Mini-review

Genetics of pseudohypoparathyroidism

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Summary

Pseudohypoparathyroidism (PHP) is a group of disorders defined by the presence of renal parathyroid hormone (PTH) resistance, resulting in biochemical hypoparathyroidism in the presence of elevated serum PTH levels. Most PHP patients have diminished urinary cyclic AMP responses to administered PTH, indicating a defect in proximal PTH signaling. Heterozygous inactivating mutations of $G_s\alpha$, the G protein which couples hormone and other receptors to intracellular cyclic AMP production, lead to Albright hereditary osteodystrophy (AHO), a disorder characterized by skeletal defects, short stature, obesity, and neurobehavioral defects. Maternal inheritance of $G_s\alpha$ mutations leads to both AHO and resistance to multiple hormones, including PTH, a condition referred to as PHP type 1a. In contrast, paternal inheritance of the same mutations leads to AHO alone. This is because $G_s\alpha$ is imprinted in a tissue-specific manner, and is poorly expressed from the paternal allele in various tissues, including renal proximal tubules. PHP type 1b patients have renal PTH resistance in the absence of AHO resulting from imprinting defects of the $G_s\alpha$ gene (*GNAS*) in which both parental alleles have a paternal-specific imprinting pattern. The maternal imprint is lost in one specific region located just upstream of the $G_s\alpha$ promoter, which likely leads to $G_s\alpha$ deficiency in specific tissues (such as proximal tubules) where $G_s\alpha$ is normally expressed primarily from the maternal allele. Familial PHP type 1b is also associated with a deletion mutation upstream of *GNAS* within a region presumed to be important for *GNAS* imprinting. This mutation only leads to a *GNAS* imprinting defect and PTH resistance when it is inherited maternally.

KEY WORDS: pseudohypoparathyroidism, genomic imprinting, G protein, cyclic AMP.

Introduction

Pseudohypoparathyroidism (PHP) is a group of disorders in which patients develop the signs and symptoms of hypoparathyroidism due to end organ resistance to parathyroid hormone (PTH) (1, 2). Patients with this disorder always present with elevated levels of serum PTH, which is usually, although not always, associated with hypocalcemia and hyperphosphatemia. PTH resistance in PHP is primarily manifested in the renal proximal tubule. Because this tissue is unable to respond to PTH, patients have reduced renal phosphate clearance, leading to hyperphosphatemia. The combined effects of hyperphosphatemia and reduced PTH responsiveness leads to reduced synthesis of 1,25 dihydroxyvitamin D (1,25D) in proximal tubules. 1,25D deficiency leads to hypocalcemia through reduced gastrointestinal calcium absorption and PTH-stimulated calcium release in bone.

The PTH resistance in PHP appears to be limited to renal proximal tubules. Osteoblastic cells isolated from PHP patients have normal PTH responsiveness (3, 4) and some PHP patients present with hyperparathyroid bone disease due to the skeletal effects of chronically elevated PTH levels (5, 6). PTH action in the distal nephron (which promotes calcium reabsorption) also remains intact, and this is why PHP patients, unlike patients with primary hypoparathyroidism, are not prone to hypercalciuria upon treatment (7).

PTH mediates its actions by binding to a seven transmembrane receptor that can bind PTH and PTH related peptide (PTHrP) with similar affinities (8, 9). Upon hormone binding, this receptor activates two heterotrimeric G proteins. At lower hormone concentrations the G protein G_s is activated, leading to stimulation of adenylyl cyclase and generation of the second messenger cyclic AMP (cAMP). cAMP mediates most of its actions by interacting with the cAMP-dependent protein kinase (protein kinase A), although other cAMP effectors have been more recently identified (10). cAMP mimics the effects of PTH on renal phosphate handling and vitamin D metabolism (11). At higher hormone concentrations the PTH/PTHrP receptor is also able to activate the G protein G_q, which stimulates phospholipase C.

Most PHP patients (PHP type 1) have a markedly reduced urinary cAMP response to administered PTH (12, 13), indicating the presence of a signaling defect involving the receptor, G_s, or adenylyl cyclase in renal proximal tubule cells. Rarely patients will have a normal cAMP response but a reduced phosphaturic response to PTH (PHP type 2), consistent with a defect downstream of cAMP generation (14). However the defect in PTH responsiveness in PHP type 2 patients is usually reversed after treatment with calcium or vitamin D, indicating that this is not a fixed genetic defect but rather a secondary and reversible effect of hypocalcemia and/or vitamin D deficiency (15).

In most cases PHP type 1 results from reduced G_s activity due to genetic or epigenetic defects of the gene encoding it's specific -subunit G_s . Like all heterotrimeric G proteins, G_s is composed of three subunits (, , and) which are all the products of separate genes (16). G_s interacts with both receptors and effectors, such as adenylyl cyclase, and has a guanine nucleotide binding site. The and subunits form tightly bound heterodimers. In the inactive state G_s has GDP bound to the guanine nucleotide binding site and is associated with . The hormone bound receptor promotes GDP release, which leads to GTP binding and dissociation of G_s from . The active GTP-

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bound G_s is capable of interacting with and stimulating adenylyl cyclase. G_s is inactivated by an intrinsic GTPase activity that hydrolyzes bound GTP to GDP. Mutations within specific residues (Arg^{201}, Gln^{227}) critical for the GTPase reaction lead to constitutively active forms of G_s, and such somatic mutations are the genetic cause of various endocrine tumors, fibrous dysplasia of bone, and the McCune-Albright syndrome (2, 17-19). Recent studies suggest that G_s may have other effectors besides adenylyl cyclase, such as *src* tyrosine kinase (20).

