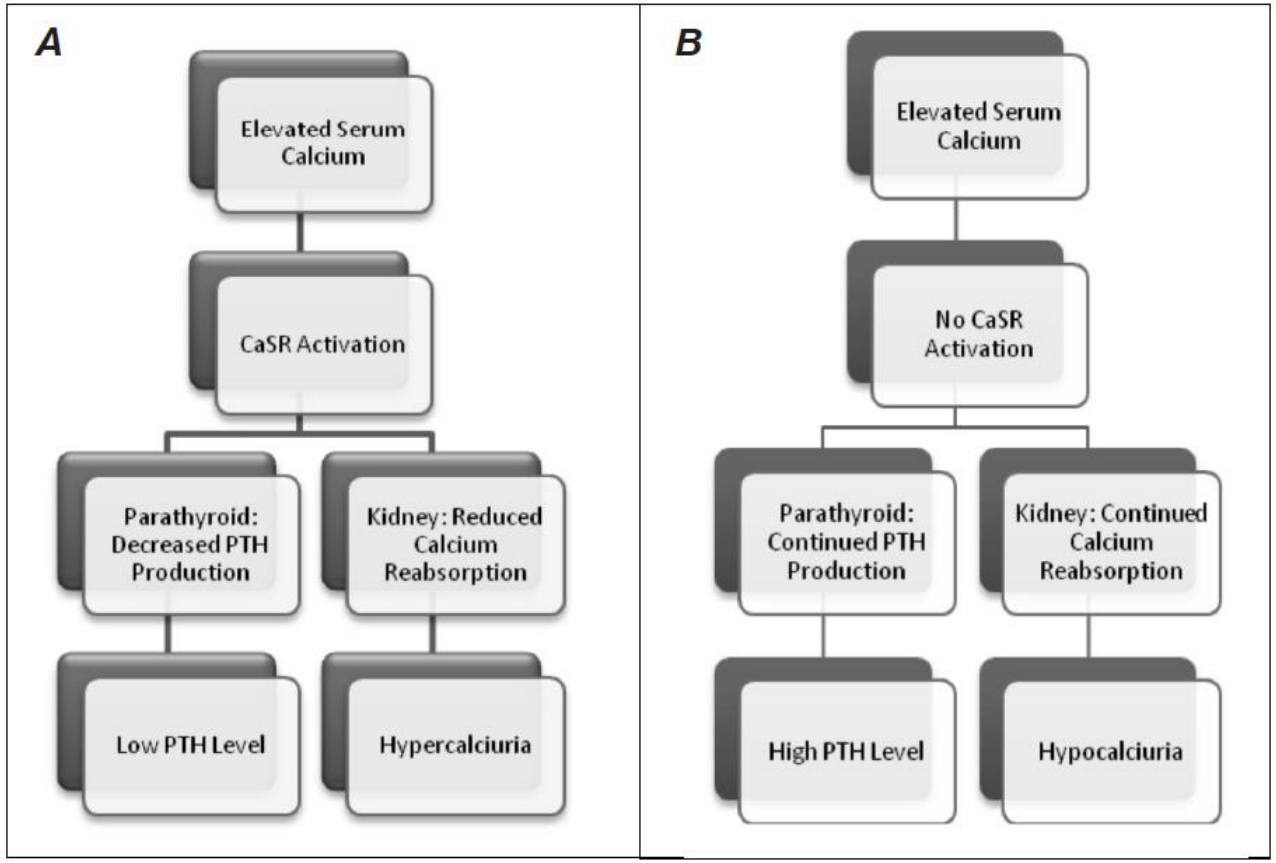
มหาวิทยาลัยมหิดล
คณะแพทยศาสตร์
ศิริราชพยาบาล

