MAYO CLINIC LABORATORIES

Test Definition: CASRG

CASR Full Gene Sequencing with Deletion/Duplication, Varies

Overview

Useful For

Providing a genetic evaluation of individuals with a personal or family history of familial hypocalciuric hypercalcemia, neonatal severe primary hyperparathyroidism, or autosomal dominant hypoparathyroidism (autosomal dominant hypocalcemia)

Establishing a diagnosis of familial hypocalciuric hypercalcemia, neonatal severe primary hyperparathyroidism, or autosomal dominant hypoparathyroidism (autosomal dominant hypocalcemia)

As a part of the workup for patients with primary hyperparathyroidism, idiopathic hypoparathyroidism, and Bartter syndrome

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide, deletion-insertion, and copy number variants in the *CASR* gene, which is associated with autosomal dominant familial hypocalciuric hypercalcemia, autosomal dominant and autosomal recessive neonatal severe primary hyperparathyroidism, autosomal dominant hypocalcemia (hypoparathyroidism), and autosomal dominant hypocalcemia with Bartter syndrome. See Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for autosomal dominant familial hypocalciuric hypercalcemia, autosomal dominant and autosomal recessive neonatal severe primary hyperparathyroidism, autosomal dominant hypoparathyroidism (also known as autosomal dominant hypocalcemia), and autosomal dominant hypoparathyroidism with features of Bartter syndrome.

Special Instructions

- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Hereditary Renal Genetic Testing Patient Information

Method Name

Sequence Capture and Next-Generation Sequencing (NGS)

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

Testing for the *CASR* gene as part of a customized panel is available. For more information, see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Any anticoagulant
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot**.
Specimen Stability Information: Ambient (preferred)/Refrigerated

Forms

1. New York Clients-Informed consent is required. Document on the request form or electronic order that a copy is on file. The following documents are available:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing (Spanish) (T826)
2. Hereditary Renal Genetic Testing Patient Information (T918)

Specimen Minimum Volume

1 mL

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

The extracellular G-protein-coupled calcium-sensing receptor (CASR) is an essential component of calcium homeostasis. CASR is expressed at high levels in the parathyroid glands and kidneys. In the parathyroid glands, an increase in serum calcium results in downregulation of gene expression of the main short-term regulator of calcium homeostasis, parathyroid hormone (PTH), as well as diminished secretion of already synthesized PTH. At the same time, kidney calcium excretion is upregulated, and sodium chloride excretion is downregulated.(1) Both activating and inactivating genetic variants have been described in *CASR* and result in altered calcium sensing and subsequent inappropriate PTH release relative to serum calcium concentration.

Inactivating (loss-of-function) *CASR* variants result in undersensing of calcium concentrations and consequent PTH overproduction. This leads to either familial hypocalciuric hypercalcemia (FHH) or neonatal severe primary hyperparathyroidism (NSPHT), depending on the severity of the functional impairment. Except for a very small percentage of cases with no apparent *CASR* variants, FHH is due to heterozygous inactivating *CASR* variants. In FHH, serum calcium levels are mildly-to-moderately elevated, PTH may be normal or only modestly elevated, phosphate is normal or slightly low, and urinary calcium excretion is low for the degree of hypercalcemia.(1) Unlike patients with primary hyperparathyroidism, the majority of FHH patients do not seem to experience adverse long-term effects from hypercalcemia and elevated PTH levels. On the other hand, NSPHT is usually caused by homozygous or compound heterozygous inactivating *CASR* variants but can occasionally be caused by dominant-negative heterozygous variants.(1) NSPHT presents at birth, or shortly thereafter, with severe hypercalcemia requiring urgent parathyroidectomy.

Activating (gain-of-function) *CASR* variants lead to oversensing of calcium, resulting in suppression of PTH secretion and consequently hypoparathyroidism and hypocalcemia. This disorder is referred to as autosomal dominant hypocalcemia or autosomal dominant hypoparathyroidism. To date, all activating variants described are functionally dominant and inheritance is therefore autosomal dominant. However, sporadic (no known genetic etiology) cases also occur. Autosomal dominant hypoparathyroidism caused by *CASR* variants may account for many cases of idiopathic hypoparathyroidism. In addition, while the majority of patients exhibit only hypoparathyroidism, a small subgroup has extreme gain-of-function variants. These individuals may present with additional symptoms that are consistent with type V Bartter syndrome, including hypokalemic metabolic alkalosis, hyperreninemia, hyperaldosteronism, and hypomagnesemia.(1-2)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

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 in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact Mayo Clinic Laboratories genetic counselors at 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; 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 by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:
This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

This test is not designed to detect low levels of mosaicism or 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.

For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory Genetic Counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent heterologous blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants
At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages health care providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time.

Variant Evaluation

Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(3) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools are interpreted with caution and professional clinical judgement.

Rarely, incidental findings or secondary findings may implicate another predisposition or presence of active disease. Incidental findings may include, but are not limited to, results related to the sex chromosomes. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Vahe C, Benomar K, Espiard S, et al: Diseases associated with calcium-sensing receptor. Orphanet J Rare Dis. 2017 Jan 25;12(1):19. doi: 10.1186/s13023-017-0570-z
2. Roszko KL, Bi RD, Mannstadt M: Autosomal dominant hypocalcemia (hypoparathyroidism) Types 1 and 2. Front Physiol. 2016 Oct;7:458. doi: 10.3389/fphys.2016.00458
3. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing is performed to test for the presence of variants in coding regions and intron/exon boundaries of the *CASR* gene, as well as some other regions that have known disease-causing 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 deletions-insertions (delins) 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-based quantitative method is performed to test for the presence of deletions and duplications in the *CASR* gene.

There may be regions of the *CASR* gene that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences.(Unpublished Mayo method)

The reference transcript for *CASR* gene is NM_000388.4. Reference transcript numbers may be updated due to transcript reversioning. Always refer to the final patient report for gene transcript information referenced at the time of testing. Confirmation of select reportable variants may be performed by alternate methodologies based on internal

laboratory criteria.

PDF Report
Supplemental

Day(s) Performed
Varies

Report Available
28 to 42 days

Specimen Retention Time
Whole blood: 2 weeks (if available); Extracted DNA: 3 months

Performing Laboratory Location
Rochester

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81405

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
CASRG	CASR Full Gene Analysis	82534-9

Result ID	Test Result Name	Result LOINC® Value
618059	Test Description	62364-5
618060	Specimen	31208-2
618061	Source	31208-2
618062	Result Summary	50397-9
618063	Result	82939-0
618064	Interpretation	69047-9

618065	Additional Results	82939-0
618066	Resources	99622-3
618067	Additional Information	48767-8
618068	Method	85069-3
618069	Genes Analyzed	48018-6
618070	Disclaimer	62364-5
618071	Released By	18771-6