MAYO CLINIC

1-800-533-1710

Comprehensive Nephrology Gene Panel

NEPHP

PATIENT NAME				ORDER NUMBER
TESTINGRNV, NEPHP				**M008000187**
PATIENT ID SA00153595	DATE OF BIRTH 11/01/1990	AGE 31 Y	SEX Male	REQUESTED BY CLIENT CLIENT
COLLECTED 7/8/2022, 7:00 AM	RECEIVED 7/8/2022, 11:22 AM	REPORTED 7/14/2022, 12:02 PM		
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TEST DESCRIPTION

Evaluation of 302 genes associated with hereditary renal disease, including targeted assessment of haplotypes and risk alleles in the CFH, CD46, C5, and APOL1 genes.

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
PKD1 (NM_001009944.2)	p.N116Kfs*2 (p.Asn116Lysfs*2) c.348_352del Chr16(GRCh37):g.2169122_2169126del	Heterozygous	Pathogenic

The following heterozygous PATHOGENIC variant was detected: PKD1 (NM_001009944.2), Chr16 (GRCh37):g.2169122_2169126del, c.348_352del, p.Asn116Lysfs*2 (p.N116Kfs*2)

No additional reportable pathogenic variants, likely pathogenic variants, or variants of uncertain significance were detected within all other tested genes. See the Genes Analyzed section for a complete list of genes evaluated by the assay. See the Additional Results section for information on genetic risk factors assessed by this panel.

INTERPRETATION

PKD1 c.348_352del (p.Asn116Lysfs*2): The heterozygous c.348_352del (p.Asn116Lysfs*2) variant in the PKD1 gene (MIM: 601313) is classified as pathogenic. The PKD1 gene encodes polycystin-1, a protein which forms a complex with polycystin-2 and regulates multiple signaling pathways to maintain normal renal tubular structure and function. Pathogenic variants in this gene are associated with autosomal dominant polycystic kidney disease 1. This variant has been reported in several individuals with clinically diagnosed autosomal dominant polycystic kidney disease (ADPKD) (1-4), including one reportedly de novo occurrence (4). Other truncating variants in the PKD1 gene have been reported in association with ADPKD. This variant has not been observed in exome and/or genome sequencing data gathered from large, multi-ethnic cohorts, suggesting it is a rare variant (5-6). Taken together, this result is supportive of a diagnosis of autosomal dominant polycystic kidney disease type 1 (ADPKD1) for this individual. Clinical correlation is recommended.

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

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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) Garcia-Gonzalez MA, Jones JG, Allen SK, et al. Evaluating the clinical utility of a molecular genetic test for polycystic kidney disease. Mol Genet Metab. 2007;92(1-2):160-167. doi:10.1016/j.ymgme.2007.05.004 (PMID 17574468)
2)Xu D, Ma Y, Gu X, et al. Novel Mutations in the PKD1 and PKD2 Genes of Chinese Patients with Autosomal Dominant Polycystic Kidney Disease. Kidney Blood Press Res. 2018;43(2):297-309. doi:10.1159/000487899 (PMID 29529603)
3) Benson KA, Murray SL, Senum SR, et al. The genetic landscape of polycystic kidney disease in Ireland. Eur J Hum Genet. 2021;29(5):827-838. doi:10.1038/s41431-020-00806-5 (PMID 33454723)
4) Shi H, Niu W, Liu Y, et al. A novel monogenic preimplantation genetic testing strategy for sporadic polycystic kidney caused by de novo PKD1 mutation. Clin Genet. 2021;99(2):250-258. doi:10.1111/cge.13871 (PMID 33111320)
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)

ADDITIONAL RESULTS

MCP/CD46 RISK HAPLOTYPE-HETEROZYGOUS

This individual is heterozygous for the MCP/CD46 risk haplotype. The variants that comprise this risk haplotype are common in the general population, but in the context of additional pathogenic genetic and environmental factors, the presence of this risk haplotype is associated with an increased risk for development or progression of atypical hemolytic uremic syndrome. Clinical correlation with other genetic and laboratory findings is recommended. See Method for details. See www.mayocliniclabs.com (Test code NEPHP) for additional information regarding this result.

