Pseudohypoparathyroidism, Albright’s Hereditary Osteodystrophy: Disorders Caused by Inactivating GNAS Mutations

DeGroot Endocrinology 2016

Dr Parichehr Vahabi Anaraki
ADULT ENDOCRINOLOGIST
7th March, 2017
In 1942, Albright and colleagues described a group of patients who displayed certain physical features, including obesity, short stature, brachydactyly, and cognitive impairment, combined with hypocalcemia and hyperphosphatemia. In these patients, exogenous, biologically active parathyroid hormone (PTH) extracts failed to result in a full phosphaturic response; hence, the term pseudohypoparathyroidism (PHP) was introduced.
The primary site of PTH resistance in PHP is the renal proximal tubule, as the actions of PTH in bone and the distal tubule appear normal.
• Patients with PHP have reduced serum concentrations of 1,25-dihydroxyvitamin D \([1,25(\text{OH})2\text{D}]\), which is the main cause of hypocalcemia.

• Both low serum 1,25(\text{OH})2\text{D} and hyperphosphatemia are the direct results of PTH resistance at the proximal tubule.
• Hyperphosphatemia is typically worsened by the elevation of PTH in the circulation and the absence of resistance to the bone resorptive actions of this hormone; on the other hand, the increase in serum PTH can prevent symptomatic hypocalcemia in some PHP patients due largely to its unimpaired actions on the bone and the renal distal tubule, and thus calcium release from bone and enhanced calcium reabsorption, respectively.
• However, at some point in their lives, most patients manifest hypocalcemia and, therefore, present with associated clinical findings.
• PTH exerts its actions by binding to a seven-transmembrane, G protein–coupled receptor (the PTH/PTH-related protein receptor, PTHR1).

• Although the PTHR1 can couple to several different G proteins,16 most PTH actions are mediated primarily through the stimulatory G protein, which acts on adenylyl cyclases, thereby increasing the formation of intracellular second-messenger cyclic adenosine monophosphate (cAMP).
PTH-induced cAMP formation is used as an important indicator of renal tubular PTH function, since most PHP patients display an inadequate or absent increase of urinary cAMP in response to exogenous, biologically active PTH.
However, currently used high-sensitivity PTH assays often suffice to make the diagnosis when serum PTH is elevated in the presence of hypocalcemia and hyperphosphatemia.
• Nonetheless, depending on the nature of the nephrogenous response to exogenous PTH, PHP is subdivided into two main types.

• PHP type 1 is defined by blunted urinary excretion of both cAMP and phosphate, and PHP type 2 is defined by blunted urinary excretion of phosphate only.
Signs and Symptoms
• Signs and symptoms of decreased serum calcium level often reflect secondary prolongation of the QT interval on EKG and increased neuromuscular excitability leading to Trousseau’s and Chvostek’s signs as well as bronchospasm.

• In more severe cases, patients present with seizures. Other neurologic symptoms can also arise from hypocalcemia, and some patients with PHP have initially been diagnosed with movement disorders.
As another complication of the changes in serum calcium and phosphorous, brain imaging studies frequently show intracranial calcifications in PHP patients.
• PHP is a congenital disorder, but only few reports describe findings consistent with PTH resistance during the neonatal period.

• Clinical manifestation of hypocalcemia typically occurs only later in childhood, suggesting that PTH resistance and the resultant changes in serum calcium and phosphorous develop only gradually
• It thus appears that PTH responses are intact during the early postnatal period despite the existence of the molecular defect underlying PHP.

• The mechanisms that allow normal PTH signaling during this developmental stage remain unknown.
PSEUDOHYPOPARATHYROIDISM
TYPE 1a
PSEUDOHYPOPARATHYROIDISM TYPE 1a:

• Of the two main PHP types, PHP type 1 is much more common.

• Various clinical variants of PHP type 1 have been described based on the presence or absence of clinical manifestations that coexist with PTH resistance, diminished stimulatory G protein activity in easily accessible cells, and silenced expression of the GNAS-derived α-subunit of the stimulatory G protein (Gsα)
PSEUDOHYPOPARATHYROIDISM TYPE 1a:

- PHP patients often exhibit characteristic physical features that may include obesity, round facies, short stature, brachydactyly, ectopic ossification, and mental impairment.
- These features are termed Albright’s hereditary osteodystrophy (AHO) and occur primarily in PHP patients who are now classified as having pseudohypoparathyroidism type 1a (PHP 1a).
PSEUDOHYPOPARATHYROIDISM TYPE 1a

• The brachydactyly observed in patients with AHO typically involves the metacarpal and/or metatarsal bones and, thus, the pattern of shortening of the hand bones differs from other disorders with brachydactyly, such as familial brachydactyly and Turner’s syndrome.
PSEUDOHYPOPARATHYROIDISM TYPE 1a

• Due to shortened metacarpals, dimpling over the knuckles of a clenched fist (Archibald sign) is often observed.

