In 1942, Albright and colleagues\(^1\) 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, indicating that hypocalcemia and hyperphosphatemia in these patients resulted from target-organ resistance to, rather than deficiency of, PTH. Consistent with resistance to the actions of this hormone, it was later shown that patients affected by PHP have elevated concentrations of immunoreactive PTH.\(^2\) Subsequently, it was also shown that some patients affected by PHP have resistance toward other hormones; however, PTH resistance is the most prominent feature of the disease.

\(^1\)Chapter titles shaded in green indicate chapters dedicated predominantly to pediatric endocrinology content.
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.

**DIAGNOSIS AND PROGRESSION OF PTH RESISTANCE**

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, 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 (Fig. 66-1). In fact, the nephrogenous cAMP response to the exogenously administered PTH is utilized as a test for establishing the diagnosis of PHP, which is more sensitive than measuring the increase in urinary phosphate excretion used in the original Ellsworth-Howard test. 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 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 chonchosplasm. Although the most common manifestations of hypocalcemia include muscle tetany and spasms, findings vary markedly among patients. 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. In one report, two sisters with PHP type 1b (see later) presented with paroxysmal kinesigenic choreoathetosis, and the diagnosis of PTH resistance in one sister was made after approximately 4 years of oral antiepileptic treatment when biochemical evaluation and genetic testing was performed. Some patients presenting with seizures demonstrate epileptiform EEG changes and, because this activity typically responds to antiepileptic treatment, the diagnosis of PHP can be delayed. 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. In a longitudinal study of a child with PHP 1a (see later), cAMP response to PTH was found to be normal at 3 months of age, whereas it was blunted at 2.6 years of age. In another PHP 1a case, a gradual decline of serum calcium, preceded by increasing serum phosphorous and PTH levels, was demonstrated. In addition, a PHP 1b patient diagnosed by genetic analysis at birth (see later) was shown to have normal serum PTH levels until 18 months of age, when an elevation of PTH was first detected despite normal serum calcium and phosphorous. 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**

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
TABLE 66-1  Clinical and Molecular Features of the Different PHP Forms and ADOHR

<table>
<thead>
<tr>
<th></th>
<th>PTH Resistance</th>
<th>Additional Hormone Resistance</th>
<th>Typical AHO Features</th>
<th>Genetic Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHP 1a/1c</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Coding GNAS mutations</td>
</tr>
<tr>
<td>PHP</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Coding GNAS mutations</td>
</tr>
<tr>
<td>POH*</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Coding GNAS mutations</td>
</tr>
<tr>
<td>PHP 1b</td>
<td>Yes</td>
<td>Some cases</td>
<td>No†</td>
<td>Microdeletions affecting GNAS imprinting, patUPD20q, or unknown defects.</td>
</tr>
<tr>
<td>PHP 2</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Coding PRKAR1A mutations</td>
</tr>
<tr>
<td>ADOHR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

ADOHR, Acrodysostosis with hormonal resistance; AHO, Albright’s hereditary osteodystrophy; PHP, pseudohypoparathyroidism; POH, progressive osseous heteroplasia; PTH, parathyroid hormone.

*Note that POH-like severe heterotopic ossifications have been reported in some patients with multiple hormone resistance.
†Some recent studies have demonstrated coexistence of AHO features and GNAS imprinting defects.

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 (Gsat) (Table 66-1).

As described originally by Albright and colleagues,1 PHP patients often exhibit characteristic physical features that may include obesity, round facies, short stature, brachydactyly, ectopic ossification, and mental impairment (Fig. 66-2). 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). 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.41 Due to shortened metacarpals, dimpling over the knuckles of a clenched fist (Archibald sign) is often observed.42 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.43 Mental impairment is mild, often presenting as cognitive defects. It is possible that the cause of mental impairment is the deficiency of Gsat signaling in the brain. While hypocalcemia and/or hypothyroidism may also play a role in this phenotype, correction of these biochemical defects does not prevent mental impairment in all cases. There is remarkable patient-to-patient variability in AHO, even among patients that carry the same genetic mutation and belong to the same family (see later for a discussion of the underlying genetic defect). 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, for example, acrodysostosis caused by PDE4D mutations44,45 or brachydactyly–mental retardation syndrome caused by HDAC4 mutations.46 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 (see later).