CFH-H3 RISK HAPLOTYPE-HETEROZYGOUS

This individual is heterozygous for the extended CFH-H3 risk haplotype. The variants that comprise this risk haplotype are common in the general population, but in the context of additional pathogenic genetic and environmental factors, the presence of this risk haplotype is associated with an increased risk for development or progression of atypical hemolytic uremic syndrome. Clinical correlation with other genetic and laboratory findings is recommended. See Method for details. See www.mayocliniclabs.com (Test code NEPHP) for additional information regarding this result.

C5 GENOTYPE-HETEROZYGOUS

This individual is heterozygous for the p.Arg885His variant in the C5 gene associated with poor response to eculizumab and potentially ravulizumab. Clinical correlation with other genetic and laboratory findings is recommended. See Method for details. See www.mayocliniclabs.com (Test code NEPHP) for additional information regarding this result.

APOL1 GENOTYPE-HOMOZYGOUS G2

This individual is homozygous for the G2 risk allele in the APOL1 gene. The G1 risk allele was not detected. This result suggests that this individual may be at an increased risk for development or progression of chronic kidney disease associated with these alleles. These alleles have been associated with increased risk for development or progression of

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nondiabetic chronic kidney diseases and in the setting of renal transplantation, donor APOL1 genotype may influence graft survival. Clinical correlation with other genetic and laboratory findings is recommended. See Method for details. See www.mayocliniclabs.com (Test code NEPHP) for additional information regarding this result.

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. 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. 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.
Reporting of the CD46 (NM_002389.4) (also known as the MCP gene) risk haplotype is based on the presence of the following variants: c.989-78G>A (rs1962149); c.-652A>G (rs2796267); c.-366A>G (rs2796268); c.1127+638G>A (rs859705); c.897T>C (rsID not available).

Reporting of the CFH(H3) (NM_000186.3) risk haplotype is based on the presence of the following variants: CFH (NM_000186.3) gene: c.-331C>T (rs3753394); c.1204C>T (rs1061170) ; c.2016A>G (rs3753396); c.2808G>T (rs1065489).

In addition, reporting of the CFH(H3) NM_000186.3 risk haplotype is based on the absence of the following variants: CFH (NM_000186.3) gene: c.184G>A (rs800292); c.2237-543G>A (rs1410996).

Reporting of C5 (NM_001735.2) variants associated with complement inhibitor resistance is based on the presence of the following variants: c.2653C>T, p.Arg885Cys (rs373359894); c.2654G>A, p.Arg885His (rs56040400).

Reporting of the APOL1 (NM_003661.3) G1 and G2 alleles is based on the presence of the following variants: G1 allele: c.1024A>G (p.Ser342Gly) (rs73885319) and c.1152T>G (p.Ile384Met) (rs60910145), G2 allele: c.1164_1169del (p.Asn388_Tyr389del) (rs1317778148).
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 NEPHP) for details regarding genes with regions not routinely covered.

GENES ANALYZED

ABCC6, ACE, ACTN4, ADAMTS13, ADCY10, AGT, AGTR1, AGXT, AHI1, ALG1, ALG8, ALG9, ALMS1, ALPL, ANKS6, ANLN, ANOS1, APOA1, APOE, APOL1 (Chr22(GRCh37):g.36661895-36661916 g.36662023-36662062 only), APRT, AP2S1, AQP2, ARHGAP24, ARHGDIA, ARL13B, ARL6, ATP6V0A4, ATP6V1B1, ATP7B, AVP, AVPR2, B9D1, B9D2, BBIP1, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7, BBS9, BICC1, BSND, C2, C2CD3, C3, C5 (Chr9

