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Familial Hypocalciuric Hypercalcemia (FHH) due to a c.571G>A (p.Glu191Lys) variant in the GNA11 gene

Henry S. Jeng Dr
CMH, hjeng@cmh.edu

Research Abstract Title

Submitting/Presenting Author (must be a trainee): Henry Jeng, DO
Primary Email Address: hjeng@cmh.edu

☐ **Resident/Psychology Intern**
■ **Fellow**

Primary Mentor (one name only): Dr. Max Feldt, DO
Other authors/contributors involved in project: Michelle Knoll, MD, Florencia Del Viso, Darren Baker, Elena Repnikova

IRB Number: N/A (Case report)

Describe role of Submitting/Presenting Trainee in this project (limit 150 words):
Will present case via a poster presentation.

Background, Objectives/Goal, Methods/Design, Results, Conclusions limited to 500 words

Background: Familial hypocalciuric hypercalcemia (FHH) type 1 is caused by inactivating pathogenic variants in the calcium sensing receptor (CASR) gene and clinically presents with serum hypercalcemia, low urine calcium excretion, and inappropriately normal PTH response. In a minority of patients with CASR-negative FHH (up to 26%), variants in *AP2S1* are linked to FHH type 3. Similarly, inactivating pathogenic variants in the GNA11 gene have been shown to cause FHH type 2 in up to 10% of *CASR* and *AP2S1* negative cases.[1]

Objectives/Goal: To report a novel variant found in the GNA11 gene, which is associated with a diagnosis of familial hypocalciuric hypercalcemia. To our knowledge, this is the first case demonstrating the presence of this variant in a child with familial hypocalciuric hypercalcemia, as well as his mother.

Methods/Design: A four-month old male presented to the ED for symptoms of polyphagia and polyuria. Biochemical evaluation found a serum calcium of 11.9 mg/dL (8.7-11.0 mg/dL), magnesium 2.4 mg/dL (1.6-2.3 mg/dL), 25-OH Vit D 38 ng/mL (30 -100 mg/dL) and intact PTH 27.8 pg/mL (15-65 pg/mL). His further labwork fit clinically with FHH with a Urine calcium-creatinine ratio < 0.09 (<= 0.20), accompanied by a serum calcium level of 11.9 mg/dL and iCal of 1.48 mmol/L (1.13 – 1.37 mmol/L). Subsequent monitoring of serum calcium levels showed improvement with time, along with improvement in polyphagia and polyuria.

Of note, mother also has a history of hypercalcemia that was diagnosed at age fifteen as part of a rheumatology evaluation. At diagnosis, her calcium was 12.1 mg/dL (9.3-10.6 mg/dL), Mg 2.3 mg/dL, phosphorous 3.3 mg/dL (2.3-4.8 mg/dL), intact PTH 39 pg/mL, and urine calcium-

creatinine ratio of 0.04 (<= 0.20). She was treated with calcitonin, during which she developed hypercalciuria with elevated PTH of 88 pg/mL. A parathyroid uptake scan was concerning for adenomatous changes in the right upper parathyroid gland, but she was subsequently lost to follow-up without additional evaluation.

Results: Next-generation sequencing of the *AP2S1*, *CASR*, *CDC73*, *CYP24A1*, *GCM2*, *GNA11*, *MEN1*, *PTH1R*, or *SLC34A1* genes was completed in the patient and only revealed a maternally inherited missense variant of unknown significance of c.571G>A (p.Glu191Lys) in *GNA11*. This G to A transition in exon 4 substitutes a glutamic acid for a lysine at codon 191 of a highly conserved amino acid. This variant has not been previously reported in affected individuals nor has it been observed in the healthy population per the gnomAD population database. It is predicted to be deleterious/probably damaging by in silico tools (SIFT, PolyPhen2).

Conclusions: To our knowledge, this is the first case demonstrating the presence of a c.571G>A (p.Glu191Lys) variant in the *GNA11* gene, in a child with familial hypocalciuric hypercalcemia as well as in his affected mother. In cases with strong suspicion of FHH despite negative *CASR* and *AP2S1* analyses, genetic analysis of *GNA11* should be considered.

1. Hovden, S., Rejnmark, L., Ladefoged, S., & Nissen, P. (2017). AP2S1 and GNA11 mutations – not a common cause of familial hypocalciuric hypercalcemia, *European Journal of Endocrinology*, 176(2), 177-185.