



PATIENT NAME TESTRNV, IMPLEMENTATION				ORDER NUMBER M312000324
PATIENT ID X100399590	DATE OF BIRTH 02/19/1968	AGE 54 Y	SEX Male	REQUESTED BY CLIENT TEST
COLLECTED 10/12/2022, 7:33 AM	RECEIVED 10/13/2022, 3:34 PM	REPORTED 10/17/2022, 2:05 PM		
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TEST DESCRIPTION

Evaluation of 7 genes associated with Emery-Dreifuss muscular dystrophy

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
LMNA (NM_170707.3)	c.1583C>G p.Thr528Arg (p.T528R) chr1(GRCh37):g.156106998C>G	heterozygous	LIKELY PATHOGENIC

The following heterozygous **LIKELY PATHOGENIC** variant was detected:
LMNA (NM_170707.3), chr1(GRCh37):g.156106998C>G, c.1583C>G, p.Thr528Arg (p.T528R)

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

LMNA c.1583C>G (p.Thr528Arg), **LIKELY PATHOGENIC**

The heterozygous c.1583C>G (p.Thr528Arg) missense variant in the LMNA gene (MIM:150330) is classified as likely pathogenic. Pathogenic variants in the LMNA gene have been associated with both autosomal dominant and autosomal recessive forms of Emery-Dreifuss muscular dystrophy, autosomal recessive mandibuloacral dysplasia, and autosomal dominant dilated cardiomyopathy, familial partial lipodystrophy, Malouf syndrome, congenital muscular dystrophy, and limb-girdle muscular dystrophy. This variant occurs in a known mutational hotspot (1). This variant has been reported in several patients with Emery-Dreifuss muscular dystrophy (2-4). Additionally, the c.1583C>G variant was found to track with disease in a family with Emery-Dreifuss muscular dystrophy (5). However, functional studies have not been performed to either support or refute the pathogenicity of this variant. This variant is absent from large control databases (6,7). Due to the multiple established inheritance patterns for the condition(s) associated with this gene, this result is supportive of either carrier status for, or a diagnosis of, a LMNA-related disorder for this individual. Clinical correlation is recommended.

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

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



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laboratory at 1-800-533-1710 or the online test catalog at www.mayocliniclabs.com for information about FMTT.

REFERENCES:

- 1) Scharner J, Lu HC, Fraternali F, Ellis JA, Zammit PS. Mapping disease-related missense mutations in the immunoglobulin-like fold domain of lamin A/C reveals novel genotype-phenotype associations for laminopathies. *Proteins*. 2014;82(6):904-915. doi:10.1002/prot.24465 (PMID 24375749)
- 2) Vytöpi M, Benedetti S, Ricci E, et al. Mutation analysis of the lamin A/C gene (LMNA) among patients with different cardiomyopathy phenotypes. *J Med Genet*. 2003;40(12):e132. doi:10.1136/jmg.40.12.e132 (PMID 14684700)
- 3) Park HJ, Jang H, Kim JH, et al. Discovery of pathogenic variants in a large Korean cohort of inherited muscular disorders. *Clin Genet*. 2017;91(3):403-410. doi:10.1111/cge.12826 (PMID 27363342)
- 4) Lee Y, Lee JH, Park HJ, Choi YC. Early-Onset LMNA-Associated Muscular Dystrophy with Later Involvement of Contracture. *J Clin Neurol*. 2017;13(4):405-410. doi:10.3988/jcn.2017.13.4.405 (PMID 29057633)
- 5) Zhang L, Shen H, Zhao Z, Bing Q, Hu J. Cardiac effects of the c.1583 C→G LMNA mutation in two families with Emery-Dreifuss muscular dystrophy. *Mol Med Rep*. 2015;12(4):5065-5071. doi:10.3892/mmr.2015.4065 (PMID 26165385)
- 6) 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)
- 7) 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. 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. 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. 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. See www.mayocliniclabs.com (TEST ID EDMDP) for details regarding genes with regions not routinely covered.

GENES ANALYZED

EMD, FHL1, LMNA, SUN1, SUN2, SYNE1 and TMEM43

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.



1-800-533-1710

Emery-Dreifuss Gene Panel

EDMDP

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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 Emery-Dreifuss 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

See www.mayocliniclabs.com (TEST ID EDMDP) 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.

PATIENT NAME	TESTRNV, IMPLEMENTATION	22-40891
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1-800-533-1710
Emery-Dreifuss Gene Panel

EDMDP

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