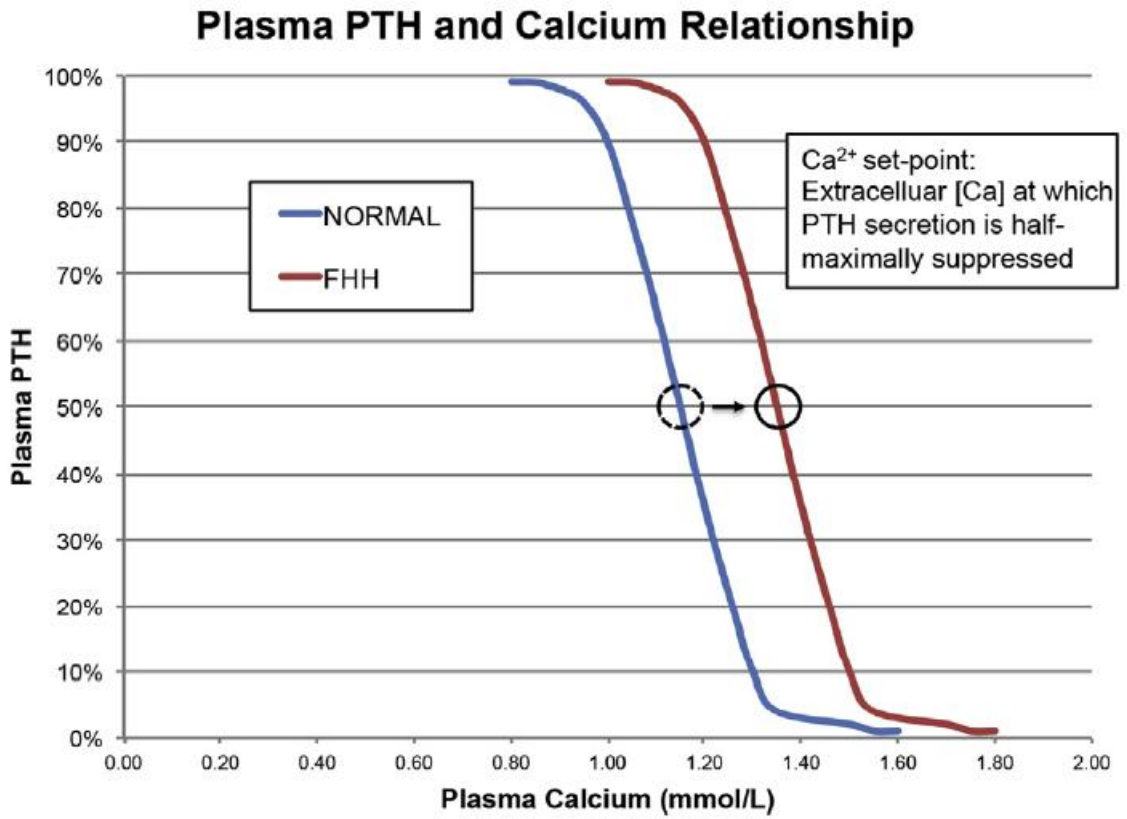
Interhospital Endocrine Conference

24/3/66

ปัญญาของแผ่นดิน

Pathophysiology





This set point is increased (shifted rightward)

Endocr Pract. 2013 Jul-Aug;19(4):697-702., Best Pract Res Clin Endocrinol Metab. 2018 Oct;32(5):609-619.

Clinical Presentation

- While typically asymptomatic, FHH has been associated with at least a few clinically significant manifestations, particularly in those who come to medical attention
- In the earlier analyses of index cases and their kindreds, those who had FHH (genotype unknown at the time) with mild hypercalcemia reported more symptoms of muscle weakness, fatigue, arthralgias, and increased thirst than their normocalcemic relatives

- Other case reports have described acute pancreatitis, chondrocalcinosis, and even nephrolithiasis, but a separate group has challenged the link between FHH and pancreatitis
- The phenotypes of these different subtypes of FHH are generally similar, aside from some reports of more symptomatic disease with certain cases of FHH3 with AP2S1 mutations

