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**

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<th>Specimen Type</th>
<th>Temperature</th>
<th>Time</th>
<th>Special Container</th>
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**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**


**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

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