



Disease Information

Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant condition caused by mutations in the calcium sensing receptor gene (*CASR*). FHH is characterized by hypercalcemia, hypocalciuria, hypermagnesemia, and normal to high levels of parathyroid hormone (PTH). The prevalence is estimated as high as 1 in 16,000 and most cases is asymptomatic however some may present with lifelong hypercalcemia. Those with FHH are at increased risk for developing chondrocalcinosis, pancreatitis, gallstones or kidney stones.^{1, 2, 3, 4}

Patients with FHH are often misdiagnosed with a more common and more severe condition called primary hyperparathyroidism (PHPT). PHPT is also characterized by hypercalcemia; treatment for this condition requires parathyroidectomy, a procedure not necessary for those with FHH.³ A feature that distinguishes PHPT from FHH is elevated circulating PTH levels, however approximately 5 to 15% of individuals with PHPT show circulating PTH in the upper normal limit.⁵

FHH is caused by loss-of-function mutations in the *CASR* gene. Gain-of-function mutations in this gene are responsible for autosomal dominant hypocalcemia (ADH) which is characterized by hypocalcemia, hypercalciuria, and sporadic hypothyroidism.⁸ Homozygous or compound heterozygous loss-of-function mutations in *CASR* result in neonatal severe hyperparathyroidism (NSHPT) a severe and possibly lethal condition. Symptoms appear in infancy and include extreme hypercalcemia, failure to thrive, hypotonia, skeletal demineralization, and severe parathyroid hyperplasia.^{6, 7} Some *de novo* mutations may cause a mild or transient version of NSHPT. Treatment may require parathyroidectomy.¹

Testing Benefits & Indications

Diagnostic testing is recommended for individuals known or suspected to have familial hypocalciuric hypercalcemia (FHH). Diagnostic testing is also indicated in individuals suspected of having primary hyperparathyroidism (PHPT). Distinguishing between FHH and PHPT can help prevent unnecessary parathyroidectomy in those with FHH. Carrier screening is available for relatives of FHH patients with a known mutation. Diagnostic testing is also available for pregnancies at risk for neonatal severe hyperparathyroidism (NSHPT).

Test Description

This Ambry Test is a gene sequence analysis performed by PCR-based double-stranded automated sequencing in the sense and antisense directions for exons 2-7 of the *CASR* gene, plus at least 20 bases into the 5' and 3' ends of all the introns. Specific mutation analysis for individual *CASR* mutations known to be in the family is also available.

Mutation Detection Rate

Mutations are present in about 90% of FHH families (clinical sensitivity), and approximately 99% of *CASR* mutations are detectable by this test (analytical sensitivity).

Turn-Around-Time

Gene sequence analysis	14 – 21 days
Specific mutation analysis	10 – 14 days

Specimen Requirements

Blood: Collect 3-5 cc from adult or 2 cc minimum from child into EDTA purple-top tube (first choice) or ACD yellow-top tube (second choice). Store at room temperature or refrigerate. Ship at room temperature.

Blood Spot: Call for availability.

Saliva: Collect 2 ml into Oragene™ DNA Self-Collection container. Store and ship at room temperature.

DNA: Send 20 µg in TE at 50-100 ng/µl. Store frozen and ship on ice or dry ice.

Prenatal: Prenatal testing is available. Please call an Ambry Genetic Counselor to discuss your case.

CPT Codes

Gene sequence or specific mutation analysis83891, 83894x10, 83898x9, 83904x18, 83909x18, 83912

References

¹ Marx SJ et al. *Medicine*. 1981;60:397-412.

² Law WM & Heath H. *Ann Intern Med*. 1985;102:511-519.

³ Paterson CR & Gunn A. *Lancet*. 1981;2:61-63.

⁴ Heath H III. *Endocrinol Metab Clin North Am*. 1989;18:723-740.

⁵ Gunn & Wallace. *Ann Clin Biochem*. 1992;29:52-586.

⁶ Spiegel AM et al. *J Pediatr*. 1977;90:269-272.

⁷ Cole DEC et al. *J Craniofac Genet Dev Biol*. 1990;10:205-214.

⁸ Pollak MR et al. *Nat Genet*. 1994;8:303-307.