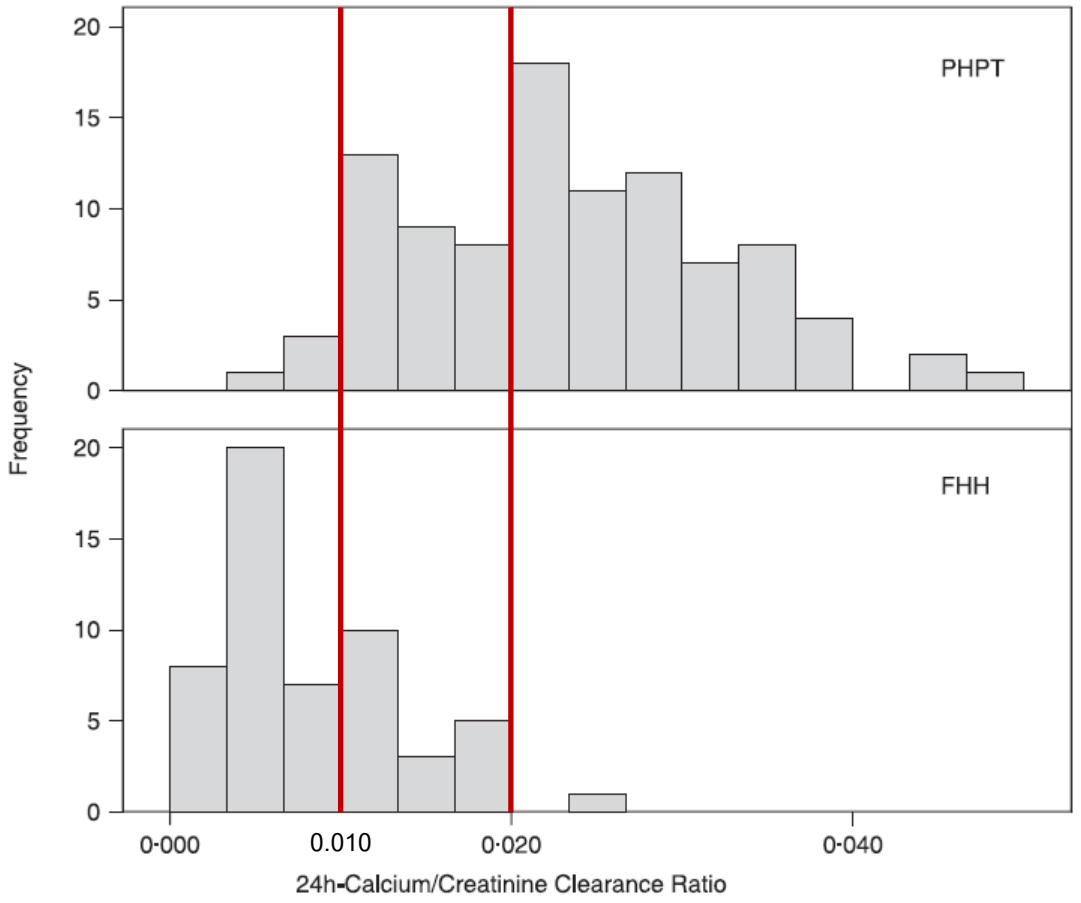
Best Pract Res Clin Endocrinol Metab. 2018 Oct;32(5):609-619.

Differentiating FHH from PHPT

Feature	PHPT	FHH
Serum calcium	increased (mild to severe)	increased (mild)
Symptoms of hypercalcemia	absent, present	absent, present (FHH3)
Complications of hypercalcemia	absent, present	absent, present (FHH3)
Previous normocalcemia	present	absent
Parathyroid hormone	normal (10%), elevated (90%)	normal (80%), elevated (20%)
Phosphorus	normal or decreased	normal
Magnesium	normal or decreased	normal or elevated
Calcium to creatinine clearance ratio	> 0.02	< 0.01
Family history	none	present (70-85%)
Neck ultrasonography	adenoma	negative
Pathologic findings	adenoma or hyperplasia	normal or mild hyperplasia

Endocr Pract. 2012 May-Jun;18(3):412-7., Endocr Pract. 2013 Jul-Aug;19(4):697-702.

Calcium/Creatinine Clearance Ratio



The optimal cut-off point for diagnosing FHH using CCCR was < 0.0115, which yielded

