MAYO CLINIC

1-800-533-1710

PKLR Full Gene Analysis

PKLRZ

PATIENT NAME				ORDER NUMBER
BATCHTESTING, MELINDA				**O604000514**
PATIENT ID 11256962	DATE OF BIRTH 02/23/1940	AGE 84 Y	SEX Female	REQUESTED BY CYBELE ABAD
COLLECTED 9/4/2024, 3:01 PM	RECEIVED 9/4/2024, 3:01 PM	REPORTED 9/5/2024, 1:48 PM		

The collected, received, and reported dates and times on the report are in the time zone of the performing location.

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TEST DESCRIPTION

Evaluation of PKLR gene associated with hereditary nonspherocytic hemolytic anemia and pyruvate kinase deficiency

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Likely Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
PKLR (NM_000298.6)	c.101-1G>A Chr1(GRCh37):g.155270072C>T	homozygous	LIKELY PATHOGENIC

The following LIKELY PATHOGENIC variant was detected:
PKLR (NM_000298.6), chr1(GRCh37):g.155270072C>T, c.101-1G>A, homozygous

INTERPRETATION

A homozygous splice variant in the PKLR gene was detected and is classified as likely pathogenic. This result is supportive of a diagnosis of autosomal recessive pyruvate kinase (PK) deficiency for this individual. Clinical correlation is recommended.

PKLR GENE AND VARIANT DETAILS
PKLR encodes for pyruvate kinase (PK), an enzyme that catalyzes the final step in glycolysis. Clinically significant alterations in PKLR cause chronic nonspherocytic hemolytic anemia due to pyruvate kinase deficiency (OMIM #266200, autosomal recessive). Most hemolytic anemias due to PK deficiency are associated with enzyme activity levels less than 40% of mean normal. However, some patients with clinically significant hemolysis can have normal or only mildly decreased PK enzyme activity, which paradoxically occurs in individuals with the most severe symptoms or after splenectomy. Carriers (heterozygotes) may show mildly decreased enzyme activity but are expected to be asymptomatic. PK deficiency carrier state may possibly exacerbate other RBC disorders, such as G6PD deficiency or Hb S trait.

PKLR c.101-1G>A: The homozygous c.101-1G>A splice variant in the PKLR gene (MIM:609712) is classified as likely pathogenic. This variant alters a canonical splice site. This variant has been reported in two patients in a compound heterozygous state with associated reduced PK enzyme activity and reticulocytosis(1,2). Furthermore, functional studies show this variant gives alternatively spliced mRNA carrying a premature stop codon, encoding a severely truncated PK and likely undergoing nonsense-mediated decay(3). This variant is absent from large control databases (4,5). Based on the available information, this variant is interpreted as likely pathogenic.

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This result should be interpreted in the context of clinical findings, family history, and other laboratory testing (e.g. (PK) enzyme activity assays (preferably as a part of EEEV1 / Red Blood Cell [RBC] Enzyme Evaluation, Blood)).

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.

REFERENCES:

1) Lenzner C, Nürnberg P, Jacobasch G, Gerth C, Thiele BJ. Molecular analysis of 29 pyruvate kinase-deficient patients from central Europe with hereditary hemolytic anemia. Blood. 1997;89(5):1793-1799. (PMID 9057665)
2) Lenzner C, Nürnberg P, Thiele BJ, et al. Mutations in the pyruvate kinase L gene in patients with hereditary hemolytic anemia. Blood. 1994;83(10):2817-2822. (PMID 8180378)
3) Maciak K, Jurkiewicz A, Strojny W, et al. PKLR mutations in pyruvate kinase deficient Polish patients: Functional characteristics of c.101-1G > A and c.1058delAAG variants. Blood Cells Mol Dis. 2024;107:102841. doi:10.1016/j.bcmd.2024.102841 (PMID 38581917)
4) 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)
5) 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)

ADDITIONAL INFORMATION

No patient information sheet provided.

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 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 PKLRZ) for details regarding genes with regions not routinely covered.

GENES ANALYZED

PATIENT NAME	BATCHTESTING, MELINDA	24-41004

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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.

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 PKLRZ) 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.

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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
BENJAMIN VANSTEINBURG

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