

CASR Gene Analysis in Calcium Homeostasis Disorders

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

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 (Pollak et al., 1993; Pearce et al., 1995; Chou et al., 1995). There is some evidence for an increased risk of diabetes mellitus and cardiovascular disease. One study indicated a population prevalence for FHH of 74.1 per 100,000 in a cohort of individuals of predominantly northern European ancestry (Dershem et al., 2020).

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 (Pearce et al., 1996; Hendy et al., 2003). ADH has a prevalence of 3.9 per 100,000 individuals of predominantly northern European ancestry (Dershem et al., 2020).

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 (Lienhardt et al., 2001; Simonds et al., 2002; Warner et al., 2004).

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 (Pollak et al., 1993; Pearce et al., 1995; Hendy et al., 2000). 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 variant has been reported to act in a dominant-negative fashion. Paternal and de novo variants tend to have a less severe clinical course due to the influence of maternal-fetal calcium regulations.

Genetics:

FHH: Autosomal dominant due to loss-of-function (inactivating) variant.

ADH, including FIH: Autosomal dominant due to gain-of-function (activating) variant.

NSHPT: Autosomal recessive due to loss-of-function (inactivating) variants. Rare cases of heterozygous variants acting in a dominant-negative fashion have been reported.

Test Sensitivity:

A CASR pathogenic variant 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 variants in CASR. For ADH, one small study found CASR gene variants in 42% of patients with isolated hypoparathyroidism. Previous studies have identified a pathogenic variant in the CASR gene in 14-18% of individuals with FIH.

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely

pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

References:

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