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Review

Genetic hypercalcemia

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ABSTRACT

A genetic disorder should be suspected in patients with hypercalcemia, notably those who are young; have family members with hypercalcemia; or have had a tumor of the endocrine pancreas, thyroid, pituitary, adrenal gland, or jaw bone. All forms of hypercalcemia should be interpreted according to the serum level of parathyroid hormone (PTH). Genetic forms are thus classified as related or unrelated to a parathyroid gland disorder. When the PTH level is elevated or is not depressed despite the hypercalcemia, findings that suggest family history of hypercalcemia due to a genetic cause include syndromic manifestations in the patient or family members, parathyroid cancer (either suspected before surgery or confirmed during parathyroidectomy), multiple or recurrent parathyroid tumors, a family history of primary hyperparathyroidism, and the onset of primary hyperthyroidism before 50 years of age. In patients with moderate hypercalcemia, a normal PTH level, and relative hypocalciuria, the first hypothesis is a mutation in the calcium-sensing receptor gene, which is often difficult to distinguish from primary hyperparathyroidism, particularly when there is no known family history of hyperparathyroidism, as is often the case. A low PTH level suggests non-parathyroid hypercalcemia due to a genetic defect in patients with no evidence of other conditions associated with hypercalcemia and low PTH levels and in those whose calcitriol levels are elevated or normal (instead of depressed as expected when PTH is elevated). Patients with hypercalciuria but no evidence of conditions such as granulomatous diseases should be evaluated for increased vitamin D sensitivity due to a CYP 4A1 mutation. Other very rare causes include hypophosphatasia due to *ALPL* mutations, which is characterized by a low alkaline phosphatase level; and renal phosphate wasting due to an *NPT2A* mutation, in which serum phosphate levels are low. A thorough analysis of the clinical and laboratory data can point toward a genetic disorder in patients with hypercalcemia. The diagnosis is then confirmed by obtaining genetic tests tailored to the clinical and laboratory test abnormalities. The current development of diagnostic genetic testing is shedding new light on the phenotypes, thereby improving their management.

A genetic disorder should be suspected in patients with hypercalcemia, notably those who are young; have family members with hypercalcemia; or have had a tumor of the endocrine pancreas, thyroid, pituitary, adrenal gland, or jaw bone. All forms of hypercalcemia should be interpreted according to the serum level of parathyroid hormone (PTH). Genetic forms are thus classified as related or unrelated to a parathyroid gland disorder. In non-parathyroid forms of hypercalcemia, findings that suggest a genetic defect include a high serum level of calcitriol [1.25 $(OH)_2D$] and a low serum level of alkaline phosphatase or phosphate (Fig. 1).

1. Genetic causes of parathyroid hypercalcemia

Genetic causes of parathyroid hypercalcemia account for about 10% of all cases of primary hyperparathyroidism (PHPT). One or more family members may be known to be affected, pointing toward a hereditary disorder. However, sporadic cases arise, either because of a lack of family data (because the family is unknown or a relative with the genetic defect died before experiencing symptoms) or because of a de novo mutation, whose identification is nonetheless crucial to assess the risk in the offspring. Parathyroid tumors are under the dependence of oncogenes and tumor suppressor genes. Several genes are involved in sporadic and inherited forms [1].

Among genetic forms of parathyroid hypercalcemia, some are associated with syndromes due to known mutations. These forms provide insights into the genesis of parathyroid tumors (Fig. 1) [2].

1.1. Syndromic parathyroid hypercalcemia due to genetic defects

The term multiple endocrine neoplasia (MEN) designates several syndromes that combine primary hyperparathyroidism with other endocrine disorders. In addition, familial

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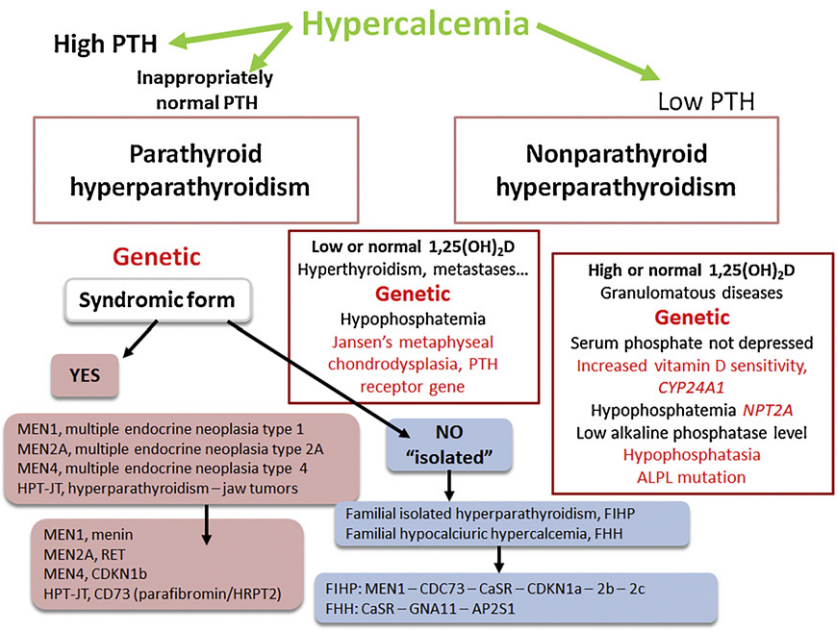

