



1-800-533-1710

Whole Exome Sequencing Panel Reflex

WESPR

PATIENT NAME IMPLEMENTATION, TEST T					ORDER NUMBER 0812000951
PATIENT ID X100482776	DATE OF BIRTH 05/01/1973	AGE 51 Y	SEX Female	REQUESTED BY CLIENT TESTING	
COLLECTED 11/12/2024, 7:00 AM	RECEIVED 11/13/2024, 8:12 AM	REPORTED 11/14/2024, 12:13 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 X100482776 CLIENT MRN 321

SPECIMEN

WB Whole Blood

INTERPRETATION

A full copy of the interpretative report is available as a PDF appended to this cover sheet and is ready to review.

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.

A portion of the testing process was performed at Mayo Clinic Laboratories site #322287, #440046.

RELEASED BY

Cherisse A. Marcou, Ph.D.

Code : MCR Laboratory : Mayo Clinic Laboratories - Rochester Main Campus

Lab Director : NIKOLA A BAUMANN

PHD

CLIA Certificate : 24D0404292

Address : 200 FIRST STREET SW

ROCHESTER MN 55905

IMPLEMENTATION, TEST T

Patient ID: 24-53640 | Family ID: F6363 | Date of birth: 5/1/1973 (51 years old) | Female | Order number: O812000951

Requested by: TESTING, CLIENT
Requesting Institution: 7028846 | MCL
Rochester Campus | Rochester, MN 55901Client MRN: 321
Client Order Number: X100482776Collected: 11/12/2024 7:00 AM
Received: 11/13/2024 8:12 AM
Report Generated: 11/14/2024
Specimen: Whole Blood

Clinical Information Summary

Indication for Testing:

Aortic dissection, Tall stature, Pectus excavatum

No comparator samples were submitted for analysis.

Results Summary

A consultation with a genetics professional is recommended. Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Evaluation for additional features and appropriate screening and/or management measures should be considered.

RESULTS

Likely Causative

Likely Pathogenic	SMAD3	NM_005902.4 c.278G>A, p.Arg93Gln Associated Condition: Loeys-Dietz syndrome 3, Autosomal dominant	Inherited from Unknown	Zygosity Het

Possibly Relevant

No reportable possibly relevant variants were identified.

Secondary Findings (v3.2)

No reportable secondary findings were identified.

INTERPRETATION

Likely Causative

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Likely Pathogenic | SMAD3: c.278G>A, p.Arg93Gln

NM_005902.4 | chr15:g.67457304G>A (hg19)

Zygosity	Proband: Het
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The heterozygous c.278G>A (p.Arg93Gln) missense variant in the SMAD3 gene (MIM:603109) is classified as likely pathogenic. Pathogenic variants in the SMAD3 gene have been associated with autosomal dominant Loeys-Dietz syndrome 3. This condition is characterized by aneurysms and tortuosity of the cerebral, thoracic, and/or abdominal arteries, osteoarthritis, and mild craniofacial features (1).

This variant occurs in a moderately constrained region of the gene in an established functional domain known to be involved in DNA binding, MH1(2,3). The c.278G>A (p.Arg93Gln) variant has been reported previously in a 47 year old individual with aortic dissection involving the ascending aortic arch (4). Functional studies have not been performed. This variant has been reported in ClinVar (Variation ID: 213800). This variant is absent from large control databases (5,6). This amino acid is highly conserved across species and an in silico meta-predictor suggests that this amino acid change may impact protein function.

This result is supportive of a diagnosis of autosomal dominant Loeys-Dietz syndrome 3 for this individual. Clinical correlation is recommended. Testing is available for other family members, if desired (FMTT / Familial Variant, Targeted Testing).

REFERENCES:

- 1) GeneReviews: Loeys-Dietz Syndrome (<https://www.ncbi.nlm.nih.gov/books/NBK1133/>) (PMID: 20301312)
- 2) Regalado ES, Guo DC, Villamizar C, et al. Exome sequencing identifies SMAD3 mutations as a cause of familial thoracic aortic aneurysm and dissection with intracranial and other arterial aneurysms. Circ Res. 2011;109(6):680-686. doi:10.1161/CIRCRESAHA.111.248161 (PMID 21778426)
- 3) Chai J, Wu JW, Yan N, Massagué J, Pavletich NP, Shi Y. Features of a Smad3 MH1-DNA complex. Roles of water and zinc in DNA binding. J Biol Chem. 2003;278(22):20327-20331. doi:10.1074/jbc.C300134200 (PMID 12686552)
- 4) Weerakkody R, Ross D, Parry DA, et al. Targeted genetic analysis in a large cohort of familial and sporadic cases of aneurysm or dissection of the thoracic aorta. Genet Med. 2018;20(11):1414-1422. doi:10.1038/gim.2018.27 (PMID 29543232)
- 5) dbSNP: www.ncbi.nlm.nih.gov/snp/
- 6) gnomAD Browser: gnomad.broadinstitute.org/

Possibly Relevant

No reportable variants in genes possibly relevant to the patient's reported clinical features were identified.

