Supplementary Data

Clinical and biochemical data available for the FHH and ADH cases in Table 2

Number refers to the case number in Table 2.
Abbreviations: PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; 1,25(OH)₂D, 1,25-dihydroxyvitamin D, ALP, alkaline phosphatase, AHO, Albright’s hereditary osteodystrophy.
Values for normal ranges are in parentheses.

No. 2, NSHPT
Mutation: Exon 2 F42S (TTT>TCT).
Proband: Male infant presenting respiratory distress on day one of life.
Laboratory data: Serum total calcium initially normal rising to 2.8 mmol/L (2.25-2.62) at d 30 with increased PTH 110 ng/L (10-65); serum phosphate 1.7 mmol/L (1.55-2.62) and 25(OH)D 30 mmol/L (20-80) were normal and 1,25(OH)₂D was increased at 188 pmol/L (25-110).
Father: Normal. Laboratory data: calcium, phosphate, alkaline phosphate, PTH levels all normal. CASR genotype: Normal.
Mother: Normal. Laboratory data: calcium, phosphate, alkaline phosphate, PTH levels. CASR genotype: Normal.

No. 3, FHH
Mutation: Exon 2 P55L (CCG>CTG).
Laboratory data: Serum calcium, 11.2 mg/dL (8.2-10.4); phosphate, 2.7 mg/dL (3.0-4.5); PTH, 33 ng/L (11-54); hypocaliuria.
Daughter: 27-yr-old.
Laboratory data: Total serum calcium, 10.8 mg/dL. CASR genotype not examined.
Son: 30-yr-old.
Laboratory data: Hypercalcemia. CASR genotype not examined.
Parathyroidectomy (3 and 1/2 glands removed). Serum calcium initially dropped to 10.4 mg/dL but 2-weeks later back at 11 mg/dL.

**No. 5, FHH**

Mutation: Exon 3 I81M (ATA>ATG).

Proband: 56-yr-old woman with hypercalcemia.

Laboratory data: Serum total calcium, 10.4 mg/dL (8.2-10.2); ionized calcium, 1.41 mmol/L (1.13-1.32); phosphate, 2.9 mg/dL (2.5-4.5). Urinary calcium clearance to creatinine clearance ratio, 0.010.

**No. 6, ADH**

Mutation: Exon 3 N118K (AAC>AAA).

We were asked to evaluate the proband, the 1-month-old son of Patient B, for CASR mutation. Patient B with sporadic hypoparathyroidism was described in, De Luca F et al. 1997 J Clin Endocrinol Metab 82: 2710-2715.

Patient B: 23-yr-old woman with history of hypocalcemic seizures at age 7 months, Laboratory and intervention data: Serum calcium, 1.75 mmol/L (2.05-2.4); phosphate, 9 mmol/L (2.3-4.3); PTH, <3ng/L (10-65); urinary calcium, 7.05 mmol/24 h (1.25-6.25). Basal ganglia calcifications. Treated with oral calcium and vitamin D since diagnosis. Has nephrocalcinosis.

Proband: Cesarean section: Birth weight, 3.235 kg; birth length, 49 cm.

Laboratory data: at 17 d, serum calcium, 11.1 mg/dL (8.8-10.8); phosphate, 6.2 mg/dL (4.5-5.5); PTH, 81 ng/L (10-65); ALP, 408 IU/L (50-165); urine Ca/Cr, 0.93.

CASR genotype: Normal. The DNA of the mother was examined as a positive control for the mutation.

**No. 7, ADH**

Mutation: Exon 3 Heterozygous L125F (CTT>TTT).

Proband: Newborn girl presenting at day 4 with seizures and hypocalcemic.

Laboratory and intervention data: Serum calcium, 0.94 mmol/L (2.2-2.7). IV calcium and magnesium replacement. Discharged at 11 days. Medication: Calcitriol, calcium
glubionate, magnesium sulfate. At 2 years 3 months; Laboratory data: potassium, 3.6 mEq/L (4.0-5.5); calcium, 7.9 mg/dL (8.7-11.0); phosphate, 7.2 mg/dL (3.8-6.5); magnesium, 1.5 mg/dL (1.8-2.4); ALP, 136 IU/L (145-320); PTH, 7 ng/L (11-54); 1,25(OH)2D, 65 pg/ml (15-75); 25(OH)D, 41 ng/ml (15-57); urine Ca/Cr ratio 0.7 (0-0.2) Negative renal ultrasound examination. No evidence of nephrocalcinosis.

Mother: Laboratory, clinical and genotype data, None.

Father: Laboratory, clinical and genotype data, None.