• The shortening of the distal phalanx of the thumb, however, is the most common skeletal abnormality (called murderer’s thumb or potter’s thumb), and some patients have shortening of all digits
PSEUDOHYPOPARATHYROIDISM TYPE 1a

• Mental impairment is mild, often presenting as cognitive defects. It is possible that the cause of mental impairment is the deficiency of Gsα signaling in the brain.

• There is remarkable patient-to-patient variability in AHO, even among patients that carry the same genetic mutation and belong to the same family
PSEUDOHYPOPARATHYROIDISM TYPE 1a

- Some patients may exhibit a single AHO feature only, such as obesity, while others may present with multiple AHO features.
- Furthermore, the severity of each feature differs vastly among the patients. In addition, individual AHO features are not unique to PHP, as they can be observed in other unrelated disorders.
PSEUDOHYPOPARATHYROIDISM TYPE 1a

The variable expressivity and the lack of specificity of individual features can make the AHO diagnosis challenging.

While the coexistence of hormone resistance in PHP 1a patients is often helpful, it can also be misleading. This is particularly important for the differential diagnosis of different PHP forms characterized by the presence of AHO features alone or hormone resistance alone.
In addition to having PTH resistance and AHO, patients with PHP 1a show clinical evidence that is consistent with target-organ resistance to other hormones. The most common additional hormone resistance involves the actions of TSH, leading to hypothyroidism.
PSEUDOHYPOPARATHYROIDISM TYPE 1a

- Unlike PTH resistance, which typically develops later in life, TSH resistance can be present at birth.
- Resistance to gonadotropins and growth hormone–releasing factor has been reported, whereas resistance to other peptide hormones that also mediate their actions through Gsα-coupled receptors, such as vasopressin or ACTH, does not appear to become clinically overt.
PSEUDOHYPOPARATHYROIDISM TYPE 1a

• The genetic mutation that causes PHP 1a is located within the Gsα-coding GNAS exons. A protein that is essential for the actions of many hormones, Gsα primarily mediates agonist-induced generation of intracellular cAMP.

• Activation of a stimulatory G protein–coupled receptor by its agonist, such as PTH, leads to a GDPGTP exchange on Gsα, causing dissociation of the latter from Gβγ subunits.
**PHP type 1a:** This allows both Gsα and Gβγ to stimulate their respective effectors. In its GTP-bound state, Gsα can directly activate several different effectors, such as Src tyrosine kinase,63 and certain Cachannels.

- Apart from these effectors, however, adenylyl cyclase is by far the most ubiquitous and the most extensively investigated effector molecule stimulated by Gsα. An integral membrane protein, adenylyl cyclase catalyzes the synthesis of the ubiquitous cAMP, which then triggers various cell-specific responses.
PHP type 1a:

- The activation of adenyl cyclase and other effectors by Gsα is regulated by the intrinsic GTP hydrolase (GTPase) activity of Gsα.
- Conversion of GTP into GDP results in the re-assembly of the G protein heterotrimer and, thereby, prevents further effector stimulation.
PHP type 1a:

- Mutations identified in PHP 1a patients are heterozygous and scattered throughout all of the 13 GNAS exons encoding Gsα and the intervening sequences, including missense and nonsense amino acid changes, insertions/deletions that cause frameshift, and nucleotide alterations that disrupt pre-mRNA splicing
PHP type 1a:

- Consistent with this mutational spectrum, Gsα level/activity is reduced by approximately 50% in easily accessible tissues from PHP 1a patients, such as erythrocytes, skin fibroblasts, and platelets.
- Deficiency of Gsα has also been demonstrated in renal membranes from a patient with PHP
PHP type 1a:

- The detection of reduced Gsα activity is important for the establishment of PHP 1a diagnosis, particularly for cases in which genetic analysis fails to reveal a GNAS mutation.
- Reduction of Gsα activity in PHP 1a is consistent with the fact that PTH and the other hormones with impaired actions in this disorder act via cAMP-mediated signaling pathways.
PHP type 1a:

- A missense mutation in exon 13 (A366S) was identified in two unrelated boys, who presented with PHP 1a and precocious puberty.
- This mutant Gsα protein is temperature-sensitive and thus rapidly degraded at normal body temperature. The amino acid substitution, however, renders the protein constitutively active, resulting in elevated cAMP signaling in the cooler temperature of the testis. More recently, another mutant Gsα protein has been described in a unique case of familial PHP 1a and transient neonatal diarrhea.
PHP type 1a:

- Another pediatric case has been described in whom a de novo missense mutation (R231C) on the paternal allele was found together with a maternally inherited combination of three C-to-T substitutions, resulting in aberrant GNAS splicing. The patient with these compound heterozygous mutations had morbid obesity, TSH and PTH resistance, and a prothrombotic state due to marked Gsα hypofunction in platelets.
• Paternal Gsα expression is silenced in a small subset of tissues through as-yet-undefined mechanisms, so that the maternal allele is the predominant source of Gsα expression.

• These tissues include the renal proximal tubule, thyroid, pituitary, and gonads
Although devoid of differential methylation, the Gsα promoter exhibits parent-of-origin–specific histone modifications in those tissues where it is monoallelic. The active maternal Gsα promoter shows a greater ratio of tri- to di-methylated histone-3 Lys4 compared to the silenced paternal promoter in the proximal tubule, whereas the amount of methylated histones is similar in maternal and paternal Gsα promoters in liver, a tissue in which Gsα is biallelic.

As discussed later, the tissue-specific, paternal Gsα silencing has a key role in the development of PTH resistance in patients with PHP 1a and PHP 1b.
PHP 1c has been described as a distinct variant of PHP 1a but the clinical and laboratory features of patients with PHP 1c are identical to those with PHP 1a, as they have both AHO and multihormone resistance. In contrast to PHP 1a, however, biochemical assays demonstrate no reduction in Gsα activity in erythrocytes obtained from PHP 1c patients, suggesting the absence of mutations within the Gsα gene. Nevertheless, recent molecular characterizations have revealed Gsα mutations at least in some PHP 1c patients.
CLINICALLY DISTINCT, GENETICALLY RELATED PHP 1a VARIANTS

1- Pseudopseudohypoparathyroidism
2- Progressive Osseous Heteroplasia
Pseudopseudohypoparathyroidism

• Physical abnormalities similar to those observed in patients with PHP 1a but without evidence for an abnormal regulation of calcium and phosphate homeostasis were first reported in 1952.

• Because of the lack of an abnormal regulation of mineral ion homeostasis, the name pseudopseudohypoparathyroidism (PPHP) was coined to describe this disorder.
Pseudopseudohypoparathyroidism:

- Interestingly, patients with PPHP also carry GNAS mutations that lead to diminished Gsα function, and these mutations can be found in the same kindred as those with PHP 1a.

- However, both disorders are never seen in the same sibling kinship, and a careful analysis of multiple families has revealed that the mode of inheritance of each disorder depends on the gender of the parent transmitting the Gsα mutations:
Pseudopseudohypoparathyroidism:

Thus, an inactivating Gsα mutation causes PHP 1a (i.e., hormone resistance and AHO) after maternal inheritance, whereas the same mutation on the paternal allele results in PPHP (AHO only).
Pseudopseudohypoparathyroidism

- Most AHO features, except obesity and mental retardation, appear to develop regardless of the parent of origin, and it is therefore primarily hormone resistance that displays an imprinted mode of inheritance.
- Recent studies have furthermore revealed that most PPHP patients are considerably smaller at birth, particularly if their inactivating Gsα mutation is located in GNAS exons 2 to 13 of the paternal allele:
Pseudopseudohypoparathyroidism

- The tissue-specific imprinting of Gsα expression can explain the parent-of-origin–specific inheritance of hormone resistance.
- In those tissues where Gsα expression is paternally silenced (i.e., Gsα is expressed exclusively or predominantly from the maternal allele), an inactivating mutation located on the paternal allele is not predicted to alter Gsα function, whereas the same mutation located on the maternal allele is predicted to abolish Gsα function completely.
Pseudopseudohypoparathyroidism

