MAYO CLINIC

1-800-533-1710

Renal Stone/Electrolyte Gene Panel

RSCGP

PATIENT NAME				ORDER NUMBER
TESTINGRNV, RSCGP				**M007000489**
PATIENT ID SA00153574	DATE OF BIRTH 04/30/1992	AGE 30 Y	SEX Male	REQUESTED BY CLIENT CLIENT
COLLECTED 7/7/2022, 10:30 AM	RECEIVED 7/7/2022, 3:58 PM	REPORTED 7/14/2022, 12:27 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
SA00153574

CLIENT MRN
SA00153574

TEST DESCRIPTION

Evaluation of 72 genes associated with nephrocalcinosis, nephrolithiasis, and renal electrolyte imbalance.

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
CASR (NM_000388.2)	p.G509R (p.Gly509Arg) c.1525G>A Chr3(GRCh37):g.121994806G>A	Heterozygous	Pathogenic

The following heterozygous PATHOGENIC variant was detected: CASR (NM_000388.2), Chr3 (GRCh37):g.121994806G>A, c.1525G>A, p.Gly509Arg (p.G509R)

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

CASR c.1525G>A (p.Gly509Arg): The heterozygous c.1525G>A (p.Gly509Arg) variant in the CASR gene (MIM: 601199) in the CASR gene is classified as pathogenic. The CASR gene encodes the extracellular calcium-sensing receptor, a G-protein coupled receptor essential in regulating calcium homeostasis. Pathogenic variants in this gene are associated with multiple phenotypes with both autosomal dominant and autosomal recessive inheritance. Phenotype is determined by the functional impact of the CASR variant. Loss-of-function variants are associated with autosomal dominant familial hypocalciuric hypercalcemia (FHH) and autosomal recessive neonatal severe primary hyperparathyroidism (NSPHT). Variants leading to a dominant negative effect can cause autosomal dominant NSPHT. Lastly, gain-of-function variants are associated with autosomal dominant hyperparathyroidism.

This variant has been previously reported in association with familial hypocalciuric hypercalcemia (FHH) and was found to segregate with disease in multiple families (1-4). This variant has also been reported in the compound heterozygous state in association with neonatal severe primary hyperparathyroidism (NSPHT) (5-6). Lastly, one functional study indicates that this variant results in absent calcium-sensing receptor response, leading to hypercalcemia (4). This result is supportive of a diagnosis of autosomal dominant familial hypocalciuric hypercalcemia (FHH) for this individual. Clinical correlation is recommended.

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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.

REFERENCES:

1) Nissen PH, Christensen SE, Heickendorff L, Brixen K, Mosekilde L. Molecular genetic analysis of the calcium sensing receptor gene in patients clinically suspected to have familial hypocalciuric hypercalcemia: phenotypic variation and mutation spectrum in a Danish population. J Clin Endocrinol Metab. 2007;92(11):4373-4379. doi:10.1210/jc.2007-0322 (PMID 17698911)
2) Hureaux M, Ashton E, Dahan K, et al. High-throughput sequencing contributes to the diagnosis of tubulopathies and familial hypercalcemia hypocalciuria in adults. Kidney Int. 2019;96(6):1408-1416. doi:10.1016/j.kint.2019.08.027 (PMID 31672324)
3) Jakobsen NF, Rolighed L, Nissen PH, Mosekilde L, Rejnmark L. Muscle function and quality of life are not impaired in familial hypocalciuric hypercalcemia: a cross-sectional study on physiological effects of inactivating variants in the calcium-sensing receptor gene (CASR). Eur J Endocrinol. 2013;169(3):349-357. Published 2013 Aug 28. doi:10.1530/EJE-13-0224 (PMID 23764372)
4) Magno AL, Leatherbarrow KM, Brown SJ, Wilson SG, Walsh JP, Ward BK. Functional Analysis of Calcium-Sensing Receptor Variants Identified in Families Provisionally Diagnosed with Familial Hypocalciuric Hypercalcaemia. Calcif Tissue Int. 2020;107(3):230-239. doi:10.1007/s00223-020-00715-1 (PMID 32638038)
5) Kulkarni A, Mohite M, Vijaykumar R, Bansode P, Murade S, Tamhankar PM. Neonatal severe hyperparathyroidism due to compound heterozygous mutation of calcium sensing receptor (CaSR) gene presenting as encephalopathy. Indian J Pediatr. 2014;81(11):1228-1229. doi:10.1007/s12098-014-1442-3 (PMID 24763815)
6) Dong Q, Song F, Du M, Qiu M, Chen X. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2020;37(11):1247-1249. doi:10.3760/cma.j.cn511374-20191118-00587. (PMID 33179231)

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

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GENES ANALYZED

ABCC6, ADCY10, AGXT, ALPL, AP2S1, APRT, AQP2, ATP6V0A4, ATP6V1B1, ATP7B, AVP, AVPR2, BSND, CA2, CASR, CLCN5, CLCNKA, CLCNKB, CLDN16, CLDN19, CNNM2, CUL3, CYP11B1, CYP11B2, CYP24A1, CYP27B1, CYP2R1, DMP1, EGF, ENPP1, FAM20A, FGF23, FOXI1, FXYD2, GALNT3, GATA3, GNA11, GRHPR, HNF4A, HOGA1, HPRT1, KCNJ1, KCNJ5, KL, KLHL3, MAGED2, MOCOS, NR3C2, OCRL, PHEX, PRPS1, SCNN1A, SCNN1B, SCNN1G, SLC12A1, SLC12A3, SLC22A12, SLC26A1, SLC2A9, SLC3A1, SLC34A1, SLC34A3, SLC4A1, SLC4A4, SLC7A9, SLC9A3R1, TRPM6, UMOD, VDR, WNK1, WNK4 and XDH

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.

Genes may be added or removed based on updated clinical relevance. Please refer to the Targeted Genes and Methodology Details for the Renal Stone/Electrolyte Gene Panel in the Special Instructions section of the Test Catalog for

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the most up to date list of genes included in this test.

Reclassification of Variants Policy
See www.mayocliniclabs.com (TEST ID RSCGP) 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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