No. 8, ADH
Mutation: Exon 3 heterozygous C129R (TGC>CGC).
Proband: Baby girl presenting with neonatal seizures.
Laboratory and intervention data: 7 days of age: Serum total calcium, 4.0 mg/dL (8.8-10.8); phosphate, 15.0 mg/dL (4.5-5.5); magnesium, 0.9 mEq/L (1.3-2.1); PTH, 13 ng/L (11-54); 25(OH)D, 21 ng/ml (2-21); 1,25(OH)2D, 120 pg/ml. Oral magnesium and IV calcium initiated. Two years of age: medications: dihydrotachysterol, calcium carbonate, magnesium sulphate.
Laboratory and other data: serum total calcium, 7.3 mg/dL (8.8-10.8); phosphate, 9.3 mg/dL (4.5-5.5); magnesium, 14 mEq/L (1.3-2.1); Urinary Ca/Cr, 0.7 (elevated). Kidney ultrasound: no evidence of nephrolithiasis or nephrocalcinosis.
Family history: Parents and five siblings negative for seizures, congenital heart disease or other episodes of hypocalcemia.

No. 10, FHH
Mutation: Exon 3 heterozygous G143R (GGA>AGA).
Laboratory data: Serum total calcium, 10.7 mg/dL (8.5-10.5); ionized calcium, 5.68 mg/dL (4.48-5.28); phosphate, 3.0 mg/dL (2.2-4.1); PTH, 40 ng/L (10-65); 25(OH)D, 38 ng/ml (9.0-52.0); 24 h urine calcium, 40 mg (50-250). Spine T score = –2.3 SD low BMD.
Brother: Laboratory data: mild hypercalcemia. CASR genotype not known.
**No. 11, FHH**
Mutation: Exon 3 heterozygous G158R (GGG>AGG).
Proband: One-year-old girl with hypercalcemia.
Laboratory data: Serum calcium, 3.0-3.3 mmol/L (2.2-2.7); hypocalciuria.
Father: Normal. CASR genotype: normal.

**No. 13, FHH**
Mutation: Exon 4 heterozygous S166G (AGT>GGT).
Proband: Twelve-month-old girl with hypercalcemia.
Laboratory data: Serum calcium, 11-13 mg/dL (8.8-10.8); phosphate, 6.0 mg/dL (4.5-5.5); urine Ca/Cr, 0.2; inappropriately normal or relatively hypocalciuric given the hypercalcemia.
Father: Said to have FHH. Laboratory and clinical data: none. CASR genotype: Mutation: Exon 4 heterozygous S166G (AGT>GGT).
Strong family history of hypocalciuric hypercalcemia on the father’s side. Nine hypercalcemic members.

**No. 14, FHH**
Mutation: Exon 4 heterozygous R220W (CGG>TGG).
Proband: Thirty-three-year-old woman with hypercalcemia initially noted at age 24 yrs. Laboratory data: serum total calcium, 2.74 mmol/L (2.1-2.55) at initial diagnosis. Eight years later; blood ionized calcium, 1.63 mmol/L (1.12-1.23); serum magnesium, 1.02 mmol/L (0.65-1.05); PTH, 9.3-17.7 pmol/L (1.3-7.6); urinary calcium/creatinine clearance ratio, 0.004; 24-h urine calcium, 2.71 mmol; magnesium, 2.42 mmol (3.0-5.0 mmol/d).
Also heterozygous for factor V Leiden with slight decrease in factor S. Has atypical arthralgia. Ultrasound and sestamibi scintigraphic exam indicated possible parathyroid adenoma embedded in right thyroid (no information as to whether any action was taken on this finding).
Mother: Diagnosed with FHH; has progressive increase in serum calcium over time with elevated PTH levels. Has the factor V Leiden mutation like her daughter. Has atypical arthralgia like her daughter. A nephew of the mother has asymptomatic hypercalcemia.

**No. 15, ADH**

Mutation: Exon 4 Heterozygous E228K (GAG>AAG).

Proband: Ten-week-old male infant admitted for seizure and tetany. Chvostek sign positive.

Laboratory data: Serum total calcium, 4.5 mg/dL (8.5-10.5), phosphate, 10 mg/dL (3.0-4.5); PTH <10 ng/L (10-60); 25(OH)D <5 ng/ml (8-80), 1,25(OH)₂D, 62 (16-56).

Mother: Clinically normal. CASR genotype, normal.

Laboratory data: Serum total calcium, 9.2 mg/dL(8.5-10.5); PTH, 44 ng/L (10-60); 25(OH)D, 19 ng/ml (13-67); 1,25(OH)₂D, 102 pg/ml (16-56).