- a sensitivity of 0.80
- a specificity of 0.88

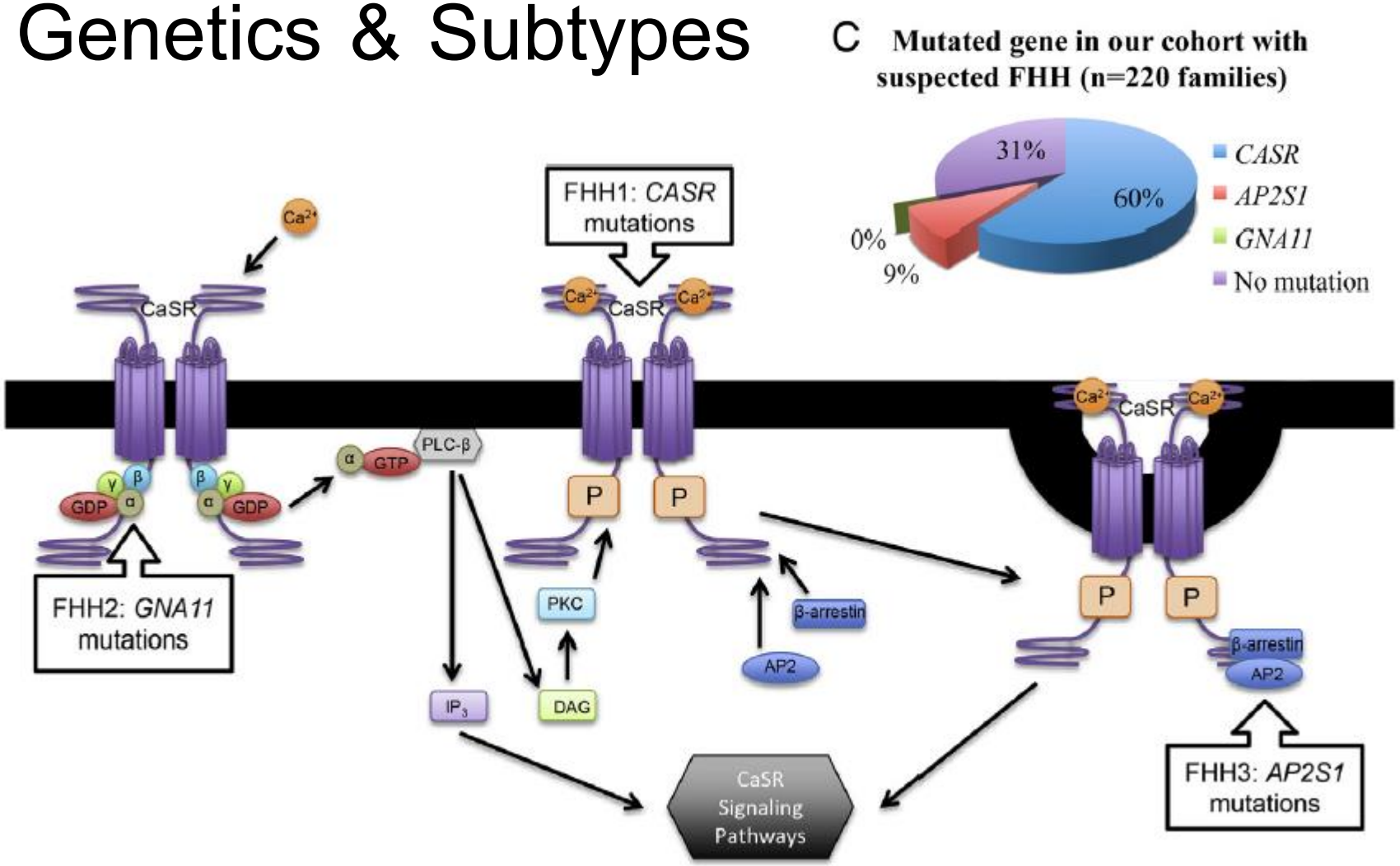
Overlap analysis revealed that a cut-off point for CCCR at < 0.020 would

- sample 98% (53/54) of all patients with FHH
- include 35% (34/97) of the PHPT patients

Clin Endocrinol (Oxf). 2008 Nov;69(5):713-20.