• Hormone resistance is observed in those tissues where Gsα is imprinted, such as the proximal renal tubule and the thyroid gland, while hormone responses are unimpaired in those tissues where Gsα is biallelic, such as the distal renal tubules.
• A recent study furthermore showed that the silencing of the paternal Gsα allele in the renal proximal tubule develops after the early postnatal period in mice, thus providing a plausible explanation for the finding that the manifestation of PTH resistance occurs mostly after infancy in patients with PHP 1a and PHP 1b.
The finding that most AHO features develop regardless of the parent transmitting a Gsα mutation has led to the hypothesis that the inheritance of AHO is due to Gsα haploinsufficiency in various tissues, which appears to be true in certain settings. PTHrP-induced cAMP generation is critical for proper control of hypertrophic differentiation of growth plate chondrocytes, and Gsα haploinsufficiency has been demonstrated in this tissue through the study of mice chimeric for wild-type cells and mutant cells heterozygous for disruption of GNAS exon 2.
Regardless of the parental origin of the GNAS exon 2 disruption, the mutant cells displayed premature hypertrophy compared to their wild-type neighbors, although the paternal disruption (i.e., loss of one Gsα allele combined with a complete loss of XLαs) resulted in significantly more premature hypertrophy than the maternal disruption (loss of one Gsα allele only). Thus, the brachydactyly and/or short stature observed in the context of AHO likely result from diminished Gsα signaling in growth plate chondrocytes.
PPHP:

• While these data correlate well with the notion that AHO develops after both maternal and paternal inheritance of a Gsα mutation, recent evidence suggests that individual AHO features can also be subject to imprinting
• A careful analysis of multiple patients with PHP 1a and PPHP revealed that obesity is primarily a feature of PHP 1a patients, developing after maternal inheritance.
• Considering that Gsα is biallelic in the white adipose tissue, it was proposed that Gsα may also be imprinted (predominantly maternal expression) in areas of the central nervous system that control satiety and body weight
• A recent report has also demonstrated that cognitive impairment is more prevalent in PHP 1a than in PPHP, thus indicating that tissue-specific Gsα imprinting may involve additional brain regions.
• On the other hand, imprinted inheritance has not been reported regarding short stature, despite the finding that Gsα is maternally expressed in the pituitary gland and that PHP 1a patients display GHRH resistance that results in growth hormone (GH) deficiency.
• Conversely, as outlined earlier, the small for gestational age phenotype is associated more strongly with Gsα mutations on the paternal allele than with Gsα mutations on the maternal allele
Progressive Osseous Heteroplasia
Progressive Osseous Heteroplasia:

- A disorder termed progressive osseous heteroplasia (POH) has been described in patients with severe extraskeletal ossifications that involve deep connective tissue and skeletal muscle.
Progressive Osseous Heteroplasia

• In POH, the ectopic bone is primarily intramembranous, as opposed to a similar disease termed fibrodysplasia ossificans progressiva (FOP) in which extraskeletal bone formation occurs via endochondral mechanisms, and is accompanied by skeletal malformations.

• **Few patients** with POH demonstrate AHO features and, consistent with the occasional coexistence of these two sets of clinical defects, heterozygous inactivating Gsα mutations have been identified as a cause of POH.
Progressive Osseous Heteroplasia

• Patients who are mosaic for heterozygous GNAS mutations that result in constitutive Gsα activity develop fibrous dysplasia of bone characterized by irregular woven bone disrupted by fibrous tissue.

• Moreover, in human mesenchymal stem cells, reduction of Gsα protein levels has been shown to cause osteogenic differentiation, while inhibiting the formation of adipocytes
Progressive Osseous Heteroplasia:

• Nevertheless, clinical and genetic data demonstrate several important differences between patients with AHO and those with POH.

• First, the ectopic bone in AHO is limited to subcutaneous tissue. In addition, in nearly all patients with POH, the severe ectopic bone formation is isolated (i.e., other typical AHO features are not manifest).

• Moreover, mutations leading to isolated POH are inherited from male obligate gene carriers only (i.e., inheritance pattern is exclusively paternal).
Progressive Osseous Heteroplasia:

• Based on these findings, which redefine the clinical definition of this disorder, it was hypothesized that the pathogenesis involves progenitor cells of somitic origin, which may undergo loss of heterozygosity at the GNAS locus and thereby cause severe or complete Gsα deficiency
PSEUDOHYPOPARATHYROIDISM TYPE 1b:

• This PHP form is characterized by the presence of PTH-resistant hypocalcemia and hyperphosphatemia, but without evidence of AHO in most cases.