Father: Normal. CASR genotype, normal.

Laboratory data or clinical details: None.

**No. 16, FHH?**

Variant/Polymorphism: Exon 5 Heterozygous S497S (TCC>TCT).

Proband: Five-year-old boy evaluated for suspicion of FHH.

Laboratory data or clinical details: None.

Mother: CASR genotype, Variant/Polymorphism Exon 5 Heterozygous S497S (TCC>TCT)

Laboratory data or clinical details: None.

**No. 18, FHH**

Mutation: Exon 6 heterozygous C562Y (TGC>TAC). Also heterozygous for the Exon 7 R990G polymorphism.

Proband: 51-year-old woman with hypercalcemia that had been noted 8-10 yrs earlier by her previous doctor and ascribed to high dairy intake.
Laboratory data: Serum total calcium, 12.2-12.4 mg/dL; phosphate, 2.6 mg/dL (2.7-4.5); PTH, 60 ng/L (10-65); 25(OH)D, 26ng/ml (14-78); 24-h urine creatinine, 0.78 g; urine calcium, 39 mg. Family history not known.

**No. 19, FHH**
Mutation: Exon 6 heterozygous C565G (TGT>GGT). Also heterozygous for common polymorphism IVS5-88T>C.
Proband: 38-year-old man diagnosed with familial hypocalciuric hypercalcemia
Laboratory data: Serum total calcium 2.82 mmol/L (2.1-2.55); Urinary calcium/creatinine clearance ratio, <0.01.
Mother: Was hypercalcemic. Had 3 and 1/2 parathyroid glands removed and six months later had serum calcium 2.88 mmol/L.
Aunt: Was hypercalcemia. Had 3 and 1/2 parathyroid glands removed and remains hypercalcemic.

**No. 20, FHH**
Mutation: Exon 7 heterozygous C582Y (TGT>TAC).
Proband: Premature girl born after 33 weeks gestation. Hypercalcemic.
Laboratory and other data: First two days of life; blood ionized calcium, 1.3-1.4 mmol/L (1.0-1.2) rising to 1.4-15 mmol/L thereafter. Feeding poorly, sleepy, with gastrointestinal symptoms. At 5 months; serum PTH, 127 ng/L (10-65). Urine calcium almost undetectable. Alendronate therapy initiated and serum calcium level decreased and the infant became more alert.
Brother: Normal. CASR genotype: Normal.
Mother: Laboratory data: Serum total calcium, 2.38 mmol/L (2.1-2.55). CASR genotype: Normal.
Father: Laboratory data: Serum total calcium, 2.38 mmol/L (2.1-2.55). CASR genotype: Normal.

**No. 22, ADH**
Mutation: Exon 7 heterozygous E604K (GAG>AAG).
Proband: 10-yr-old girl presented at age 6 years with seizures associated with hypocalcemia.
Laboratory and intervention data: Serum total calcium, 6.4 mg/dL (8.8-10.4); ionized calcium, 0.85 mmol/L (1.12-1.23); phosphate, 7.1 mg/dL (4.5-5.5); PTH, <8 pg/ml (10-65). Hypoparathyroidism diagnosed and treatment with calcium and vitamin D initiated. Achieved normal serum calcium levels (9.0 mg/dL), however, developed hypercalciuria (Ca/Cr 0.58) and nephrocalcinosis after two years of treatment. Currently asymptomatic on low dose calcium with serum total calcium, 7 mg/dL, and PTH, 1.0 pg/ml.
Sister: 12-year-old recently found to have basal ganglia calcification on CT for sinusitis. Laboratory and other data: Serum total calcium, 7.1 mg/dL (8.8-10.4); phosphate, 5.3 mg/dL (4.5-5.5); PTH, 4.0 pg/ml (10-65); urinary Ca/Cr, 0.07. Has paraesthesiae with no other symptoms but did have episodes of febrile seizures in early childhood. CASR genotype: Mutation: heterozygous E604K (GAG>AAG).
Mother: Laboratory data: Normal. CASR genotype: Normal.
Father: Laboratory data: serum total calcium 6.4 mg/dL (8.8-10.4), phosphate 6.0 mg/dL (2.7-4.5). Asymptomatic. CASR genotype: Mutation: heterozygous E604K (GAG>AAG).