Fig. 1. Genetic causes of hypercalcemia.

hyperparathyroidism-jaw tumor syndrome (HPT-JT) is characterized by hyperparathyroidism with no other endocrine disorders and by a jaw bone tumor.

1.1.1. *Multiple endocrine neoplasia (MEN)*

1.1.1.1. MEN type 1 (MEN1). MEN1 has a prevalence of about 2–3/100 000. The cause is an inactivation mutation in the tumor suppressor gene encoding menin (Fig. 2). Transmission is autosomal and dominant, with 90% penetration by 40 years of age. About 10% of patients with MEN1 have de novo mutations.

Clinical PHPT is found in 75% to 95% of patients, and MEN1 contributes 2% of all cases of PHPT. The first symptoms usually develop between 20 and 25 years of age. Males and females are equally affected, whereas sporadic PHPT has a female-to-male ratio of 3/1. Histology usually shows diffuse hyperplasia of all four parathyroid glands, often with supernumerary glands and multiple adenomas. MEN1 contributes 2% of all cases of parathyroid hyperplasia. Patients with MEN1 develop asynchronous involvement of other endocrine glands, including the pituitary in 15% to 55% of cases, chiefly in the form of prolactinoma; gastric and pancreatic tumors in 20% to 50% of cases; and malignant gastrinoma or insulinoma in 33% of cases. Tumors of the adrenal glands, thymus, and/or bronchi may arise, as well as lymphoma and meningioma. The involvement of multiple parathyroid glands is often asynchronous and ectopic. Recurrences develop in about 50% of cases, on average 12 years after parathyroidectomy. Consequently, extensive parathyroid imaging studies are often performed in patients with a family history of MEN1. More specifically, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the neck is often obtained to look for ectopic parathyroid glands.

The treatment of the parathyroid over-activity in MEN1 differs from that of sporatic primary hyperparathyroidism. It consists in subtotal parathyroidectomy, removing three glands and half of the gland identified by the surgeon as the most normal, as well as the thymus. The risk of persistent or recurrent PHPT is lower after subtotal parathyroidectomy [3]. When the diagnosis of MEN1 is not established before surgery, it may be suspected by the surgeon based on the young age of the patient and enlargement of all four parathyroid glands if she are big. Except for age, patient selection criteria for parathyroidectomy are the same as in sporadic PHPT and include osteoporosis and renal complications. Patients should be monitored for complications, as the risk of hypoparathyroidism is high after subtotal parathyroidectomy, although lower than after total parathyroidectomy [3]. A multidisciplinary management approach by specialized teams is required [4].

1.1.1.2. MEN type 4 (MEN4). MEN4 is an extraordinarily rare disease that is due to an inactivating mutation in *CDKN1B* and inherited on an autosomal dominant basis. The presentation resembles that of MEN1 but there is no mutation in the menin gene (Fig. 2).

PHPT is a feature in 80% of patients and is the inaugural manifestation, with symptom onset at about 50 years of age and multi-glandular involvement. Other endocrine tumors may include pituitary adenoma (50% of patients), gastric carcinoma, bronchial carcinoma, neuroendocrine pancreatic tumor, cervical cancer, testicular cancer, and pheochromocytoma. As with MEN1, patients with PHPT should undergo CT or MRI of the neck to look for ectopic parathyroid glands.

No consensus exists about the management of MEN4. As the phenotype resembles that of MEN1, the same treatment is usually applied.

1.1.1.3. MEN type 2 A (MEN2 A). PHPT occurs in MEN2 A but not in MEN2B, which is therefore not discussed here. MEN2 A has a prevalence of about 2.5/100 000 and is due to an activating mutation in the *RET* proto-oncogene, which is inherited on an autosomal dominant basis. About 20% to 40% of patients with MEN2 A develop PHPT. Onset is at about 40 years of age, and 40% to 80% of patients have no symptoms. There may be a single adenoma (30%–50% of patients) or diffuse hyperplasia. Involvement of ectopic parathyroid glands is common. In contrast to MEN1, recurrences are rare. The other endocrine abnormalities usually antedate the PHPT. Medullary thyroid cancer develops in 90% of patients and pheochromocytoma, which is often bilateral, in 50% [5]. As with MEN1, CT or MRI of the neck should be obtained to look for ectopic parathyroid glands.