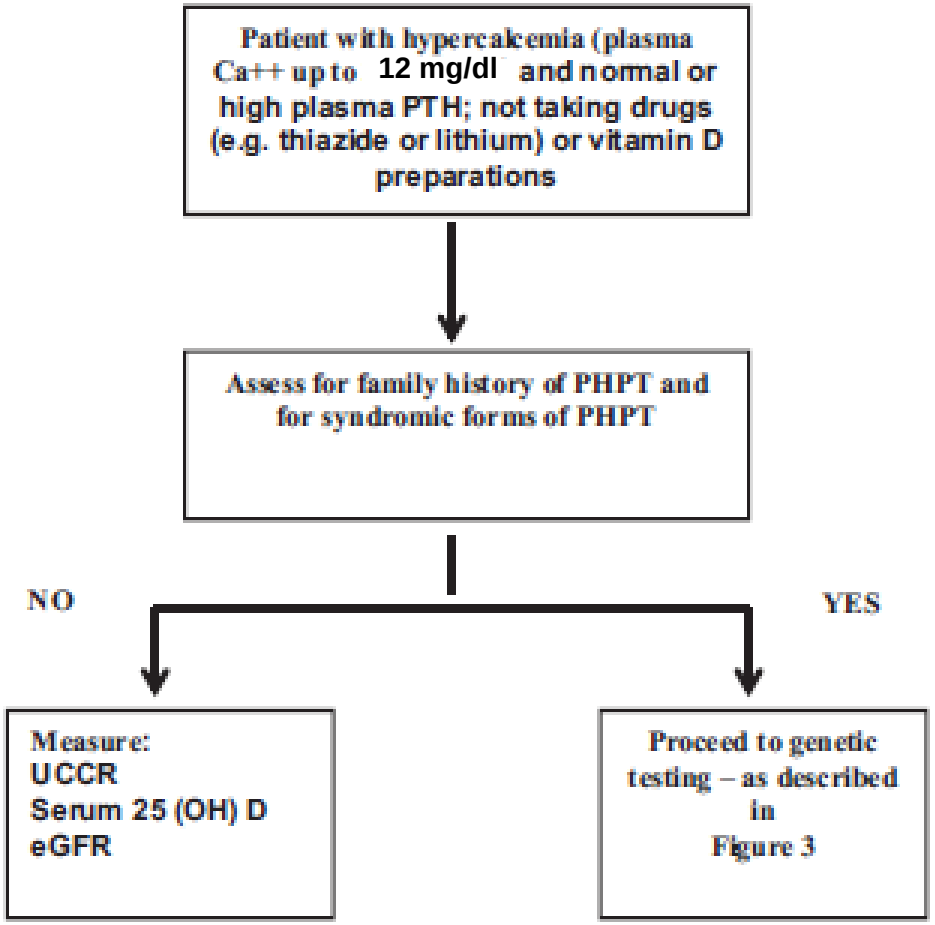
Genetics & Subtypes

- FHH1 has almost complete penetrance and follows an autosomal dominant pattern of disease inheritance
- The majority of cases are FHH1, due to heterozygous inactivating mutations in CASR on chromosome 3
- Sporadically occurring new mutations are not uncommon either occurring in 15-30% of new index cases

