TABLE 424-6 CLASSIFICATION OF PSEUDOHYPOPARATHYROIDISM (PHP) AND PSEUDOPSEUDOHYPOPARATHYROIDISM (PPHP)

Type	Hypocalcemia, Hyperphosphatemia	Response of Urinary cAMP to PTH	Serum PTH	$G_s\alpha$ Subunit Deficiency	AHO	Resistance to hormones other than PTH
PHP-Ia	Yes	↓	↑	Yes	Yes	Yes
PPHP	No	Normal	Normal	Yes	Yes	No
PHP-Ib	Yes	↓	↑	No	No	Yes (in some patients)
PHP-II	Yes	Normal	↑	No	No	No
Acrodysostosis with hormonal resistance	Yes	Normal (but ↓ phosphaturic response)	↑	No	Yes	Yes

Abbreviations: ↓, decreased; ↑, increased; AHO, Albright's hereditary osteodystrophy; PTH, parathyroid hormone.

PHP-IA AND PHP-IB Individuals with PHP-I, the most common of the disorders, show a deficient urinary cAMP response to administration of exogenous PTH. Patients with PHP-I are divided into type Ia and type Ib. Patients with PHP-Ia show evidence for AHO and reduced amounts of $G_s\alpha$ protein/activity, as determined in readily accessible tissues such as erythrocytes, lymphocytes, and fibroblasts. Patients with PHP-Ib typically lack evidence for AHO and they have normal $G_s\alpha$ activity. PHP-Ic, sometimes listed as a third form of PHP-I, is really a variant of PHP-Ia, although the mutant $G_s\alpha$ shows normal activity in certain in vitro assays.

Most patients who have PHP-Ia reveal characteristic features of AHO, which consist of short stature, round face, obesity, skeletal anomalies (brachydactyly), intellectual impairment, and/or heterotopic calcifications. Patients have low calcium and high phosphate levels, as with true hypoparathyroidism. PTH levels, however, are elevated, reflecting resistance to hormone action.

Amorphous deposits of calcium and phosphate are found in the basal ganglia in about one-half of patients. The defects in metacarpal and metatarsal bones are sometimes accompanied by short phalanges as well, possibly reflecting premature closing of the epiphyses. The typical findings are short fourth and fifth metacarpals and metatarsals. The defects are usually bilateral. Exostoses and radius curvus are frequent.

Inheritance and Genetic Defects Multiple defects at the *GNAS* locus have now been identified in PHP-Ia, PHP-Ib, and PPHP patients. This gene, which is located on chromosome 20q13.3, encodes the α-subunit of the stimulatory G protein ($G_s\alpha$), among other products (see below). Mutations include abnormalities in splice junctions associated with deficient mRNA production, point mutations, insertions, and/or deletion that all result in a protein with defective function resulting in a 50% reduction of $G_s\alpha$ activity in erythrocytes or other cells.

Detailed analyses of disease transmission in affected kindreds have clarified many features of PHP-Ia, PPHP, and PHP-Ib (Fig. 424-7). The former two entities, often traced through multiple generations, have an inheritance pattern consistent with genetic imprinting. The phenomenon of gene imprinting, involving methylation of genetic loci, independent of any mutation, impairs transcription from either the maternal or the paternal allele (Chap. 82). The $G_s\alpha$ transcript is biallelically expressed in most tissues; expression from paternal allele is silenced through as-of-yet unknown mechanisms in some tissues including the proximal renal tubules and the thyroid; consequently, inheritance of a defective paternal allele has no implications with regard to hormonal function. Thus, females affected by either PHP-Ia or PPHP will have offspring with PHP-Ia, if these children inherit the allele carrying the *GNAS* mutation; in contrast, if the mutant allele is inherited from a male affected by either disorder, the offspring will exhibit PPHP. Consistent with these data in humans, gene-ablation studies in mice have shown that inheritance of the mutant $G_s\alpha$ allele from the female causes much reduced $G_s\alpha$ protein in renal cortex, hypocalcemia, and resistance to PTH. Offspring inheriting the mutant allele from the male showed no evidence of PTH resistance or hypocalcemia.

