MAYO CLINIC

1-800-533-1710

ADAMTS13 Gene, Full Gene NGS

GNADM

PATIENT NAME				ORDER NUMBER
GNADM, ABNORMAL				**M724000364**
PATIENT ID SA00158416	DATE OF BIRTH 12/12/1963	AGE 59 Y	SEX Female	REQUESTED BY CLIENT CLIENT
COLLECTED 2/23/2023, 12:00 AM	RECEIVED 2/24/2023, 2:38 PM	REPORTED 3/1/2023, 2:44 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
SA00158416

CLIENT MRN
SA00158416

TEST DESCRIPTION

Evaluation of the ADAMTS13 gene associated with hereditary thrombotic thrombocytopenic purpura.

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
ADAMTS13 NM_139025.4	c.4143dupA p.Glu1382Argfs*6 Chr9:g.136324161dup	heterozygous	PATHOGENIC

The following heterozygous PATHOGENIC variant was detected:
ADAMTS13 (NM_139025.4), chr9(GRCh37):g.136324161dup, c.4143dupA, p.Glu1382Argfs*6 (p.E1382Rfs*6)

INTERPRETATION

ADAMTS13 c.4143dup (p.Glu1382Argfs*6), PATHOGENIC
The heterozygous c.4143dup (p.Glu1382Argfs*6) duplication in the ADAMTS13 gene (MIM:604134) is classified as pathogenic. Pathogenic variants in the ADAMTS13 gene have been associated with autosomal recessive thrombotic thrombocytopenic purpura (TTP). This variant has been reported as both homozygous and compound heterozygous in many unrelated individuals with a clinical diagnosis of hereditary thrombotic thrombocytopenic purpura (TTP) (1-6). Furthermore, functional studies have been performed to support the pathogenicity of this variant. Functional studies demonstrate this truncating alteration impairs protein secretion and results in reduced ADAMTS13 protease activity levels in vitro (2,4,7,8). This alteration is observed in the large population genetics database gnomAD in the heterozygous state in 19 out of 64,051 European (non-Finnish) individuals (minor allele frequency [MAF] = 0.01%) and not in any other population. (9,10). This result is supportive of carrier status for thrombotic thrombocytopenic purpura (TTP). However, the presence of an undetectable second variant cannot be ruled out. Clinical correlation is recommended.

Individuals may have a pathogenic variant in the ADAMST13 gene that is not detectable by the methods utilized. Additionally, pathogenic variants in other genes not interrogated by this assay may cause a similar phenotype.

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

PATIENT NAME				ORDER NUMBER
GNADM, ABNORMAL				**M724000364**
PATIENT ID SA00158416	DATE OF BIRTH 12/12/1963	AGE 59 Y	SEX Female	REQUESTED BY CLIENT CLIENT
COLLECTED 2/23/2023, 12:00 AM	RECEIVED 2/24/2023, 2:38 PM	REPORTED 3/1/2023, 2:44 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 SA00158416 CLIENT MRN SA00158416

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:

1) Schneppenheim R, Budde U, Oyen F, et al. von Willebrand factor cleaving protease and ADAMTS13 mutations in childhood TTP. Blood. 2003;101(5):1845-1850. doi:10.1182/blood-2002-08-2399 (PMID 12393505)
2) Pimanda JE, Maekawa A, Wind T, Paxton J, Chesterman CN, Hogg PJ. Congenital thrombotic thrombocytopenic purpura in association with a mutation in the second CUB domain of ADAMTS13. Blood. 2004;103(2):627-629. doi:10.1182/blood-2003-04-1346 (PMID 14512317)
3) Schneppenheim R, Kremer Hovinga JA, Becker T, et al. A common origin of the 4143insA ADAMTS13 mutation. Thromb Haemost. 2006;96(1):3-6. doi:10.1160/TH05-12-0817 (PMID 16807643)
4) Hassenpflug WA, Obser T, Bode J, et al. Genetic and Functional Characterization of ADAMTS13 Variants in a Patient Cohort with Upshaw-Schulman Syndrome Investigated in Germany. Thromb Haemost. 2018;118(4):709-722. doi:10.1055/s-0038-1637749 (PMID 29554699)
5) van Dorland HA, Taleghani MM, Sakai K, et al. The International Hereditary Thrombotic Thrombocytopenic Purpura Registry: key findings at enrollment until 2017. Haematologica. 2019;104(10):2107-2115. doi:10.3324/haematol.2019.216796 (PMID 30792199)
6) Kentouche K, Budde U, Furlan M, Scharfe V, Schneppenheim R, Zintl F. Remission of thrombotic thrombocytopenic purpura in a patient with compound heterozygous deficiency of von Willebrand factor-cleaving protease by infusion of solvent/detergent plasma. Acta Paediatr. 2002;91(10):1056-1059. doi:10.1080/080352502760311548 (PMID 12434890)
7) Shang D, Zheng XW, Niiya M, Zheng XL. Apical sorting of ADAMTS13 in vascular endothelial cells and Madin-Darby canine kidney cells depends on the CUB domains and their association with lipid rafts. Blood. 2006;108(7):2207-2215. doi:10.1182/blood-2006-02-002139 (PMID 16597588)
8) Garagiola I, Valsecchi C, Lavoretano S, Oren H, Bohm M, Peyvandi F. Nonsense-mediated mRNA decay in the ADAMTS13 gene caused by a 29-nucleotide deletion. Haematologica. 2008;93(11):1678-1685. doi:10.3324/haematol.13102 (PMID 18835837)
9) 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)
10) 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 gene 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 >30X. Sensitivity is estimated

PATIENT NAME				ORDER NUMBER
GNADM, ABNORMAL				**M724000364**
PATIENT ID SA00158416	DATE OF BIRTH 12/12/1963	AGE 59 Y	SEX Female	REQUESTED BY CLIENT CLIENT
COLLECTED 2/23/2023, 12:00 AM	RECEIVED 2/24/2023, 2:38 PM	REPORTED 3/1/2023, 2:44 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 SA00158416 CLIENT MRN SA00158416

at >99% for single nucleotide variants, >94% for indels up to 39 base pairs, >95% for deletions up to 75 base pairs and insertions up to 47 base pairs. NGS and/or a PCR-based quantitative method was performed to test for the presence of deletions and duplications in the gene analyzed. See the Genes Analyzed field for a list of gene(s) 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 GNADM) for details regarding genes with regions not routinely covered.

GENES ANALYZED

ADAMST13

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.

PATIENT NAME				ORDER NUMBER
GNADM, ABNORMAL				**M724000364**
PATIENT ID SA00158416	DATE OF BIRTH 12/12/1963	AGE 59 Y	SEX Female	REQUESTED BY CLIENT CLIENT
COLLECTED 2/23/2023, 12:00 AM	RECEIVED 2/24/2023, 2:38 PM	REPORTED 3/1/2023, 2:44 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 SA00158416 CLIENT MRN SA00158416

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.

Reclassification of Variants Policy
See www.mayocliniclabs.com (TEST ID GNADM) 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
SHANDA VOELTZ

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