MAYO CLINIC

1-800-533-1710

Erythrocytosis Full Panel, NGS

NHEP

PATIENT NAME				ORDER NUMBER
TESTINGRNV, NHEP				**M618000223**
PATIENT ID SA00157219	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, 11:35 AM	REPORTED 1/23/2023, 2:40 PM		
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TEST DESCRIPTION

Evaluation of 24 genes associated with hereditary erythrocytosis

SPECIMEN

WB Whole Blood

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
EPAS1 (HIF2A) NM_001430.5	c.1609G>A p.Gly537Arg (p.G537R) Chr2(GRCh37):g.46607420G>A	heterozygous	PATHOGENIC

The following heterozygous PATHOGENIC variant was detected:
EPAS1 (HIF2A) (NM_001430.5), chr2(GRCh37):g.46607420G>A, c.1609G>A, p.Gly537Arg (p.G537R)

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 EPAS1 gene (MIM:603349) was detected and is classified as pathogenic. This result is supportive of a diagnosis of autosomal dominant familial erythrocytosis type 4 for this individual. Clinical correlation is recommended.

EPAS1 GENE AND VARIANT DETAILS
EPAS1 encodes for the alpha subunit of the hypoxia-inducible factor (HIF)-2a transcription factor, a positive effector in the oxygen-sensing pathway. HIF2a is tightly regulated by hydroxylation by PHD2 and subsequent degradation by von Hippel Lindau complex proteins. Clinically significant gain of function alterations in EPAS1 are associated with familial erythrocytosis type 4 (ECYT4; OMIM 611783, autosomal dominant).(1,2) Rare de novo cases have been reported. Patients have increased hemoglobin but are otherwise typically asymptomatic although individuals with thrombosis and pulmonary hypertension have been reported. Some alterations in EPAS1 have been implicated in the occurrence of neuroendocrine tumors with and without polycythemia.(3)

EPAS1 c.1609G>A, p.(Gly537Arg): The heterozygous c.1609G>A (p.Gly537Arg) missense variant in the in the EPAS1 gene is classified as pathogenic. It has been reported in association with familial erythrocytosis type 4 (ECYT4; OMIM 611783) and is a common pathogenic variant in the HGMD database.(4-9) It is seen in a highly conserved amino acid in the oxygen dependent degradation domain of HIF2A. Several studies have shown cosegregation of the variant with the

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disease in affected family members, including a four-generation pedigree.(4)(7)(9) Functional studies further demonstrate the variant's effect on stabilizing the HIF2A protein.(7,8)(10) This variant is absent from large control databases.(11,12) Based on the available information, this variant is interpreted as pathogenic.

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 erythrocytosis is desired and hemoglobin disorders have not been excluded, consider ordering REVE2 / Erythrocytosis Evaluation.

REFERENCES:
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2) Gangat N, Oliveira JL, Porter TR, et al. Erythrocytosis associated with EPAS1(HIF2A), EGLN1(PHD2), VHL, EPOR or BPGM mutations: The Mayo Clinic experience. Haematologica. 2022;107(5):1201-1204. Published 2022 May 1. doi:10.3324/haematol.2021.280516 (PMID 35142155)
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5) Oliveira JL, Coon LM, Frederick LA, et al. Genotype-Phenotype Correlation of Hereditary Erythrocytosis Mutations, a single center experience [published online ahead of print, 2018 May 23]. Am J Hematol. 2018;10.1002/ajh.25150. doi:10.1002/ajh.25150 (PMID 29790589)
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9) Liu Q, Tong D, Liu G, et al. HIF2A germline-mutation-induced polycythemia in a patient with VHL-associated renal-cell carcinoma [published correction appears in Cancer Biol Ther. 2018 Feb 1;19(2):139]. Cancer Biol Ther. 2017;18(12):944-947. doi:10.1080/15384047.2017.1394553 (PMID 29172931)
10) Furlow PW, Percy MJ, Sutherland S, et al. Erythrocytosis-associated HIF-2alpha mutations demonstrate a critical role

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for residues C-terminal to the hydroxylacceptor proline. J Biol Chem. 2009;284(14):9050-9058. doi:10.1074/jbc.M808737200 (PMID 19208626)
11) 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)
12) 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. See www.mayocliniclabs.com (TEST ID NHEP) for details regarding genes with regions not routinely covered.

GENES ANALYZED

ACO1, ANKRD26, BHLHE41, BPGM, CYB5A, CYB5R3, EGLN1, EGLN2, EGLN3, EPAS1, EPO, EPOR, GFI1B, HIF1A, HIF1AN, HIF3A, JAK2, KDM6A, PFKM, PIEZO1, PKLR, SH2B3, SOCS3 and VHL

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

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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 Erythrocytosis Full Panel, 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 NHEP) 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
MATTHEW BAYERKOHLER

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