Imprinting is tissue selective. Paternal $G_s\alpha$ expression is not silenced in most tissues. It seems likely, therefore, that the AHO phenotype recognized in PPHP as well as PHP-Ia reflects $G_s\alpha$ haploinsufficiency during embryonic or postnatal development.

The complex mechanisms that control the *GNAS* gene contribute to challenges involved in unraveling the pathogenesis of these disorders, especially that of PHP-Ib. Much intensive work with families in which multiple members are affected by PHP-Ib, as well as studies of the complex regulation of the *GNAS* gene locus, have now shown that PHP-Ib is caused by microdeletions within or upstream of the *GNAS* locus, which are associated with a loss of DNA methylation at one or several loci of the maternal allele (Table 424-6). These abnormalities in methylation silence the expression of the gene. This leads in the proximal renal tubules—where $G_s\alpha$ appears to be expressed exclusively from the maternal allele—to PTH resistance.

PHP-Ib, lacking the AHO phenotype in most instances, shares with PHP-Ia the hypocalcemia and hyperphosphatemia caused by PTH resistance, and thus the blunted urinary cAMP response to administered PTH, a standard test to assess the presence or absence of hormone resistance (Table 424-6). Furthermore, these endocrine abnormalities become apparent only if the disease-causing mutation is inherited maternally. Bone responsiveness may be excessive rather than blunted in PHP-Ib (and in PHP-Ia) patients, based on case reports that have emphasized an osteitis fibrosa–like pattern in several PHP-Ib patients.

PHP-II refers to patients with hypocalcemia and hyperphosphatemia, who have a normal urinary cAMP but an impaired urinary phosphaturic

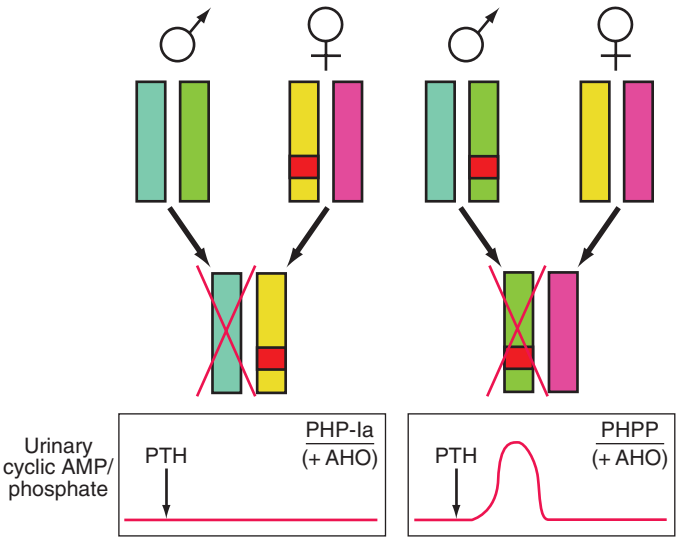

FIGURE 424-7 Paternal imprinting of renal parathyroid hormone (PTH) resistance. An impaired excretion of urinary cyclic AMP and phosphate is observed in patients with pseudohypoparathyroidism type Ia (PHP-Ia). In the renal cortex, there is selective silencing of paternal $G_s\alpha$ expression. The disease becomes manifest only in patients who inherit the defective gene from an obligate female carrier (*left*). If the genetic defect is inherited from an obligate male gene carrier, there is no biochemical abnormality; administration of PTH causes an appropriate increase in the urinary cyclic AMP and phosphate concentration (pseudo-PHP [PPHP]; *right*). Both patterns of inheritance lead to Albright's hereditary osteodystrophy (AHO), perhaps because of haplotype insufficiency—i.e., both copies of $G_s\alpha$ must be active for normal bone development.