No. 23, FHH
Mutation: Exon 7 Heterozygous C661Y (TGC>TAC).
Proband: 67-year-old woman noted previously to have hypercalcemia.
Laboratory and other data: At age 48 years, during general clinical evaluation: serum total calcium, 10.2-11.2 mg/dL (8.4-10.2); serum PTH, mid-normal range; urine calcium 51 mg/dL (100-300). BMD normal at this time. With increased calcium intake acute pancreatitis developed (no known causes and empiric cholecystectomy unhelpful).
At age 67 years, BMD indicating osteoporosis; Lumbar spine, T = -3.53 SD; Femoral neck, T = -2.04 SD. Has avoided dairy products and calcium and vitamins. Active and has no other risk factors for osteoporosis.
Laboratory data: At age 67-yr. Serum calcium, 1.37 mmol/L (1.15-1.32); PTH, 58-79 ng/dL (10-65).
No family history. None of the proband’s siblings (nine living) has hypercalcemia.
No. 24, NSHPT/FHH
Mutation: Exon 7 Homozygous R680H (CGC>CAC).
Proband: Two-month-old female child evaluated for NSHPT.
Laboratory data: Serum total calcium, 5.95 mmol/L (2.1-2.8); PTH 842 ng/L (10-60).
Clinical details: None.
Mother: Mutation: Exon 7 Heterozygous R680H (CGC>CAC).
Laboratory data: Serum total calcium 2.6, mmol/L; PTH 46.8 ng/L; Hypocalciuria.
Father: Mutation: Exon 7 Heterozygous R680H (CGC>CAC).
Laboratory data: Total serum calcium, 2.5 mmol/L; PTH 33.7 ng/L; Hypocalciuria

No. 26, FHH
Mutation: Exon 7 heterozygous I761del.
Proband: Patient diagnosed with FHH.
No details available.

No. 28, ADH
Mutation: Exon 7 Heterozygous N802I (AAT>ATT).
Proband: Seven-month-old girl admitted with seizures; diagnosis hypoparathyroidism.
Laboratory data: Serum total calcium 6.7 mg.dL (8.8-10.4), PTH 9 ng/L (10-65), hypercalciuria.
Mother: Laboratory and clinical data, None. CASR genotype, Normal.
Father: Laboratory and clinical data, None. CASR genotype, Normal.

No. 29, ADH
Mutation: Exon 7 heterozygous G830S (GGC>AGC).
Proband: Three-day-old baby girl presenting with convulsions.
Laboratory data: Serum total calcium, 1.89 mmol/L (2.1-2.7); phosphate, 2.97 mmol/L (1.0-1.5); PTH, 2 ng/L (11-35).
Brother: Had also presented with convulsions as a neonate.
Laboratory data: Hypocalcemia;, hyperphosphatemia; PTH 3.8 ng/L (11-35).
Father: History of bone and dental problems as a child. Had generalized seizure at age 15 years. Diagnosed with epilepsy. Calcification in basal ganglia, both thalami and the cerebellum.
Laboratory data: Recent serum total calcium, 1.89 mmol/L (2.1-2.7); phosphate, normal; PTH, 11.5 ng/L (9-74).

No. 30, ADH
Mutation: Exon 7 F832L (TTT>CTT).
Proband: 47-year-old women with hypocalcemia and seizures.
Laboratory and other data: Serum total calcium, 7.2 mg/dL (8.4-10.2); phosphate, 4.3 mg/dL (2.7-4.5); PTH, undetectable 25(OH)D, 22 ng/ml (9-52); 24 h urine calcium, 43 mg/dL (5-40).
Patient is not on calcium or vitamin D supplementation last 4-5 years but has been in the past. Episodes of seizures over the past 4-5 years have been controlled with carbamazepine, benzodiazepin and benzodiazepin-derivative drugs. Severe and progressive basal ganglia calcification. Examination: No Chvostek or Trousseau signs (or stigmata of AHO). Previous medical history: Delayed dental eruption (at 3 years of age) and deciduous tooth loss (at 8 years of age). Systemic lupus erythematosus since age 30 yr (inactive on plaquenil). Encephalitis 12 yr. Acute post-streptococcal glomerulonephritis in adolescence. Bacterial meningitis 40 yr.
Father: 80 years of age; also hypocalcemic.
Laboratory data: Serum total calcium 7.6 mg/dL (8.4-10.2); 24 h urinary calcium 130 mg/dL; relatively hypercalciuric.
No other family members are known to be hypocalcemic.

No. 31, ADH
Mutation: Exon 7 Heterozygous F832S (TTT>TCT).
Proband: Female presenting at 6 d of life with seizures; diagnosed with congenital hypoparathyroidism.
Laboratory data: Total serum calcium, 4.3 mg/dL; phosphate 9.8 mg/dL; magnesium 1.1 mg/dL; PTH, <2 ng/L.
Mother: Laboratory, clinical and genotype data, None.
Father: Laboratory, clinical and genotype data, None.