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.47,48 In fact,
The heterotrimeric G protein activation cycle. The heterotrimeric complex is assembled at the basal state, with the α-subunit being associated with a GDP molecule. Upon binding of an agonist (A) to its Gs-coupled receptor (R), the GDP molecule bound to the α-subunit is replaced with a GTP molecule, that is, the activated receptor acts as a guanine nucleotide exchange factor for the α-subunit. The GTP-bound form of the α-subunit dissociates from the βγ subunits and thereby stimulates its downstream effectors, which, in the case of Gsα, includes adenyl cyclase. Note that the free Gsαβγ dimer can also stimulate different downstream effectors. The intrinsic GTP hydrolyase activity of the α-subunit converts the GTP into GDP, resulting in the re-association of the heterotrimer and, therefore, termination of effector stimulation.

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. 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 GDP-GTP exchange on Gsα, causing dissociation of the latter from Gβγ subunits (Fig. 66-3). This allows both Gsα and Gβγ to stimulate their respective effectors. In its GDP-bound state, Gsα can directly activate several different effectors, such as Src tyrosine kinase and certain Ca2+ channels. Apart from these effectors, however, adenyl cyclase is by far the most ubiquitous and the most extensively investigated effector molecule stimulated by Gsα. An integral membrane protein, adenyl cyclase catalyzes the synthesis of the ubiquitous cAMP, which then triggers various cell-specific responses. The activation of adenyl cyclase and other effectors by Gsα is regulated by the intrinsic GTP hydrolyase (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.

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 (an extensive list of these mutations can be found online at OMIM entry #139320 at http://www.ncbi.nlm.nih.gov). Constitutional deletions of the chromosomal arm containing GNAS have also been identified. 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. A complementation assay is typically used for examining Gsα activity, involving patient-derived erythrocyte membranes and membranes from turkey erythrocyte that lack endogenous Gsα (Fig. 66-4). Gsα hypofunction can also be detected in patient-derived platelets by using a functional test that examines the ability of prostaglandin E1 or prostacyclin to inhibit platelet aggregation. 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.

Among the many different inactivating GNAS mutations, a 4-bp deletion in exon 7 has been identified in numerous families, representing a genetic “hot-spot.” In addition, two different mutations are associated with additional phenotypes. 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. The mutation, which entails a repeated AVDT sequence at residues 366 to 369, generates an unstable but constitutively active Gsα.
Pseudohypoparathyroidism, Albright’s Hereditary Osteodystrophy, and Progressive Osseous Mutant due to enhanced GDP-GTP exchange and reduced GTPase activity. While hormone resistance results from the instability of the Gsα-AVDT mutant, the diarrhea is attributed to increased plasma membrane localization of the mutant protein in the small intestine epithelium. 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.

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. However, the Gsα mutants show only impaired coupling to different G protein–coupled receptors, yet show normal Gsα activity in complementation assays that use non-hydrolyzable GTP analogues for stimulation of Gsα activity rather than a receptor agonist. Thus, the mutant Gsα protein causing PHP 1c allows basal cAMP formation but is unable to trigger an increase in response to hormones. Hence, at least some PHP 1c cases are allelic variants of PHP 1a. Although it remains possible that some patients who match the description of PHP 1c develop hormone resistance and AHO due to a novel gene mutation that affects cAMP production without functionally impairing Gsα itself (e.g., inactivating mutations affecting one of the adenylyl cyclases or activating mutations in the phosphodiesterase), it appears unlikely that such putative mutations affect only few G protein–coupled receptors and thus cause limited hormonal resistance as observed in PHP 1a and PHP 1c, but instead dictate the phenotype by the tissue-specificity of their expression levels.

The Complex GNAS Locus

GNAS is a complex locus giving rise to multiple different coding and noncoding transcripts that show monoallelic, parent-of-origin–specific expression profiles (Fig. 66-5). GNAS maps to the telomeric end of the long arm of chromosome 20 (20q13.2-20q13.3). Gsα is encoded by 13 exons, but due to alternative pre-mRNA splicing, the Gsα transcript has several variants. The long and the short Gsα variants (Gsα-L and Gsα-S, respectively) differ from each other by the inclusion or exclusion of exon 3; these Gsα variants are typically detected as 52- and 45-kD protein bands on Western blots. Showing further

