MAYO CLINIC

1-800-533-1710

CDA Sequencing, NGS

NCDA

PATIENT NAME				ORDER NUMBER
TESTINGRNV, NCDA				**M618000235**
PATIENT ID SA00157223	DATE OF BIRTH 01/01/1981	AGE 42 Y	SEX Male	REQUESTED BY CLIENT CLIENT
COLLECTED 1/17/2023, 12:00 AM	RECEIVED 1/18/2023, 3:40 PM	REPORTED 1/23/2023, 3:19 PM		
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TEST DESCRIPTION

Evaluation of 6 genes associated with congenital dyserythropoietic anemia

SPECIMEN

WB Whole Blood

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
SEC23B NM_001172745.3	c.325G>A p.Glu109Lys (p.E109K) Chr20(GRCh37):g.18496339G>A	heterozygous	PATHOGENIC

The following heterozygous PATHOGENIC variant was detected:
SEC23B (NM_001172745.3), chr20(GRCh37):g.18496339G>A, c.325G>A, p.Glu109Lys (p.E109K)

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

INTERPRETATION

SUMMARY
A heterozygous missense variant in the SEC23B gene (MIM:610512) was detected and is classified as pathogenic. This result is supportive of carrier status for congenital dyserythropoietic anemia, type II. However, the presence of an undetectable second variant cannot be ruled out. Clinical correlation is recommended.

SEC23B GENE AND VARIANT DETAILS
SEC23B encodes for an essential protein in the COPII-coated vesicles that bud from the endoplasmic reticulum to export proteins to the Golgi complex. Clinically significant alterations in SEC23B are associated with congenital dyserythropoietic anemia, type II (OMIM 224100, autosomal recessive) which is characterized by ineffective erythropoiesis, and bi- or multinucleated bone marrow erythroblasts. Affected individuals present with mild to moderate anemia, jaundice, progressive splenomegaly, and iron overload.

SEC23B c.325G>A, p.(Glu109Lys): The heterozygous c.325G>A (p.Glu109Lys) missense variant in the in the SEC23B gene is classified as pathogenic. This alteration is one of the most common pathogenic mutations in CDA type II, having been found in many unrelated individuals (1-4), and was demonstrated to produce less than 5% of detectable protein compared to wild type.(1) The overall minor allele frequency for this variant is approximately 0.022% with a frequency up to 0.039% in European sub-populations.(5,6) Based on the available information, this variant is interpreted as pathogenic.

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Individuals may have a pathogenic variant in one of the interrogated genes that is not detectable by the methods utilized. Additionally, the clinical phenotype that is observed in this individual and/or family may be due to a pathogenic variant or variants in another gene not targeted by this test.

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

COMMENT
If additional testing for another cause of hemolysis is desired and hemoglobin disorders have not been excluded, consider ordering THEV1 / Thalassemia and Hemoglobinopathy Evaluation.

REFERENCES:
1) Schwarz K, Iolascon A, Verissimo F, et al. Mutations affecting the secretory COPII coat component SEC23B cause congenital dyserythropoietic anemia type II. Nat Genet. 2009;41(8):936-940. doi:10.1038/ng.405 (PMID 19561605)
2) Fermo E, Bianchi P, Notarangelo LD, et al. CDAII presenting as hydrops foetalis: molecular characterization of two cases. Blood Cells Mol Dis. 2010;45(1):20-22. doi:10.1016/j.bcmd.2010.03.005 (PMID 20381388)
3) Amir A, Dgany O, Krasnov T, et al. E109K is a SEC23B founder mutation among Israeli Moroccan Jewish patients with congenital dyserythropoietic anemia type II. Acta Haematol. 2011;125(4):202-207. doi:10.1159/000322948 (PMID 21252497)
4) Russo R, Gambale A, Esposito MR, et al. Two founder mutations in the SEC23B gene account for the relatively high frequency of CDA II in the Italian population. Am J Hematol. 2011;86(9):727-732. doi:10.1002/ajh.22096 (PMID 21850656)
5) 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)
6) 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

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

GENES ANALYZED

CDAN1, CDIN1 (C15orf41), GATA1, KIF23, KLF1 and SEC23B

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.

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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.

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Genes may be added or removed based on updated clinical relevance. Please refer to the Targeted Genes and Methodology Details for the CDA Sequencing, NGS 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 NCDA) 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
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