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(GRCh37):g.123759950-123759973 only), C8A, C8orf37, CA2, CACNA1D, CACNA1H, CASR, CC2D2A, CD151, CD2AP, CD46 (MCP), CEP104, CEP120, CEP164, CEP290, CEP41, CEP83, CFB, CFH, CFHR1, CFHR2, CFHR3, CFHR4, CFHR5, CFI, CHD7, CLCN5, CLCNKA, CLCNKB, CLDN16, CLDN19, CNNM2, COL4A1, COL4A3, COL4A4, COL4A5, COL4A6, COQ2, COQ6, COQ8B, CPLANE1, CRB2, CREBBP, CSPP1, CTNS, CUBN, CUL3, CYP11B1, CYP11B2, CYP24A1, CYP27B1, CYP2R1, DCDC2, DDX59, DGKE, DHCR7, DMP1, DNAJB11, DYNC2H1, DZIP1L, EGF, EMP2, ENPP1, EYA1, FAH, FAM20A, FAN1, FAT1, FGA, FGF20, FGF23, FGFR1, FGFR2, FN1, FOXI1, FOXP1, FRAS1, FREM1, FREM2, FXYD2, GALNT3, GANAB, GATA3, GLA, GLI3, GLIS2, GNA11, GPC3, GREB1L, GRHPR, GRIP1, GSN, HNF1B, HNF4A, HOGA1, HPRT1, HPSE2, HSD11B2, IFT122, IFT140, IFT172, IFT27, IFT43, IFT80, IFT81, INF2, INPP5E, INVS, IQCB1, ITGA3, ITGA8, ITGB4, JAG1, KANK2, KCNA1, KCNJ1, KCNJ10, KCNJ5, KIAA0556 (KATNIP), KIAA0586, KIAA0753, KIF12, KIF14, KIF7, KL, KLHL3, LAMA5, LAMB2, LMNA, LMX1B, LRIG2, LRP2, LRP5, LYZ, LZTFL1, MAGED2, MAGI2, MAPKBP1, MEFV, MKKS, MKS1, MMACHC, MOCOS, MYH9, MYO1E, NEK1, NEK8, NLRP3, NOTCH2, NPHP1, NPHP3, NPHP4, NPHS1, NPHS2, NR3C2, NUP107, NUP133, NUP160, NUP205, NUP85, NUP93, OCRL, OFD1, PAX2, PBX1, PCBD1, PDE6D, PDSS2, PHEX, PKD1, PKD2, PKHD1, PLCE1, PLCG2, PLG, PMM2, PODXL, PRKCSH, PRPS1, PTPRO, REN, ROBO2, RPGRIP1L, SALL1, SALL4, SARS2, SCARB2, SCLT1, SCNN1A, SCNN1B, SCNN1G, SDCCAG8, SEC61A1, SEC63, SGPL1, SIX1, SLC12A1, SLC12A3, SLC17A5, SLC22A12, SLC26A1, SLC2A2, SLC2A9, SLC34A1, SLC34A3, SLC3A1, SLC4A1, SLC4A4, N27, SLC5A1, SLC5A2, SLC6A19, SLC7A7, SLC7A9, SLC9A3R1, SLIT2, SMARCAL1, TBC1D8B, TBX18, TCTN1, TCTN2, TCTN3, THBD, TMEM107, TMEM138, TMEM216, TMEM231, TMEM237, TMEM67, TRAF3IP1, TRIM32, TRPC6, TRPM6, TSC1, TSC2, TTC21B, TTC8, TTR, UMOD, VDR, VHL, VIPAS39, VPS33B, WDR19, WDR35, WDR72, WDR73, WNK1, WNK4, WNT4, WT1, XDH, XPNPEP3, ZMPSTE24 and ZNF423

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.
The Comprehensive Nephrology Gene Panel does NOT include assessment or interpretation of the common APOE

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alleles e2, e3, or e4.
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 Comprehensive Nephrology Gene Panel 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 NEPHP) 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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