Figure 66-5 The GNAS locus. The complex GNAS locus gives rise to multiple transcripts. Boxes and connecting lines indicate exons and introns, respectively. Arrows show the direction of transcription for each transcript. The main transcriptions derived from GNAS and the utilized exons are depicted as rectangles below the gene schematic. Gsα is biallelically expressed except in a small number of tissues, including renal proximal tubules, thyroid glands, gonads, and pituitary gland, in which expression from the paternal allele is silenced (dashed arrow). XLαs, A/B and antisense (AS) transcripts are derived from the paternal allele, and the NESP55 transcript from the maternal allele. Promoters of XLαs, A/B, antisense, and NESP55 transcripts are methylated on the silenced allele, as indicated by CH3 (methylated CpGs) and - (unmethylated CpGs).
complexity, each Gsα form either includes or excludes a CAG trinucleotide (encoding serine) at the start of exon 4. Small, but potentially important, differences have been reported between the activities of Gsα-L and Gsα-S. For example, Gsα-L has been shown to display greater ability to mediate receptor signaling than Gsα-S when partially purified proteins from rabbit liver were examined, although the opposite finding was reported upon the use of cultured pancreatic islet cells. Furthermore, the GDP release rate from Gsα-L appears to be approximately twofold higher than Gsα-S, and, accordingly, fusion proteins involving the β2-adrenergic receptor and Gsα-L have shown higher constitutive activity than those involving the receptor and Gsα-S. Moreover, differences in the subcellular targeting of these two Gsα variants have been reported. Currently, it remains unclear whether these differences translate into biologically significant effects, such as divergence in the variety of effectors and/or the efficiency of effector activation. Nonetheless, a single nucleotide insertion in exon 3 leading to frameshift and early termination has been recently identified in two siblings affected by a mild form of PHP 1a. The mildness of the phenotype is consistent with generation of one of the two main Gsα variants (i.e., Gsα-S). It remains unknown whether this exon 3 mutation impairs agonist responses in an effector- and tissue-specific manner, and this possibility depends on the putative effector selectivity and relative expression levels of Gsα-L and Gsα-S in different tissues.

Recent studies have revealed that GNAS gives rise to multiple additional gene products that show parent-of-origin–specific, monoallelic expression. Besides Gsα, at least two translated GNAS transcripts exist, using distinct upstream promoters and alternative first exons that splice onto exons 2 to 13 encoding Gsα. The most upstream promoter relative to the Gsα promoter drives expression of a neuroendocrine secretory protein with an apparent molecular mass of 55,000 (NESP55). The paternal NESP55 promoter is methylated, and the transcription occurs from the paternal allele. In humans, NESP55 protein is encoded by a single exon, so that Gsα exons 2 to 13 compose the 3′ untranslated region. Expressed in neuroendocrine tissues, peripheral and central nervous system, and some endocrine tissues, NESP55 is a chromogranin-like protein associated with the constitutive secretory pathway. Loss of the expression of NESP55 protein does not seem to have an overt clinical outcome in humans, as evidenced from patients with PHP type 1b (see later). However, its disruption in mice result in a subtle behavioral phenotype characterized by increased reactivity to novel environments. Transcription from the NESP55 promoter is likely to play a role in the regulation of GNAS imprinting (see later).

Another GNAS product is XLαs, which is expressed from the paternal allele. XLαs is expressed abundantly in various parts of the brain and neuroendocrine tissues, and its expression can be readily detected in a variety of other fetal and postnatal tissues. XLαs also uses a distinct upstream promoter and a unique first exon that splices onto Gsα exons 2 to 13. Unlike in the NESP55 transcript, however, the latter portion of the XLαs transcript is included in the translated product, resulting in a protein that is partially identical to Gsα. Consistent with its structural similarity to Gsα, XLαs can mediate receptor-activated adenylyl cyclase stimulation in transfected cells and in transgenic mice. In fact, it appears to be basally more potent than Gsα when expressed at levels comparable to the latter and is able to prolong PTH signaling in transfected cells. However, the phenotype of mice with targeted ablation of XLαs suggests that XLαs has unique, albeit as-yet-undefined, cellular functions. These mice show high early postnatal mortality due to poor adaptation to feeding and impairment in the glucose and energy metabolism. In contrast to Gsα knockout mice, which to a large extent recapitulate the findings in patients with PHP 1a. Findings from adult mice with disrupted XLαs expression indicate that this protein is a negative regulator of increased sympathetic nervous system activity in mice.