The treatment consists in selective parathyroidectomy combined with thyroidectomy. The parathyroid glands to be removed are selected based on enlargement noted during thyroidectomy. As recurrences are extremely uncommon, there is no indication to perform prophylactic parathyroidectomy.

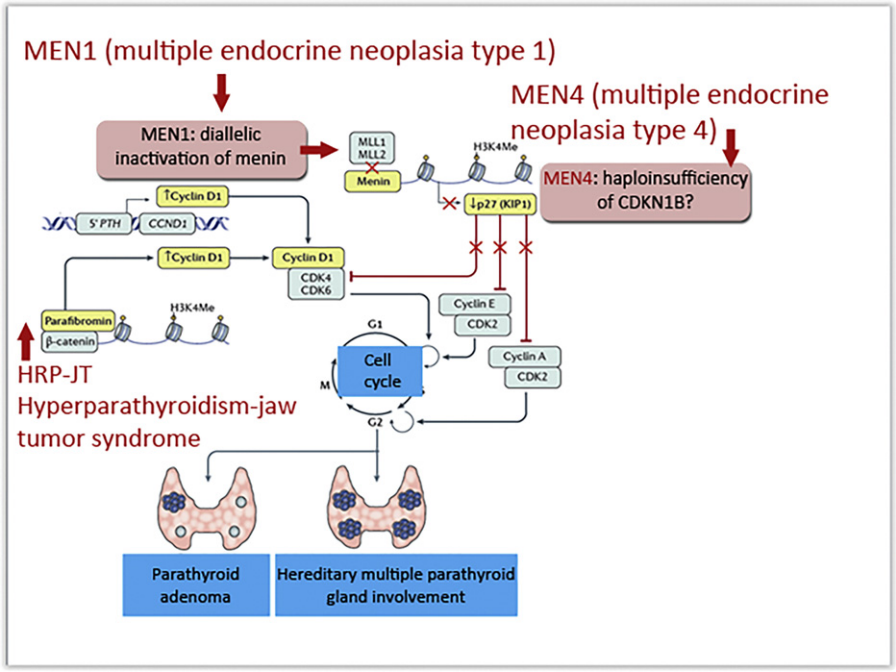

Fig. 2. Mutations responsible for genetic parathyroid hypercalcemia with syndromic manifestations. Adapted from Bilezikian [1].

1.1.2. Hyperparathyroidism-jaw tumor syndrome (HPT-JT)

The prevalence of HPT-JT is unknown. The condition is due to bi-allelic inactivation of the *CDC73* (*HRPT2*) gene encoding parafibromin [6]. Transmission is autosomal and dominant with incomplete penetration and variable expression. PHPT is a consistent feature. In 80% of patients, a single parathyroid gland is affected, although multi-glandular involvement has been reported. PHPT occurs early in life, before 10 years of age in 80% of patients. Parathyroid carcinoma with lung metastases has been reported in 20% of patients. An ossifying fibroma of the mandible or maxillary bone is found in 30% of patients and provides the diagnosis (Fig. 2). Benign uterine tumors are a feature in 50%, and renal lesions in 15%, of patients. The specific workup in young patients with PHPT should include a panoramic dental radiograph, which should be repeated every 3 years if the mutation has been identified, and ultrasonography of the kidneys and pelvis.

The surgical treatment consists in selective parathyroidectomy if a single gland is involved and there are no signs of malignancy, with a follow-up evaluation every 6 months. If a malignancy is suspected, en-bloc resection should be performed with removal of the ipsilateral thyroid lobes and lymph node dissection.

1.2. Non-syndromic parathyroid hypercalcemia due to genetic defects

1.2.1. Familial isolated hyperparathyroidism (FIHP)

This condition may be an incomplete form of syndromic parathyroid hypercalcemia. A family history of PHPT suggests the diagnosis. The genetic abnormalities are either similar to those found in syndromic PHPT or involve the calcium-sensing receptor gene *CaSR*. There are also reports of mutations in *CKN1a*, *CKN2b*, and *CKN2c* [2], as well as in *GCM2*, which encodes a transcription factor required for parathyroid gland development [7].

