Test Definition: CASRZ

CASR Gene, Full Gene Analysis

Overview

Useful For

Establishing a diagnosis of familial hypocalciuric hypercalcemia

As part of the workup of some patients with primary hyperparathyroidism

Establishing a diagnosis of neonatal severe primary hyperparathyroidism

Establishing a diagnosis of autosomal dominant hypoparathyroidism

As part of the workup of idiopathic hypoparathyroidism

As part of the workup of patients with Bartter syndrome

Special Instructions

- Calcium Sensing Receptor (CASR) Gene Testing Patient Information
- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)

Method Name

Polymerase Chain Reaction (PCR) Followed by DNA Sequence Analysis

NY State Available

Yes

Specimen

Specimen Type

Varies

Shipping Instructions

Specimen preferred to arrive within 96 hours of draw.

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.

Specimen Type: Whole blood

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 specimen in original tube.

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 in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

2. Calcium Sensing Receptor (*CASR*) Gene Testing Patient Information (T551) in Special Instructions

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	Ambient (preferred)		
	Frozen		
	Refrigerated		

Clinical and Interpretive

Clinical Information

The extracellular G-protein-coupled calcium-sensing receptor (CASR) is an essential component of calcium homeostasis. CASR is expressed at particularly high levels in the parathyroid glands and kidneys. It forms stable homodimeric cell-membrane complexes, which signal upon binding of extracellular calcium ions (Ca[++]). In the parathyroid glands, this 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, renal calcium excretion is upregulated and sodium chloride excretion is downregulated. Ca(++) binding to CASR is highly cooperative within the physiological Ca(++) concentration range, leading to a steep dose-response curve, which results in tight control of serum calcium levels.

To date, over 100 different alterations in the *CASR* gene have been described. Many of these cause diseases of abnormal serum calcium regulation. Inactivating mutations result in undersensing of Ca(++) concentrations and consequent PTH overproduction and secretion. 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* mutations, FHH is due to heterozygous inactivating *CASR* mutations. Serum calcium levels are mildly-to-moderately elevated. PTH is within the reference range or modestly elevated, phosphate is normal or slightly low, and urinary calcium excretion is low for the degree of hypercalcemia. Unlike patients with primary hyperparathyroidism (PHT), which can be difficult to distinguish from

FHH, the majority of FHH patients do not seem to suffer any adverse long-term effects from hypercalcemia and elevated PTH levels. They should, therefore, generally not undergo parathyroidectomy.

NSPHT is usually due to homozygous or compound heterozygous inactivating *CASR* mutations, but can occasionally be caused by dominant-negative heterozygous mutations. The condition presents at birth, or shortly thereafter, with severe hypercalcemia requiring urgent parathyroidectomy.

Activating mutations lead to oversensing of Ca(++), resulting in suppression of PTH secretion and consequently hypoparathyroidism. All activating mutations described are functionally dominant and disease inheritance is therefore autosomal dominant. However, sporadic cases also occur. Autosomal dominant hypoparathyroidism caused by *CASR* mutations may account for many cases of idiopathic hypoparathyroidism. Disease severity depends on the degree of gain of function, spanning the spectrum from mild hypoparathyroidism, which is diagnosed incidentally, to severe and early onset disease. In addition, while the majority of patients suffer only from hypoparathyroidism, a small subgroup with extreme gain of function mutations suffer from concomitant inhibition of renal sodium chloride transport. These individuals may present with additional symptoms of hypokalemic metabolic alkalosis, hyperreninemia, hyperaldosteronism, and hypomagnesemia, consistent with type V Bartter syndrome.

Reference Values

An interpretive report will be provided

Interpretation

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

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 predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Cautions

Some individuals who have involvement of the calcium-sensing receptor (*CASR*) gene may have a pathogenic variant that is not identified by the methods performed (eg, large genomic deletions, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of positive carrier status or affected status of neonatal severe primary hyperparathyroidism (NSPHY), hypocalciuric hypercalcemia (FHH), or autosomal dominant hypoparathyroidism (ADH). For predictive testing of asymptomatic individuals, it is important to first document the presence of a pathogenic gene variant in an affected family member.

Test results should be interpreted in context of clinical findings, family history, and other laboratory data.

Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

In some cases, DNA variants of undetermined significance may be identified. Rarely, sequence variants in primer- or probe-binding sites can result in false-negative test results. If results obtained do not match the clinical findings, additional testing should be considered.

Unless reported or predicted to cause disease, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported. These and common benign variants identified for this patient are available upon request.

Very rarely, patients with typical biochemical findings of FHH, with or without a supporting family history, will have no *CASR* mutations. In 2 such families, linkage to chromosome 19 has been established, suggesting that a small

percentage of FHH cases are caused by mutations in other genes, possibly related to CASR downstream signaling.

Up to 20% of patients with clinically typical autosomal dominant hypoparathyroidism may also lack demonstrable *CASR* mutations.

Clinical Reference

1. 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;17:405-423

2. Hendy GN, D'Souza-Li L, Yang B, et al: Mutations of the calcium-sensing receptor (*CASR*) in familial hypocalciuric hypercalcemia, neonatal severe hypocalciuric hyperparathyroidism, and autosomal dominant hypocalcemia. Hum Mutat 2000 Oct;16(4):281-296. The authors maintain a *CASR* polymorphism/mutation database available at www.casrdb.mcgill.ca/

3. Lienhardt A, Bai M, Lgarde JP, et al: Activating mutations of the calcium-sensing receptor: management of hypocalcemia. J Clin Endocrinol Metab 2001 Nov;86(1):5313-5323

4. Hu J, Spiegel AM: Naturally occurring mutations of the extracellular Ca2+ -sensing receptor: implications for its structure and function. Trends Endocrinol Metab 2003 Aug;14(6):282-288

5. Naesens M, Steels P, Verberckmoes R, et al: Bartter's and Gitelman's syndromes: from gene to clinic. Nephron Physiol 2004;96(3):65-78

6. Egbuna OI, Brown EM: Hypercalcaemic and hypocalcaemic conditions due to calcium-sensing receptor mutations. Best Pract Res Clin Rheumatol 2008;22:129-148

Performance

Method Description

Bidirectional sequence analysis was performed to test for the presence of sequence variants in all 6 coding exons and intron/exon boundaries of the *CASR* gene (GenBank accession number NM_000388; build GRCh37 [hg19]).(Unpublished Mayo method)

PDF Report

No

Day(s) and Time(s) Test Performed

Performed weekly; Varies

Analytic Time

14 days

Maximum Laboratory Time

20 days

Specimen Retention Time

Whole Blood: 2 weeks (if available) Extracted DNA: 3 months

Performing Laboratory Location

Rochester

Fees and 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 Regional Manager. 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. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

81405-CASR (calcium-sensing receptor) (eg, hypocalcemia), full gene sequence

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
CASRZ	CASR Gene, Full Gene Analysis	82534-9

Result ID	Test Result Name	Result LOINC Value
37446	Result Summary	50397-9
37447	Result	82939-0
37448	Interpretation	69047-9
37449	Additional Information	48767-8
37450	Specimen	31208-2
37451	Source	31208-2
37452	Released By	18771-6