clinic Laboratories - Rochester Main Campus Address : 200 FIRST STREET SW
Lab Director : WILLIAM MORICE MD, PHD CLIA Certificate : 24D0404292 ROCHESTER MN 55905