The paternal GNAS also gives rise to two additional transcripts. From the sense strand originates the A/B transcript (also termed 1A or 1′), which, similar to NESP55 and XLαs, utilizes an upstream promoter and an alternative first exon (exon A/B) that splices onto Gsα exons 2 to 13. Exon A/B does not comprise an in-frame translation initiation codon but, as demonstrated in vitro, the translation can be started through the use of an AUG located within exon 2, thereby giving rise to an N-terminally truncated protein that localizes to the plasma membrane when transiently expressed in cell lines. Until recently, no evidence has supported the existence of an endogenous A/B protein, and therefore, it was thought that the A/B transcript was a noncoding RNA. Endogenous A/B protein has recently been detected, however, in human fetal kidney by Western blot using an antibody against the C-terminal end of Gsα. It remains possible that A/B has functions both as a protein and as a transcript regulating the expression within the GNAS locus (see later). Another paternal GNAS transcript is derived from the antisense strand. The GNAS antisense transcript (GNAS-AS1), which is formed in humans by at least six primary exons that show multiple alternative splicing patterns, is also considered to be noncoding. Data from mouse models indicate that GNAS-AS1 plays a critical role in silencing the paternal NESP55 promoter in cis. The promoter of GNAS antisense transcript is immediately upstream of the promoter of XLαs. Although the promoters of XLαs and antisense transcript are located together within a large differentially methylated region (DMR), the female germ line–specific imprint is established at the antisense promoter only. The A/B promoter is likewise methylated in the female germ line, but not in the male germ line. Thus, the two germ line imprint marks at the GNAS locus include the promoters of the antisense and A/B transcripts. Accordingly, data from different genetically manipulated mouse models show that these noncoding transcripts are essential for the regulation of imprinted gene expression from GNAS. Imprinted A/B transcription (i.e., expression from only the non-methylated maternal allele) is particularly important for the development of hormone resistance seen in patients with PHP 1b (see later).
Unlike the promoters of NESP55, antisense, XLαs, and A/B transcripts, the promoter of Gsα is not differentially methylated and, accordingly, Gsα expression is biallelic in most tissues.103,112,139,140 Biallelic Gsα expression has been specifically shown in human bone and adipose tissue.141 However, 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.125,142-144 Although devoid of differential methylation, the Gsα promoter exhibits parent-of-origin-specific histone modifications in those tissues where it is monallelic. The active maternal Gsα promoter shows a greater ratio of tri- to di-methylated histone-3 Lys3 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.145 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.

**CLINICALLY DISTINCT, GENETICALLY RELATED PHP 1a VARIANTS**

**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 1952.146 Because of the lack of an abnormal regulation of mineral ion homeostasis, the name pseudopseudohypoparathyroidism (PPHP) was coined to describe this disorder.147 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.148 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). 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.148-150

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 (Fig. 66-6). The tissue-specific imprinting of Gsα expression also explains why the target organ resistance involves only a small subset of tissues despite the involvement of Gsα signaling in a multitude of physiologic responses. 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. The role of tissue-specific Gsα imprinting in the development of PTH resistance has been demonstrated through the generation of mice heterozygous for maternal or paternal disruption of GNAS.142 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.151

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,152 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 2.153 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. 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. A single study also showed that PPHP patients carrying mutations within exons 2 to 13 are born smaller than those carrying mutations within exon 1, thus implicating both Gsα haploinsufficiency and the deficiency of a paternally expressed GNAS product, such as XLαs, in the pathogenesis. Future analyses of patients with PHP 1a and PPHP will be helpful in determining the relative roles of genomic imprinting and haploinsufficiency in the development of individual AHO features.

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 (Fig. 66-7). In POH, the ectopic bone is primarily intramembranous, as opposed to a similar disease termed fibroplasia 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. Several of the identified mutations are identical to those found in PHP 1a/PPHP kindreds. Gsα activity and downstream signaling has been implicated in the control of osteogenic differentiation. 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. In addition, Runx2, a key regulator of osteoblast-specific gene expression, appears to suppress Gsα expression. Thus, osteoprogenitor formation and the early stages of osteoblastic differentiation require reduced levels of cAMP signaling, consistent with the association of inactivating Gsα mutations with the severe ectopic bone formation observed in POH.

Because of the presence of GNAS mutations in both AHO and POH, it appears that additional factors, such as genetic background, epigenetic events, or environmental factors, play a role in the development of POH. Further studies are needed to understand the molecular mechanisms underlying the phenotype variability observed in patients with POH.
factors may determine the penetrance and severity of the ectopic ossifications in these patients that show approximately 50% loss of Gsα activity. 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).\textsuperscript{162,167} Moreover, mutations leading to isolated POH are inherited from male obligate gene carriers only (i.e., inheritance pattern is exclusively paternal).\textsuperscript{162} In fact, in one large kindred, paternal inheritance of a GNAS mutation caused POH, while maternal inheritance of the same mutation caused typical AHO findings (without severe heterotopic ossification).\textsuperscript{162} These findings indicate that the disease mechanism underlying POH is significantly different from that underlying AHO and that deficiency of a GNAS product with exclusive paternal expression, such as XLoS, contributes to the molecular pathogenesis of POH. In addition, a recent study analyzing 12 patients with POH has revealed that the lesions follow a predominantly dermomyotomal distribution that often shows a lateralization bias.\textsuperscript{168} 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.\textsuperscript{168}

