CASR Gene Analysis in Calcium Homeostasis Disorders

Also known as: Familial Hypocalciuric Hypercalcemia, Type 1 (HHC1/FHH); Autosomal Dominant Hypocalcemia (ADH); Familial Isolated Hypoparathyroidism (FIH); Neonatal Severe Primary Hyperparathyroidism (NSHPT)

Mendelian Inheritance in Man Numbers: 145980 (HHC1/FHH); 601198 (ADH); 146200 (FIH); 239200 (NSHPT); 601199 (Calcium-Sensing Receptor; CASR)

Clinical features:
Individuals with familial (benign) hypocalciuric hypercalcemia, type 1 (HHC1/FHH) are generally asymptomatic throughout life and do not require treatment. Affected individuals have mild or moderate elevations of calcium in serum, relative hypocalciuria, inappropriately normal serum parathyroid levels and may also have increased serum magnesium levels and a renal calcium/creatinine clearance ratio below 0.01, which differs from patients with primary hyperparathyroidism and other hypercalcemic disorders. Some patients experience pancreatitis, gall stones, renal stones, or chondrocalcinosis. Affected individuals may also have fatigue, weakness, mental disturbance, and polydipsia/polyuria. There is some evidence for an increased risk of diabetes mellitus and cardiovascular disease.

Autosomal dominant hypocalcemia (ADH) most often presents with neonatal or childhood seizures, which are usually secondary to infection and fever. Mild hypocalcemia is present, usually with no overt symptoms, as is a tendency towards hyperphosphatemia. Serum parathyroid levels are usually normal. Urinary calcium excretion is higher than is typically seen in patients with hypoparathyroidism, although serum parathyroid levels are more decreased in hypoparathyroid patients than those with ADH. Clinically there is an increased risk for renal complications, including nephrocalcinosis, renal stones, and impaired renal function. The autosomal dominant form of Familial isolated hypoparathyroidism (FIH) is characterized by hypocalcemia and hyperphosphatemia due to inadequate secretion of parathyroid hormone (PTH). Symptoms are seizures, tetany and muscle cramps.

Neonatal Severe Primary Hyperparathyroidism (NSHPT) is a rare, life-threatening disorder characterized by very high serum calcium concentrations, skeletal demineralization, and multi-glandular parathyroid hyperplasia. Infants present with lethargy, hypotonia, failure to thrive, bony undermineralization, multiple fractures, and severe skeletal deformities, including thoracic narrowing that can lead to respiratory disease. Symptoms occur before the age of 6 months and, if left untreated, can lead to florid rickets, devastating neurodevelopmental disorders, and often fatality. Usually a parathyroidectomy is necessary within the first few weeks of life to prevent death. Of note, there have been milder, transient cases reported with a lack of family history of FHH or secondary hyperparathyroidism. NSHPT is inherited in an autosomal recessive manner, and affected infants are usually born to parents with FHH who may be consanguineous. Milder, transient neonatal disease may be seen when one or both of the parents are symptomatic. In rare cases, a single heterozygous mutation has been reported to act in a dominant-negative fashion. Paternal and de novo mutations tend to have a less severe clinical course due to the influence of maternal-fetal calcium regulations.

Inheritance pattern:
- FHH: Autosomal dominant due to loss-of-function (inactivating) mutation.
- ADH, including FIH: Autosomal dominant due to gain-of-function (activating) mutation.
- NSHPT: Autosomal recessive due to loss-of-function (inactivating) mutations. Rare cases of heterozygous mutations acting in a dominant-negative fashion have been reported.

Reasons for referral:
1. Distinguish FHH from primary hyperparathyroidism and other disorders of calcium homeostasis
2. Confirmation of a clinical diagnosis
3. To determine appropriate treatment, including avoidance of parathyroidectomy in FHH patients
4. Genetic counseling
5. Prenatal diagnosis in pregnancies at-risk for NSHPT

Test method:
Using genomic DNA obtained from the submitted biological material, all coding exons of the CASR gene are screened by bi-directional sequence analysis (exons 2-7). Mutations found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

**Test sensitivity:**
A CASR mutation is identified in 90% of FHH kindreds. The genetic etiology is unknown in the remainder of cases, although genetic heterogeneity has been demonstrated in at least two families in which mapping studies have shown linkage to two different loci at 19p13 and 19q13. Most patients with NSHPT also harbor mutations in CASR. For ADH, one small study found CASR gene mutation in 42% of patients with isolated hypoparathyroidism. Previous studies have identified a mutation in the CASR gene in 14-18% of individuals with FIH.

**Mutation spectrum:**
Although the majority of mutations causing FHH are missense changes, also reported are nonsense, insertion, deletion/insertion, and splice-site mutations. Published mutations in the CASR gene are distributed throughout the gene, with hot spots in the first 300 amino acids, at the NH2-terminal end of the extracellular domain, and in residues 520-881 in the transmembrane and intracellular domains. *De novo* mutation is common, particularly in FHH and NSHPT and germline mosaicism has been reported in association with familial hypocalcemia.

**Specimen Requirements and Shipping/Handling:**
- **Blood:** A single tube with 1-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- **Buccal Brushes:** As an alternative to blood, use a GeneDx buccal kit (others not accepted). Submit by mail. Buccal brushes are not accepted on children under 6 months of age.
- **Prenatal Diagnosis:** For prenatal testing for a known mutation in the *CASR* gene, please refer to the specimen requirements table on our website at: http://www.genedx.com/test-catalog/prenatal/. Ship specimen overnight at ambient temperature, using a cool pack in hot weather.

**Required Forms:**
- Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions

For test codes, prices, CPT codes, and turn-around-times, please refer to the “Calcium Homeostasis Disorders” page on our website: [www.genedx.com](http://www.genedx.com)

**Possible ICD9 Codes:**
- Disorders of calcium metabolism: 275.4

**References Cited:**