The management is the same as in sporadic primary hyperparathyroidism. Testing for *HRPT2* mutations, which carry a risk of parathyroid cancer, seems useful, although rarely positive [8]. Tests for mutations, notably involving *HRPT2*, are very time-consuming. If surgery is required on an emergent or semi-emergent basis before the genetic tests are available, to prepare for the eventuality of having to perform an en-bloc resection due to a suspicion of parathyroid carcinoma, it has been suggested that a panoramic dental radiograph be obtained to look for a jaw tumor. Second- and third-generation PTH assays may also be useful, as a ratio of third/second generation levels greater than 1 is extremely rare in non-malignant PHPT and suggests parathyroid cancer [8]. It may also be helpful to assay human chorionic gonadotropin, which is not elevated in binign primary hyperparathyroidism [9]. Other features suggestive of parathyroid cancer include a parathyroid gland measuring more than 3 cm on imaging studies and serum calcium levels above 3 mmol/L [10]. In patients with hypocalciuria and hypercalcemia remaining within the safe range, parathyroid surgery is best postponed until the results of tests for *CaSR* and similar mutations are available (see section 1.2.2) [11].

1.2.2. CaSR mutations and similar conditions

CaSR mutations include gain-of-function mutations responsible for hypocalcemia and loss-of-function mutations responsible for hypercalcemia. Only the latter are discussed here [12].

1.2.2.1. Congenital severe primary hyperparathyroidism. The cause is a *CaSR* mutation responsible for total loss of function. Transmission is autosomal, with the disease arising in homozygotes. The diagnosis is established within the first few months after birth upon evaluation for hypotonia, abnormal intestinal transit, failure to thrive, demineralization, fractures, respiratory distress, and severe hypercalcemia. Total parathyroidectomy must be performed.

1.2.2.2. Familial hypercalcemia and hypercalciuria. Familial hypercalcemia and hypercalciuria is an extremely rare condition due to partial calcium-sensing receptor (CaSR) inactivation in the renal cells. Inheritance is on a dominant basis. Patients typically have no symptoms, although a few may experience renal lithiasis. Fractional calcium excretion is above 1% and serum PTH level is elevated. Thus, the presentation is identical to that of primary hyperparathyroidism [13].

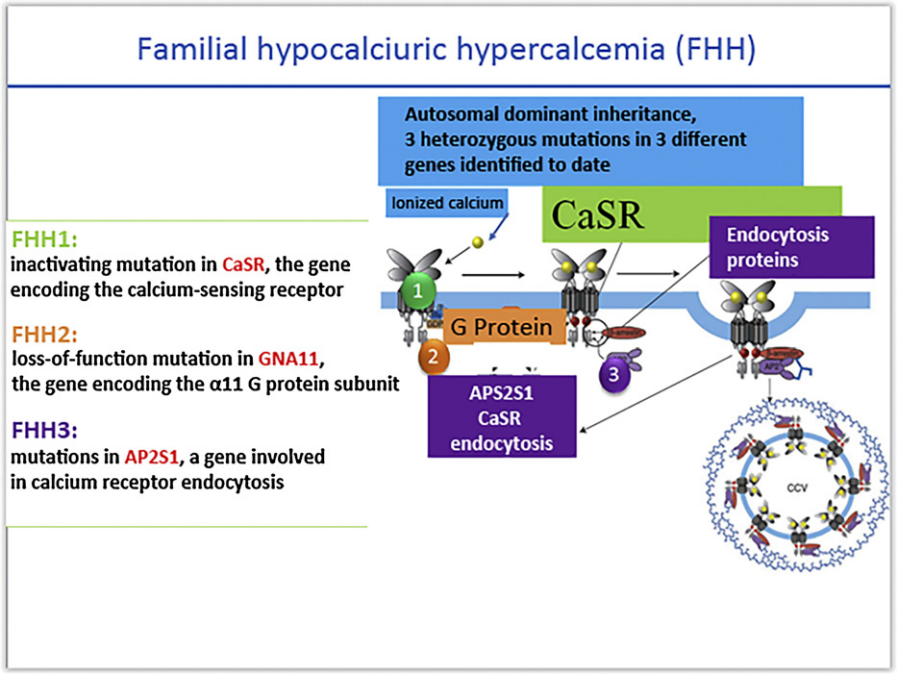

Fig. 3. Mutations known to cause familial hypocalciuric hypercalcemia. Adapted from Nesbit [15].

1.2.2.3. Familial hypocalciuric hypercalcemia (FHH). Accurately diagnosing familial hypocalciuric hypercalcemia (FHH) is crucial given the therapeutic implications. This condition contributes 2% of all cases of hypercalcemia but frequently escapes diagnosis. The cause is an inactivating *CaSR* mutation in type 1, a mutation in the *GNA11* gene encoding a G-protein that is activated by the CaSR pathway in type 2, [14] (Fig. 3), and a mutation in the *AP2S1* gene encoding an adapter protein involved in CaSR endocytosis in type 3 [15]. Inheritance is autosomal dominant with nearly complete penetrance. Most patients are heterozygous, and the condition remains mild in the tiny minority of homozygotes [16].