• In addition to increased serum PTH, patients with PHP 1b can demonstrate elevated serum alkaline phosphatase activity, which suggests normal PTH-dependent bone turnover
PSEUDOHYPOPARATHYROIDISM TYPE 1b:

• In fact, hyperparathyroid bone disease can be observed in association with PHP 1b, especially in patients with sporadic PHP 1b or in the index cases of the autosomal dominant form of PHP 1b (AD-PHP 1b).
The intact PTH response in the bone is consistent with the lack of Gsα imprinting in bone and led to the introduction of the term pseudohypoparathyroidism (PHP-HPT)
PSEUDOHYPOPARATHYROIDISM TYPE 1b:

- The hormone resistance observed in PHP 1b patients develops only after maternal inheritance of the genetic defect (i.e., the mode of inheritance is identical to the hormone resistance in PHP 1a).
- PTH resistance and related changes in calcium and phosphate homeostasis are the major laboratory findings in PHP 1b, but some PHP 1b patients also display mild hypothyroidism with slightly elevated TSH levels as well as some elevation in calcitonin level.
PSEUDOHYPOPARATHYROIDISM TYPE 1b

• Nevertheless, evidence for resistance to other hormones, such as gonadotropins, whose actions also involve tissues in which Gsα is imprinted, has not been reported for PHP 1b patients.

• A study assessed growth hormone response to GHRH plus arginine stimulation in PHP 1b, revealing a normal response in 9 of 10 patients.
PSEUDOHYPOPARATHYROIDISM TYPE 1b

• On the other hand, in addition to PTH and mild TSH resistance, hypouricemia due to increased fractional excretion of uric acid has been reported in the affected individuals of two unrelated PHP 1b kindreds. This finding implicates impaired PTH actions in the development of hypouricemia in these patients.

• However, hypouricemia resolved in one of the PHP 1b kindreds following treatment with calcium and calcitriol
Based on genomewide linkage analysis, the genetic defect underlying PHP 1b maps to a region of chromosome 20q13.3 that comprises the GNAS locus, but the critical interval excludes all the coding GNAS exons, including those that encode Gsα.

On the other hand, patients with PHP 1b display epigenetic abnormalities within the GNAS locus. The most consistent epigenetic defect is a loss of imprinting at exon A/B (also termed exon 1A), which is primarily found as an isolated defect in familial PHP 1b cases.
PSEUDOHYPOPARATHYROIDISM TYPE 1b

• In addition, many sporadic and some familial PHP 1b cases show additional loss of imprinting at the DMR comprising the XLαs and antisense promoters and a gain of imprinting at the DMR composing exon NESP55.

• These abnormalities are associated with biallelic expression of A/B, XLαs, and antisense transcripts and silencing of the NESP55 transcript.
PSEUDOHYPOPARATHYROIDISM TYPE 1b

• Despite having distinct epigenetic abnormalities at the GNAS locus (i.e., isolated A/B loss of imprinting versus broad imprinting defects that involve exon A/B and at least one other GNAS DMR), PHP 1b patients seem to have similar clinical findings with respect to serum calcium, phosphate, and PTH levels
• Analysis of 20 families in which the affected individuals show an isolated loss of A/B imprinting reveals that a significant portion of such familial cases are asymptomatic at the time of diagnosis.

• In some of these cases, the diagnosis was made only based on elevated serum PTH. Comparison of male and female patients among sporadic PHP 1b cases reveals that female patients have significantly higher serum PTH levels than male patients, suggesting that hormone resistance is more severe in females.
PSEUDOHYPOPARATHYROIDISM TYPE 1b

• By definition, PHP 1b patients do not show AHO features.
• However, some recent reports identified patients who carry genetic and epigenetic defects associated with PHP 1b yet present with mild AHO features, particularly the shortness of metacarpal bones.
• Considering that individual AHO features can be observed in other disorders, the presence of AHO features may be unrelated to the molecular genetic defects underlying PHP 1b in these cases.
PSEUDOHYPOPARATHYROIDISM TYPE 2
PSEUDOHYPOPARATHYROIDISM TYPE 2:
Dissociation regarding the impairment of PTH-induced nephrogenous cAMP formation and phosphaturia (i.e., PHP 2) appears to be the least common form of PHP. Although typically sporadic, a case with familial form of PHP 2 type has been reported, and several reports describe evidence for a self-limited form of this disease in newborns, which could indicate that it is transient in nature.
The molecular defect and pathophysiologic mechanisms underlying this PHP variant remain to be discovered. Because the defect underlying PHP 2 is associated with normal cAMP generation in response to exogenous PTH, it was postulated that it is caused by molecular defects that involve downstream of cAMP generation, such as protein kinase A.
PARATPSEUDOHYPOHYROIDISM TYPE 2