**PSEUDOHYPOPARATHYROIDISM TYPE 1b**

Another form of PHP was described by Peterman and Garvey\textsuperscript{165} and by Reynolds and associates.\textsuperscript{170} Now known as pseudohypoparathyroidism type 1b (PHP 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.\textsuperscript{171} 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). This occurs less frequently, however, in PHP 1a since this variant is associated with AHO features and is therefore diagnosed earlier in life. The intact PTH response in the bone is consistent with the lack of Gsα imprinting in bone\textsuperscript{141} and led to the introduction of the term pseudohypo-hyperparathyroidism (PHP-HPT).\textsuperscript{172-174}

The hormone resistance observed in PHP 1b patients develops only after maternal inheritance of the genetic defect\textsuperscript{175} (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\textsuperscript{26,176-178} as well as some elevation in calcitonin level.\textsuperscript{176} Hypothyroidism, as in patients with PHP 1a, likely results from mild TSH resistance and is consistent with the predominantly maternal Gsα expression in the thyroid gland.\textsuperscript{144,177} 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.\textsuperscript{178} 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.\textsuperscript{27,179} This finding implicates impaired PTH actions in the development of hypouricemia in these patients, an interpretation that is consistent with two previous reports describing hyperuricemia in association with hyperparathyroidism.\textsuperscript{180,181} However, hypouricemia resolved in one of the PHP 1b kindreds following treatment with calcium and calcitriol.\textsuperscript{27}

Patients with PHP 1b display normal Gsα bioactivity/levels in easily accessible tissues. Accordingly, coding Gsα mutations are ruled out in these patients. In one family, however, a mutation located in exon 13 (in-frame deletion of Ile,\textsuperscript{382} del382Ile) was reported, leading to the uncoupling of Gsα from the PTHR-1 but not other receptors that were expressed in LLC-PK cells, including the TSHR, LHR, and β-adrenergic receptor,\textsuperscript{182} which are of renal origin and express endogenous Gsα. These findings suggested an isolated PTH resistance as seen in PHP 1b, leading to the conclusion that the del382Ile mutation in Gsα represents a rare cause of PHP 1b. However, this conclusion has been questioned, as the use of transfected mouse embryonic fibroblasts null for endogenous Gsα showed that del382Ile leads to uncoupling from not only PTHR-1 but also the β-adrenergic receptor.\textsuperscript{43} Because of a lack of Gsα mutations and because Gsα activity/levels in easily accessible tissues are normal in PHP 1b patients, inactivating mutations that affect the gene encoding PTHR-1 was considered in the past.\textsuperscript{183} However, several different studies have excluded such mutations as the cause of this disease.\textsuperscript{184-187} Instead, homozygous or compound heterozygous, inactivating mutations of PTHR-1 have been revealed as the cause of Blomstrand’s chondrodysplasia, an embryonic lethal disorder with severe skeletal abnormalities.\textsuperscript{188} A homozygous PTHR-1 mutation was furthermore identified in patients with Eiken syndrome, an autosomal recessive skeletal dysplasia,\textsuperscript{189} and heterozygous inactivating PTHR-1 mutations were observed in several families with an autosomal dominant form of delayed tooth eruption\textsuperscript{190-193} (i.e., disorders without evidence for hypocalcemia and hyperphosphatemia because of impaired actions of PTH).

Based on genomewide linkage analysis, the genetic defect underlying PHP 1b maps to a region of chromosome 20q13.3 that comprises the GNAS locus,\textsuperscript{175} but the critical interval excludes all the coding GNAS exons, including those that encode Gsα.\textsuperscript{26,173} On the other hand, patients with PHP 1b display epigenetic abnormalities within the GNAS locus.\textsuperscript{26,194} 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.\textsuperscript{26,194} 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 NESP55.13,194 These abnormalities are associated with biallelic expression of A/B, XLαs, and antisense transcripts and silencing of the NESP55 transcript. Together with the genetic linkage data, these imprinting defects suggested that the mutation causing PHP 1b disrupts a regulatory element that controls GNAS imprinting. However, evidence for incomplete penetrance regarding the GNAS imprinting defects has been reported in one kindred, in whom some individuals lacked loss of imprinting and were healthy despite maternally inheriting the disease-associated haplotype.195 Thus, the imprinting abnormalities of GNAS appear to be required for the development of PHP 1b. Consistent with the importance of imprinting in the disease mechanism, several patients with PHP 1b have been reported to have paternal uniparental isodisomy involving whole or parts of chromosome 20 that comprise the GNAS locus.176,196-199