Clinically, a review of blood tests done in the past shows moderate asymptomatic hypercalcemia, which may start at any age. Moderate parathyroid gland hyperplasia may be found histologically. The bone is unaffected and the incidence of renal lithiasis is the same as in the general population. Chondrocalcinosis and silent vascular calcifications have been reported, although their link with the disease remains unclear. No syndrome associated with FHH has been reported. Several cases with primary hyperparathyroidism have been described [17–22]. In a study of 139 patients with primary hyperparathyroidism, 8 patients had *CaSR* mutations, including 4 with a typical picture of FHH and 4 others who underwent parathyroid surgery and were found to have single adenomas [20]. In addition, some of the mutations responsible for FHH may increase the risk of a second-hit genetic event with loss of an allele, leading to primary hyperparathyroidism [18]. Surgery is not required except in highly selected patients with concomitant primary hyperparathyroidism or very severe chronic hypercalcemia (> 3.5 mmol/L) responsible for clinical manifestations such as recurrent pancreatitis. Treatment with the CaSR activator cinacalcet can be tried before performing surgery [12]. The laboratory abnormalities are similar to those seen in primary hyperparathyroidism, raising diagnostic challenges. Features that suggest FHH include serum magnesium elevation and relative hypocalciuria, which is best assessed based on fractional calcium excretion. Fractional calcium excretion is computed based on the levels in the morning after an overnight fast of plasma calcium (PCa) and creatinine (PCr) and on the 24-hour urinary excretion of calcium (24 h UCa) and creatinine (24 h UCr), according to the formula $\frac{24h\,UCa \times PCr}{PCa \times 24hCr}$. This formula can be applied only in the absence of vitamin D deficiency and of kidney dysfunction, as loss of CaSR function decreases the sensitivity to calcium of parathyroid and renal cells, which therefore interpret hypercalcemia as normal. Thus, despite the hypercalcemia, the PTH levels remain normal instead of being depressed, and the urinary calcium excretion is inappropriately low.

The phenotypes differ across the three types of FHH. In type 3 (*AP2S1* mutation), the serum calcium and magnesium levels are higher than in type 1 (*CaSR* mutation), whereas the PTH level and urinary calcium excretion are similar. In type 3, the PTH levels increase with advancing age, suggesting gradual parathyroid gland enlargement, which increases the risk of confusion with sporadic primary hyperparathyroidism [23]. Differentiating FHH from primary hyperparathyroidism is challenging. A decision tree is suggested in the latest consensus statement on the diagnosis of primary hyperparathyroidism, issued in 2014 [24]. A study supports the use of the following cutoffs for fractional calcium excretion: < 1%, indicating a 95% likelihood of FHH; > 2%, indicating a 90% likelihood of primary hyperparathyroidism; and 1% to 2%, which is the gray zone [25]. Genetic testing is a valuable diagnostic tool in patients with suspected FHH who have clinical manifestations such as osteoporosis or renal lithiasis that raise doubts, given the similarity of the laboratory test abnormalities with those seen in primary hyperparathyroidism. Furthermore, when the fractional calcium excretion is less than 1%, confirmation of the diagnosis should be sought by testing for *CaSR*, *AP2S1*, and *GNA11* mutations. In patients in the gray zone, negative tests for mutations in all three genes strongly suggest primary hyperparathyroidism. Thus, if the tests for mutations are negative and the patient has osteoporosis or renal lithiasis, parathyroid surgery can be performed despite the low urinary calcium excretion. On the contrary, a positive test for any of the three genes indicates benign hypercalcemia that does not require treatment. Low bone mass may lead to the discovery of hypercalcemia while being independent from it. In this situation, the treatment is that of post-menopausal osteoporosis. More specifically, dietary sources of calcium should not be diminished, and vitamin D deficiency can be corrected. Persistently high PTH

Table 1
Example of a patient with both primary hyperparathyroidism and familial hypocalciuric hypercalcemia.

	1st calcium load test Before parathyroid surgery			2nd calcium load test After parathyroid surgery	
	T0	T2h	T4h	T0	T2h
Ionized calcium(mmol/L), N < 1.3	1.41	1.48	1.50	1.39	1.44
Total calcium (mmol/L), N < 2.6	2.77	2.74	2.83	2.62	2.69
Phosphatemia (mmol/L), (0.8–1.4)	0.95	1.0	1.16	1.09	1.07
PTH (pg/mL), N < 26	24.5	16	17	16	8
25(OH)D (ng/mL)	39			34	
24 h calcium excretion, N < 4 mg/kg/24 h	0.58			1.34	
Fasting calcium excretion (mmol/L)	0.08		0.44	0.08	0.31
Serum CTX (25–573 pg/mL)	847			537	

The results of the first calcium load test might suggest primary hyperparathyroidism with normal serum calcium levels. However, urinary calcium excretion is markedly diminished. The second calcium load test was performed after parathyroid surgery, and the results indicate resolution of the primary hyperparathyroidism. The persistent hypercalcemia was found to be due to a mutation in the gene for the calcium-sensing receptor, which explained the hypocalciuria. Thus, the diagnosis was familial hypocalciuric hypercalcemia with concomitant primary hyperparathyroidism.

levels despite correction of calcium and vitamin D deficiencies suggest concomitant primary hyperparathyroidism, and the decision to perform parathyroidectomy depends on the phenotype.