In fact, mutations in the regulatory subunit of protein kinase A have been identified in some patients who show, in association with characteristic skeletal abnormalities, biochemical defects similar to those seen in PHP 2. Alternatively, the PTH signaling pathways that utilize other G proteins, such as Gq or G11, may be defective in patients with PHP 2.
PSEUDOHYPOPARATHYROIDISM TYPE 2

• The signaling mediated by the Gq/G11 pathway involves activation of phospholipase C, which in turn leads to the formation of second messengers inositol 1,4,5 tris-phosphate (IP3) and diacylglycerol.

• This signaling pathway, which results in the stimulation of PKC and an increase in intracellular calcium ions, was shown to be important in sustaining the phosphaturic actions on PTH, as recently shown for mice expressing a PTHR-1 mutant that fails to activate IP3/PKC signaling.
PSEUDOHYPOPARATHYROIDISM TYPE 2

Serum calcium levels, which may affect the efficient utilization of intracellular calcium signaling pathways, appear to be important for restoring PTH responsiveness in PHP 2, as shown in some patients who normalized their phosphaturic response to PTH following normalization of serum calcium.
PSEUDOHYPOPARATHYROIDISM TYPE 2

It is also possible that the sodium phosphate transporters in the proximal renal tubule are nonresponsive to PTH, thereby resulting in a defective phosphaturic, but not cAMP, response to exogenous PTH. Such a defect, however, should preserve the action of PTH on 25(OH)D-1-α-hydroxylase and lead to normal serum 1,25(OH)2D, unless it is combined with vitamin D deficiency.
PSEUDOHYPOPARATHYROIDISM TYPE 2

Hypocalcemia as a result of vitamin D deficiency has also been associated with PTH resistance that entailed the phosphaturic effect of this hormone without altering its potential to raise urinary cAMP, suggesting that some PHP 2 cases may in fact reflect vitamin D deficiency.
TREATMENT
TREATMENT:

The primary goal of treatment entails correction of abnormal serum biochemistries that result from PTH and, in some cases, other hormone resistance, such as TSH resistance leading to hypothyroidism, which can be treated by thyroid hormone replacement.
TREATMENT:

• GH deficiency can also be treated with recombinant human GH (rhGH) and is found to be efficacious in prepubertal patients with PHP 1a.

• PPHP patients who carry de novo mutations on the paternal GNAS allele are often diagnosed late in life (often when the children of female PPHP are diagnosed with PHP 1a), making it difficult to assess GH deficiency and thus the benefits of rhGH treatment in PPHP patients.
TREATMENT:

- Clinical management of hypocalcemia in patients with PHP is less difficult than in patients with hypoparathyroidism, because the distal tubular actions of PTH in PHP patients are not impaired, providing sufficient calcium reabsorption from the glomerular filtrate.
TREATMENT:
The treatment involves oral calcium supplements and activated vitamin D analogues, such as 1,25(OH)2D (calcitriol). Note that the active form of vitamin D is required because of the lowered capacity of the proximal tubule to convert 25(OH)D into the biologically active 1,25(OH)2D.
TREATMENT:

In addition, treatment of patients with PTH resistance should aim at keeping the serum PTH level within or close to the normal range rather than simply avoiding symptomatic hypocalcemia, since persistent elevation of serum PTH will increase bone resorption and may eventually lead to hyperparathyroid bone disease.
TREATMENT:

• Due to intact PTH actions in the distal tubule, urinary calcium levels are usually low, and affected individuals do not have a significant risk for developing kidney stones and nephrocalcinosis.

• In fact, during the course of treatment, elevation of urinary calcium typically does not occur.
TREATMENT:

- Nevertheless, blood chemistries and urinary calcium excretion in patients undergoing treatment should be monitored annually, but more frequently during pubertal development and once skeletal growth is completed, as the requirements for treatment with calcium and 1,25(OH)2D may need to be reduced
THANK YOU FOR YOUR ATTENTION