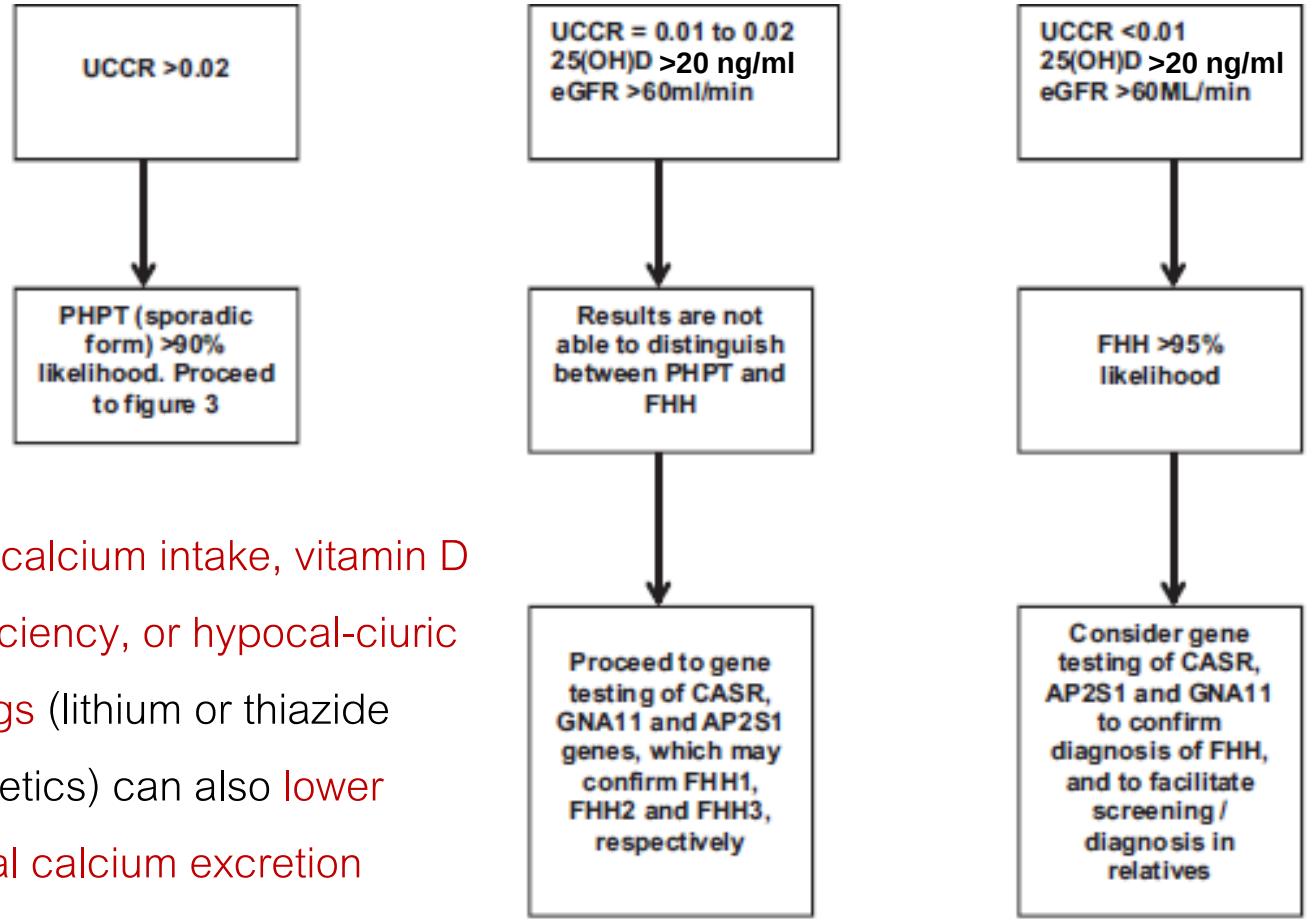


Endocr Pract. 2013 Jul-Aug;19(4):697-702., Best Pract Res Clin Endocrinol Metab. 2018 Oct;32(5):609-619.

Differentiating FHH from PHPT



Diagnosis of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Fourth International Workshop



low calcium intake, vitamin D deficiency, or hypocal-ciuric drugs (lithium or thiazide diuretics) can also lower renal calcium excretion

J Clin Endocrinol Metab. 2014 Oct;99(10):3570-9.

Prognosis & Treatment

- The majority of cases of FHH do not require any treatment, and morbidity is often a result of inappropriate surgical intervention

- Calcimimetics can be offered to adults with FHH and those in whom the serum calcium level is 1 mg/dL beyond the upper limit of normal or with possible symptoms of hypercalcemia
  - FHH cases associated with recurrent pancreatitis
  - Successful normalization of serum calcium concentrations

- Subtotal parathyroidectomy is generally ineffective and therefore not recommended
- Total parathyroidecomy is recommended only for the most severe cases, such as those with NSHPT, due to the obligatory resultant permanent hypoparathyroidism

Best Pract Res Clin Endocrinol Metab. 2018 Oct;32(5):609-619.

Conclusion

- FHH should be considered on the differential diagnosis of asymptomatic hypercalcemia
- Calculation of the 24-h urine calcium/creatinine clearance ratio may guide the diagnostic evaluation of hypercalcemia, particularly in distinguishing FHH from PHPT
- Genetic studies should be pursued when urine calcium excretion is low or inappropriately normal for serum calcium levels, particularly in younger patients
- CASR mutations comprise the majority of FHH cases, but GNA11 and AP2S1 mutations should be considered in CASR-negative cases of suspected FHH
- Morbidity is generally low in FHH, although mild symptoms of hypercalcemia and pancreatitis have been reported, and chondrocalcinosis has been reported with higher frequency in FHH
- Calcimimetics can be considered in patients with symptomatic FHH
- Surgery should generally be avoided