An example will illustrate this complex situation. A 70-year-old female presented with a spinal *T*-Score of −2.7 SD indicating osteoporosis, a serum calcium level at the upper end of the normal range (2.60 mmol/L), and hypocalciuria (35 mg/24 h) that was initially ascribed to vitamin D insufficiency (25OHD, 13 ng/L). After vitamin D supplementation had increased the 25O HD level to 45 ng/mL, her serum calcium level was elevated to 2.70 mmol/L and her PTH level was inappropriately normal at 54 pg/mL (normal, 16–65 pg/mL). She was referred for calcium load testing (Table 1). The results of the first calcium load test were consistent with primary hyperparathyroidism. Ultrasonography and ^{99m}Tc-sestamibi scintigraphy suggested enlargement of the lower left parathyroid gland. However, the very low 24-hour and fasting calcium excretion and fractional calcium excretion of 0.16% prompted genetic testing, which identified a heterozygous p. Arg795Gln mutation in exon 7 of the *CaSR* gene. Given the absence of fractures, watchful waiting was deemed appropriate. One year later, her bone mineral density values had declined by 60 mg at the spine and femur. This rapid bone loss was ascribed to primary hyperparathyroidism related to the *CaSR* mutation. The rapidly progressive osteoporosis and enlargement of the lower right parathyroid gland supported a diagnosis of primary hyperparathyroidism. After removal of the enlarged gland, which weighed 230 mg, a second calcium load test was performed (Table 1). The persistent hypercalcemia was ascribable to the *CaSR* mutation explaining the persistent hypocalciuria (Table 1). The PTH level declined satisfactorily after surgery, confirming the resolution of the primary hyperparathyroidism.

1.3. Mutation in the parathyroid hormone (PTH) receptor gene

An activating mutation in the PTH receptor gene is responsible for Jansen's metaphyseal chondrodysplasia. The diagnosis is established in childhood upon evaluation for long bone deformities and sclerosis. Laboratory tests show hypercalcemia, hypercalciuria, hypophosphatemia; and low or undetectable PTH levels. Fibroblast growth factor (FGF) −23 levels are high due to activation by the mutation of the PTH receptor on osteocytes, combined with FGF23 overexpression. Adults with the mutation experience long-lasting hypercalcemia with renal lithiasis [26].

1.4. Genetic parathyroid hypercalcemia diagnosed after parathyroid surgery

When more than two of the parathyroid glands are found during surgery to be hyperplastic, genetic tests should be performed to look for mutations in *MEN1*, *RET*, *HRPT2*, *CDKN1B*, and *CaSR* and related genes. Patients with adenomas in more than two parathyroid glands may have mutations in the menin gene or *CDKN1B* gene or, more rarely, the *HRPT2* gene. Patients with a single parathyroid carcinoma should be tested for the *HRPT2* mutation. Testing should include not only routine gene sequencing, but also whole genome sequencing to ensure that the diagnosis is not missed. Patients with persistent hypercalcemia despite a return to normal of the PTH levels should be tested for mutations in the *CaSR*, *GNA11*, and *AP2S1* genes.

1.5. In practice: when should genetic tests be done in a patient whose presentation suggests primary hyperparathyroidism?

To ensure the diagnosis of the above-described conditions, genetic testing should be performed when syndromic manifestations are present in the patient or family, as well as in patients with parathyroid cancer, multiple or recurrent parathyroid tumors, or familial primary PHPT [27]. Genetic testing is also in order if hyperparathyroidism develops before 30, or perhaps even 50 years of age [28]. In patients who have moderate hypercalcemia with normal, i.e., non-depressed, PTH levels and relative hypocalciuria, the first hypothesis is a mutation in the *CaSR*, *GNA11*, or *AP2S1* gene.

Genetic tests should be performed in the children of patients with a mutation. The tests should be performed after 3–5 years of age for *RET*, 5 years of age for *MEN1*, and 12 years of age for *HRPT2*. For *CaSR* mutations, a serum calcium assay can be performed in the other parent to assess the very low risk of a homozygous mutation in the children.