In multiple familial PHP 1b cases with isolated exon A/B loss of imprinting, a unique 3-kb microdeletion at the centromeric neighboring STX16 locus has been identified200 (Fig. 66-8). The deleted region comprises STX16 exons 4 to 6 and is flanked by two direct repeats, which may underlie the mechanism whereby this deletion occurs. This is consistent with the presence of the same microdeletion in many unrelated families with different ethnic and racial origin.13,23,27,178,179,201,202 In a single kindred, a different microdeletion within STX16 has been reported, removing exons 2 to 4 and overlapping with the 3-kb microdeletion by approximately 1.3 kb.19 Recently, a maternally inherited 24.6-kb deletion composing STX16 exons 2 to 8 has also been discovered in another family with this disorder.203 Thus, the disruption of STX16 appears to be the common genetic defect in cases with isolated loss of exon A/B imprinting. The parental origin of these STX16 deletions correlates well with the mode of inheritance of PHP 1b. It is maternally inherited in affected individuals and paternally inherited in unaffected carriers. This gene encodes syntaxin-16, a member of the SNARE family proteins. However, STX16 does not appear to be imprinted,19 and it is therefore unlikely that the loss of one STX16 copy leads to PHP 1b. Instead, since the maternal inheritance is associated with loss of exon A/B imprinting on the same allele, these deletions are presumed to disrupt a cis-acting element controlling the establishment or maintenance of exon A/B imprinting. Other than genetic evidence, however, no currently available data corroborate this prediction. A mouse model carrying a deletion equivalent to the 3-kb STX16 deletion in humans has been generated, but neither maternal nor paternal inheritance of this genetic alteration causes PTH resistance or any alterations in GNAS imprinting.204 Animals with the homozygous Stx16 deletion are also healthy. It thus appears plausible that the imprinting control element of GNAS located within STX16 in the human is not precisely at the same location in the mouse. Nonetheless, the absence of a phenotype in the Stx16 deletion mice argues against a model in which syntaxin 16, the product of this gene, is required in the oocyte for proper exon A/B imprinting.

![Figure 66-8](image_url)

**Figure 66-8** Mutations identified in AD-PHP 1b patients and their effects on GNAS imprinting. The most frequent mutation is a 3-kb deletion within STX16, a gene located more than 200 kb upstream of GNAS. This deletion and another overlapping deletion in the same gene are predicted to disrupt a cis-acting control element of GNAS that is required for the imprint mark located at exon A/B. The same prediction is also true for a 19-kb deletion of NESP55 and upstream genomic regions, which was identified in affected individuals of AD-PHP 1b kindreds with isolated loss of A/B methylation. Deletions of the NESP55 DMR including exons 3 and 4 of the antisense transcript and a more recently identified deletion that only includes antisense transcript exons 3 and 4 have been identified in some AD-PHP 1b kindreds. These reveal a cis-acting element controlling imprinting of the entire maternal GNAS allele. Boxes and connecting lines indicate exons and introns, respectively. STX16 exons and GNAS exons 2 to 13 are shown as single rectangles for simplicity. Paternal (pat) and maternal (mat) methylation (CH3), and parental origin of transcription (arrows) are indicated. Tissue-specific silencing of the paternal Gsα transcription is depicted by a dotted arrow. The identified deletions are shown by horizontal bars.
In two unrelated familial cases of PHP 1b in whom the affected individuals carried broad GNAS imprinting defects, maternally inherited deletions of the entire NESP55 DMR, including exons 3 and 4 of the antisense transcript, have been identified (see Fig. 66-8).\textsuperscript{13,133} The deletions are 4 kb and 4.7 kb large and have breakpoints located in similar locations. The unaffected carriers in these families display an apparent loss of NESP55 methylation due to the loss of this region from the normally methylated paternal allele but do not show other imprinting GNAS defects. The affected individuals show a loss of imprinting in the entire maternal allele. The presence of similarly large deletions at the NESP55 DMR has been excluded in a number of sporadic PHP 1b cases.\textsuperscript{13,133} However, a different 4.2-kb deletion has been identified in the affected individuals of a different PHP 1b kindred who displayed broad GNAS imprinting defects (see Fig. 66-8).\textsuperscript{205} This new deletion also includes antisense exons 3 and 4 but spares exon NESP55, overlapping with the previously identified two deletions by about 1.5 kb.\textsuperscript{205} Thus, these identified deletions reveal the putative location of another control element required for the imprinting of the entire maternal GNAS allele.