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No reportable secondary findings were identified in the medically actionable genes analyzed in accordance with ACMG recommendations. Whole Exome Sequencing is not specifically designed to rule out all pathogenic variants in this list of genes. If there is clinical suspicion for a condition caused by one of these genes, focused genetic testing may be indicated.

Method

Next generation sequencing (NGS) is performed on DNA extracted from the patient and all submitted comparator samples to test for the presence of variants in coding regions and intron/exon boundaries. The human genome reference GRCh37/hg19 build is used for sequence read alignment. Variants are called using an optimized bioinformatics package (Sentieon). 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 deletion-insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. This assay also detects most copy number variants (deletions/duplications) involving three or more exons. In some instances, resolution of copy number variants less than three exons may be detected, however the reliability of this detection is variable due to isolated reduction in sequence coverage or inherent genomic complexity. Resulting variants are filtered, annotated using public and proprietary resources, and presented for analysis and interpretation using a vended interpretation tool, Franklin by Genoox. Confirmation of select reportable variants in the proband and submitted comparator samples may be performed by alternate methodologies based on internal laboratory criteria.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences.

Disclaimer

CLINICAL CORRELATIONS

This report contains variants in genes related to the patient's reported clinical features. The interpretation is based upon the clinical information reported by the ordering health care provider(s) at the time of testing. Misinterpretation of results may occur if the clinical information provided is inaccurate or incomplete. Patient age, as indicated on the cover sheet, reflects age at sample collection; patient age on the report header (after the cover sheet) reflects age at time of reporting.

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Familial segregation analysis may help inform the clinical significance of reported variants. 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.

Previously reported variants in this patient may not be re-reported or detected for any of the following reasons: insufficient phenotypic overlap, minor allele frequency greater than 1%, outside of the capture region for this assay, genotype quality filters, and/or the variant is currently classified as likely benign or benign.

It is possible that a variant may not be recognized as the underlying cause of disease due to incomplete scientific knowledge about the function of all genes in the human genome and/or the impact of variants in those genes. Deidentified variant information may be shared in public genetic databases, such as GeneMatcher or ClinVar.

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 regions. 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 by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is not designed to detect deep intronic variants, trinucleotide repeat variants, balanced structural rearrangements (such as translocations and inversions), or variants in the mitochondrial genome. If separate mitochondrial genome testing is desired, please order Mitochondrial Full Genome Analysis by Next-Generation Sequencing (MITOP).

This test is not designed to detect low levels of mosaicism or 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.

If the patient has had an allogeneic marrow transplant or a recent heterologous blood transfusion, these results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

SECONDARY FINDINGS

Patients are evaluated for medically actionable secondary findings as recommended by the published ACMG guidelines unless they opt-out. Refer to the results and interpretation sections of the report for the ACMG secondary findings gene

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list version used at the time of testing. Reportable variants include pathogenic variants and likely pathogenic variants. Variants of uncertain significance (VUS) in these genes are not reported unless they overlap with the patient's phenotype. Presence of the variant in comparator samples is stated, unless they opt-out of secondary findings. Variants that are present in a family member but absent from the proband are not evaluated.

The absence of a reportable secondary finding does not guarantee that there are no known or expected pathogenic variants in these genes, as portions of the genes may not be adequately covered by this testing methodology. If a patient opts-out of receiving these results, these variants will not be reported unless they occur in a gene that is clinically related to the patient's presenting phenotype.

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.

RECLASSIFICATION OF VARIANTS

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

EXOME REANALYSIS

Healthcare providers may contact the laboratory at 800-533-1710 any time to request reanalysis of the patient's exome; a charge may apply for reanalysis.

We cannot guarantee that patient data will be stored indefinitely. Reanalysis may not be possible and a new whole exome sequencing order may be required if the original patient data is no longer available or no longer compatible with current bioinformatics processes or analysis tools.

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

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Performing Site Legend

Code	Laboratory	Address	Lab Director	CLIA Certificate
MCR	Mayo Clinic Laboratories – Rochester Main Campus	200 First Street SW, Rochester, MN 55905	Nikola A. Baumann Ph.D.	24D0404292