2. Non-parathyroid hypercalcemia with 1.25(OH)$_2$D elevation

In a patient with hypercalcemia and low PTH levels, the usual causes, such as metastases and hyperthyroidism, should be ruled out. A serum 1.25(OH)$_2$D assay should be obtained (Fig. 1). If the result is high or normal, i.e., inappropriate given the low PTH level, a granulomatous disease should be sought. If none is found, increased vitamin D sensitivity should be suspected. Mutations affecting the vitamin D-metabolizing enzyme CYP24A1 have been identified in patients with severe infantile hypercalcemia [29] (Fig. 4). Several mutations have been reported in a cohort of patients with severe hypercalcemia (> 3.5 mmol/L), hypercalciuria, and renal lithiasis by 6 months of age. Over the follow-up of 2 to 10 years, the serum calcium levels declined, sometimes to the normal range, but the 1.25(OH)$_2$D elevation and low PTH levels persisted. This pattern of laboratory test results has been found after the administration of high-dose vitamin D (three doses of 600 000 IU). The patients had

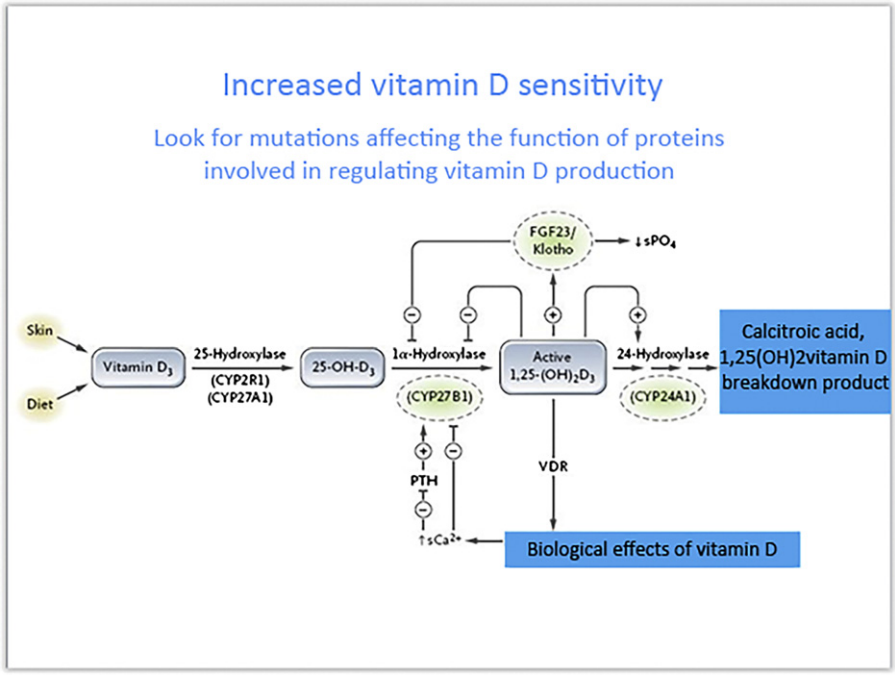

Fig. 4. Increased vitamin D sensitivity. Adapted from Schlingmann [29].

the same mutations as those described previously in this article. They had a longer follow-up of 12 to 25 years, during which the serum calcium levels declined, while remaining slightly elevated; the PTH levels remained low; and the $1.25(OH)_2D$ levels remained high. Thus, increased vitamin D sensitivity can be diagnosed in adults who present with this biochemical pattern. Identification of the *CYP24A1* mutation provides the diagnosis and rules out other conditions requiring specific treatments, such as granulomatous diseases. In patients with increased vitamin D sensitivity, vitamin D supplementation, if required (e.g., because of osteoporosis), should be given in limited doses targeting a serum 25OHD level of 20 ng/mL, which is sufficient to ensure normal calcium absorption given the increase in $1.25(OH)_2D$.

3. Hypercalcemia due to abnormalities in genes not involved in calcium metabolism

3.1. Hypophosphatasia

Patients with hypophosphatasia, particularly in its most severe forms, may have hypercalcemia, as the decreased alkaline phosphatase activity impairs calcium uptake by the bones. Hyperphosphatemia is common, and the PTH level is low or normal but not elevated. There is no increase in $1.25(OH)_2D$ levels [30], [31]. Manifestations in adults include osteomalacia, chondrocalcinosis, premature loss of teeth, osteoarticular involvement, and a history of rickets in childhood. The clinical picture varies widely, however. Therefore, patients with hypercalcemia should undergo an alkaline phosphatase assay. Hypophosphatasia contraindicates the administration of osteoporosis drugs that inhibit bone resorption.

3.2. Osteopetrosis

Osteopetrosis is characterized by bone sclerosis due to impaired osteoclast formation and function. The clinical presentation is variable but includes hypocalcemia. However, after stem cell transplantation, osteoclast activation may result in hypercalcemia. Bisphosphonate therapy is not effective, but the calcium levels decline in response to denosumab [32].