A more recent study revealed a 19-kb genomic deletion removing exon NESP55 and a large portion of the intron between NESP55 and antisense exon 4 in a kindred with AD-PHP 1b with isolated loss of A/B methylation.\textsuperscript{206} Since these patients lacked broad GNAS methylation abnormalities, the identified deletion points to the existence of another control element of A/B methylation, without effects on other DMRs. The study of a mouse model in which Nesp55 transcription was prematurely truncated revealed loss of imprinting at exon 1A (the equivalent of human exon A/B) and, less consistently, the antisense promoter and exon XL.\textsuperscript{207} Taken together with the genetic findings in PHP 1b patients, it appears that the establishment of methylation imprints on the maternal GNAS allele is essential for allowing expression of Gsα in the proximal renal tubule and other tissues, including the thyroid gland, in which this GNAS product is derived only from the maternal allele. Furthermore, the evidence that exon A/B methylation requires transcription from the NESP55 promoter\textsuperscript{207} raises the possibility that even small deletions or even point mutations can prevent the generation of NESP55 pre-mRNA, thus leading to PHP 1b.

Sporadic disease appears to be the most frequent cause of PHP 1b. These cases all show broad GNAS methylation defects. However, the maternal allele is frequently shared between affected and unaffected siblings, suggesting that these cases may carry small de novo mutations in this region. However, in some families the affected female passed either allele #1 or allele #2 to their children, who are all unaffected by PHP 1b and show no methylation abnormality at the GNAS locus.\textsuperscript{208,209} It is therefore possible that some of the sporadic PHP 1b cases carry homozygous or compound heterozygous mutations in an entirely different genomic location resulting in a putative autosomal recessive mode of inheritance.\textsuperscript{208} Consistent with this conclusion, few patients affected by imprinting disorders without obvious PTH-resistance show GNAS methylation changes.\textsuperscript{210,211} Moreover, methylation changes in some other imprinted genomic loci have been revealed in a study of sporadic PHP 1b cases.\textsuperscript{212} It has also been suggested that the broad GNAS imprinting defects observed in sporadic PHP 1b patients result from stochastic defects in the regulation of imprinting.\textsuperscript{201}

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.\textsuperscript{13} 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 who exhibit GNAS imprinting defects at two or more GNAS DMRs also reveals that female patients have significantly higher serum PTH levels than male patients, suggesting that hormone resistance is more severe in females.\textsuperscript{13}

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.\textsuperscript{27,202,213-215} This may suggest that Gsa imprinting occurs in more tissues than currently recognized, though there are alternative explanations. 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. In one case, the mother of two affected siblings with short metacarpals and loss of A/B methylation also exhibited short metacarpals despite lacking any GNAS epigenetic abnormalities,\textsuperscript{202} suggesting that the finding of short metacarpals is unrelated to the epigenetic defect in that family. In addition, the observed coexistence of GNAS imprinting defects and AHO can result from a large genomic deletion comprising at least the promoter of Gsa and one or more differentially methylated regions. In fact, such a large deletion leading to misdiagnosis of PHP 1b has been discovered in a case with apparent loss of A/B methylation and AHO features.\textsuperscript{216}

### 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,\textsuperscript{217} and several reports describe evidence for a self-limited form of this disease in newborns, which could indicate that it is transient in nature.\textsuperscript{35,218-220} The molecular defect and pathophysiological 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.\textsuperscript{19} 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 (see later). Alternatively, the PTH signaling pathways that utilize other G proteins, such as Gq or G\(11\), may be defective in patients with PHP 2. The signaling mediated by the Gq/G\(11\) 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 (DAG). 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.\(^{221,222}\) 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.\(^{223}\) 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-\(\alpha\)-hydroxylase and lead to normal serum 1,25(OH)\(_2\)D, unless it is combined with vitamin D deficiency. 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,\(^{224}\) suggesting that some PHP 2 cases may in fact reflect vitamin D deficiency.\(^{225,226}\)

**ACRODYSOSTOSIS WITH HORMONAL RESISTANCE**

A recent report has described three patients who had resistance to PTH and some other hormones but showed unimpaired urinary cAMP excretion in response to exogenously administered recombinant PTH.\(^{227}\) Consistent with resistance to the actions of PTH downstream of cAMP/PKA, PTH-induced urinary phosphate excretion was lost, and PTH-induced inhibition of urinary fractional calcium excretion was impaired. These unrelated patients, who could thus be classified as having a variant of PHP 2 based on their renal PTH responsiveness, also displayed acrodysostosis, a skeletal dysplasia that resembles, but is more severe than, the skeletal defects observed in AHO. Acrodysostosis, also known as Maroteaux-Malamut syndrome, includes severe bradydactyly, peripheral dysostosis, and nasal hypoplasia.\(^{228-230}\) This disorder is termed *acrodysostosis with hormonal resistance* (ADOHR). Analysis of DNA from these patients revealed a recurrent heterozygous nonsense mutation of the gene encoding cAMP-dependent protein kinase (PKA) type 1 alpha regulatory subunit (PRKAR1A; p.Arg368X). This mutation leads to a mutant PRKAR1A protein missing the last 14 C-terminal amino acids. Accordingly, cAMP cannot induce dissociation of this mutant regulatory subunit from the catalytic subunit, thereby keeping PKA in its inactive form. Several other patients with ADOHR have been described in more recent studies in which additional PRKAR1A mutations have been documented.\(^{44,45,231-233}\) Note that the distal tubular actions of PTH appear to be impaired in patients with ADOHR, unlike in patients with PHP 1a and PHP 1b, consistent with the normal biallelic expression of Gs\(\alpha\) in the distal renal tubule. Nevertheless, the similarity between this disorder and PHP 1a with respect to the repertoire of hormone resistance is quite striking and highlights the critical nature of the cAMP signaling pathway in the actions of these hormones (Fig. 66-9).\(^{234}\)

Genetic defects in another protein within the cAMP signaling pathway, cAMP phosphodiesterase type 4D (PDE4D), have also been identified upon exome sequencing of DNA from some patients with acrodysostosis.\(^{44,45}\) These heterozygous missense mutations in PDE4D are associated with acrodysostosis, but the patients usually lack endocrine abnormalities. Other missense mutations of PDE4D have been identified in additional patients who also show acrodysostosis in the absence of hormone resistance (termed *acrodysostosis without hormonal resistance* [ADOP4]).\(^{232,233}\) Thus, PDE4D mutations are not associated with renal PTH resistance, and accordingly, unlike patients with PRKAR1A mutations, who demonstrate elevated basal urinary cAMP levels, patients with PDE4D mutations show normal basal and PTH-induced urinary cAMP level.\(^{232}\) The biochemical mechanisms underlying ADOP4 have yet to be elucidated. It is predicted, however, that the PDE4D mutations are gain-of-function, given that PDE4D limits the intracellular level of cAMP.\(^{236}\)

**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. GH deficiency can also be treated with recombinant human GH (rhGH) and is found to be efficacious in prepubertal patients with PHP 1a.\(^{237}\) 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. 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. The treatment involves oral calcium supplements and activated vitamin D analogues, such as 1,25(OH)\(_2\)D (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)\(_2\)D. 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. 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. 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)$_2$D may need to be reduced.

**SUMMARY**

PHP refers to a group of disorders characterized by PTH resistance associated with hypocalcemia, hyperphosphatemia, and elevated serum PTH. Proximal tubular resistance to PTH is the most prominent hormonal defect but, depending on the underlying genetic defect, resistance to other hormones is also observed. PTH and these other hormones all exert their actions via receptors that couple to Gsα. The primary genetic cause of PHP 1 and related disorders is mutations that affect the complex GNAS locus, the gene encoding Gsα. These mutations result in decreased expression/activity of Gsα but also affect some of the other gene products derived from GNAS. The nature and the parental origin of the GNAS mutation is an important determinant of the clinical manifestations. Mutations that affect coding Gsα exons lead to broader clinical abnormalities than mutations that disrupt GNAS imprinting. Due to the tissue-specific imprinting of Gsα, hormone resistance develops only after maternal inheritance. AHO typically occurs after both maternal and paternal inheritance of coding Gsα mutations, although the repertoire of some AHO features also follows an imprinted mode of inheritance. PHP 2 is rare, and the molecular determinants of at least one variant with skeletal dysplasia involve the regulatory subunit of PKA.

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