3.3. Hypercalcemia in osteogenesis imperfecta (OI)

Patients with osteogenesis imperfecta (OI) due to *COLA1* and *COLA2* mutations or with type 6 OI who do not respond to bisphosphonates are treated with subcutaneous denosumab every 3 months [33]. They may experience hypercalcemia, which may be related to a rebound effect, as seen in pediatric patients upon denosumab discontinuation [34]. The antiresorptive effect may be of shorter duration in OI than in post-menopausal osteoporosis [35]. Support for this possibility comes from the unexpected finding that bone biopsies taken after 5 denosumab injections and 3 months after the last injection contain an increased number of osteoclasts. Thus, a shorter interval between denosumab injections may be appropriate in OI. Furthermore, patients with OI may have concomitant primary hyperparathyroidism [36], [37], [38]) or experience hypercalcemia due to immobilization after multiple fractures [39].

3.4. Juvenile Paget disease

Juvenile Paget disease is due to an inactivating mutation in *TNSRSF11B*, which encodes osteoprotegerin. Given the involvement of the RANK-ligand system, it made intuitive sense to evaluate the effects of denosumab. In one patient, improvements in bone turnover and bone pain were noted after 8 years, as well as severe hypocalcemia requiring denosumab discontinuation, which was followed within 7 weeks by hypercalcemia [40]. Rebound hypercalcemia in patients with genetic disorders can be likened to the hypercalcemia seen in children with giant-cell tumors or fibrous dysplasia of bone. The higher frequency of hypercalcemia in pediatric patients is related to the higher bone turnover rate. These data suggest that the use of denosumab in children should be limited to patients requiring an alternative to bisphosphonate therapy, as recommended for adults [34].

3.5. Hypercalcemia due to NPT2a mutations

Mutations in the sodium-phosphate cotransporter NPT2a manifest chiefly as hypophosphatemia with renal phosphate wasting.

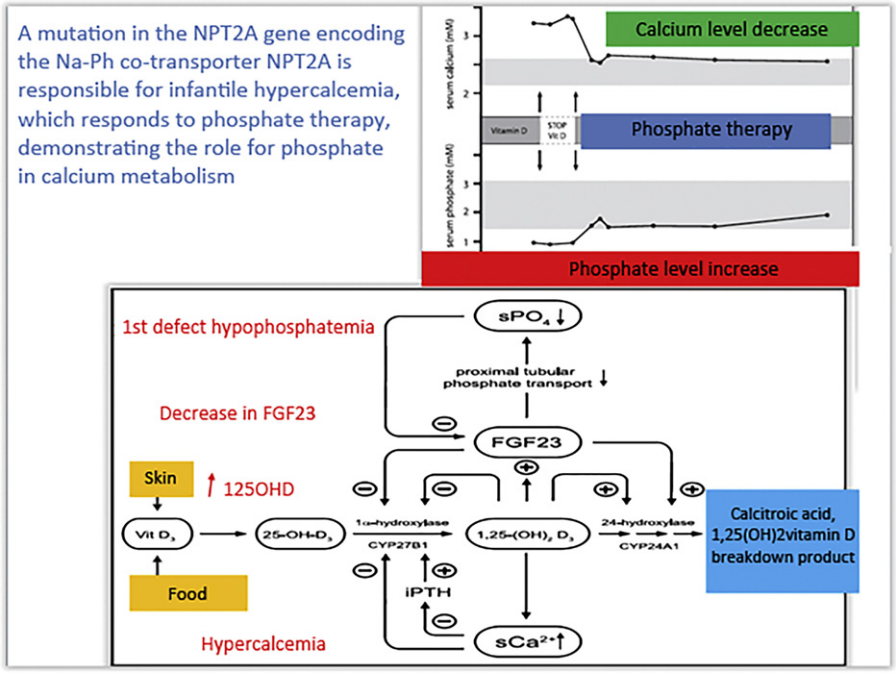

Fig. 5. *NPT2A* mutation. Adapted from Schlingmann [41].

This condition is not related to FGF23 elevation: on the opposite, FGF23 levels are low. In addition, $1.25(OH)_2D3$ is elevated and, as a result, mild hypercalcemia with negative PTH feedback may develop. A recent study has shed light on the interrelations between phosphate and calcium levels [41]. Phosphate supplementation returns the serum calcium and FGF23 levels to normal. Studies in knockout mice for the *SLC34A1* gene encoding NPT2a that were fed diets with and without phosphate have demonstrated the role for phosphate in regulating calcium levels (Fig. 5).

4. Conclusion

A thorough analysis of clinical and laboratory findings can ensure the diagnosis of hypercalcemia due to genetic disorders. The development of genetic testing has shed light on the phenotypes and management of genetic hypercalcemia.

Disclosure of interest

The authors declare that they have no competing interest.

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