The gene encoding G_s is named *GNAS* and is located at 20q13 (21). The G_s coding region is spread over 13 exons. Alternative splicing of exon 3 results in the generation of long and short forms of G_s protein that are all capable of mediating signaling between receptor and adenylyl cyclase. *GNAS* is now recognized to be a complex imprinted gene which generates multiple gene products through the use of alternative promoters and first exons which splice onto a common set of downstream exons (exons 2-13, see Fig. 1) (16). The most upstream promoter generates transcripts for the chromogranin-like protein NESP55, which is structurally and functionally unrelated to G_s. The next promoter generates transcripts for XL s, a neuroendocrine-specific G_s isoform that has an extra-long amino-terminal extension encoded within its specific first exon. NESP55 and XL s are oppositely imprinted: NESP55 is expressed only from the maternal allele and its promoter region is DNA methylated on the paternal allele while XL s is only expressed from the paternal allele and its promoter is methylated on the maternal allele (22, 23). The XL s promoter region also generates paternal-specific antisense transcripts that are likely to be important for paternal NESP55 imprinting (24). The next promoter region (the exon 1A region), which is located 35 kilobases downstream of the XL s promoter is methylated on the maternal allele and generates untranslated transcripts of unknown function from the paternal allele (25, 26). Just downstream of exon 1A is the G_s promoter, which is unmethylated even though, as discussed below, G_s is imprinted in a tissue-specific manner (26).

PHP type 1 can be further subcategorized (Table 1) based upon the type of underlying G_s defect and the presence or absence of Albright hereditary osteodystrophy (AHO), a congenital syndrome characterized by skeletal defects, short stature, and obesity. PHP type 1a is defined as the co-occurrence of renal PTH (and other hormone) resistance and AHO and is caused by heterozygous inactivating G_s mutations. PHP type 1b patients have renal PTH resistance in the absence of AHO, which results from a *GNAS* imprinting defect. Rarely patients with the PHP type 1a phenotype have no evidence for a G_s defect, and this has been referred to as PHP type 1c. In this review we will focus on the genetic and epigenetic defects associated with PHP types 1a and 1b, respectively.

Pseudohypoparathyroidism type 1a (Albright hereditary osteodystrophy)

AHO is a congenital syndrome in which patients present with short stature, brachydactyly, obesity, subcutaneous ossifications, facial features such as hypertelorism or depressed nasal bridge, and mental deficits or developmental delay (Fig. 2). The severity of the phenotype varies significantly, and 50% or less present with neurobehavioral problems (27, 28). Even within the same kindred, some affected patients also develop resistance to PTH, thyrotropin and gonadotropins (PHP type 1a) while other affected patients develop AHO but have no evidence for hormone resistance (a condition also known as pseudopseudohypoparathyroidism [PPHP]).

All AHO patients (both PHP type 1a and PPHP patients) have a ~50% reduction in G_s bioactivity in membranes from various tissues, such as blood cells and fibroblasts (29, 30), and this is due in most cases to a similar reduction in G_s mRNA and/or protein expression (31-33). As these findings would predict, most AHO (both PHP type 1a and PPHP) patients have heterozygous inactivating mutations within or surrounding the G_s coding region exons (34-36). These mutations are spread throughout the G_s coding exons and splice junctions, with the exception of exon 3, probably because transcripts with this exon spliced out still produce a functional G_s protein. There is no obvious differences in phenotype between patients with exon 1 mutations (which only affect G_s expression) from mutations in the other downstream exons which are common to all transcripts, suggesting that the phenotype results specifically from G_s deficiency. One 4 base pair deletion in exon 7 has been identified in >22 families, which probably results from pausing of DNA polymerase and slipped-strand mispairing during replication (37). Several other mutations have also been reported in more than one kindred, but most mutations have been identified in one kindred each.

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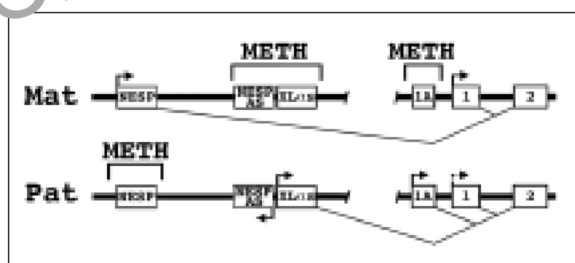

Figure 1 - General organization of the *GNAS* locus. The maternal (Mat, above) and paternal (Pat, below) alleles of *GNAS* are depicted with regions of methylation shown above (METH) and splicing patterns shown below. Transcriptionally active promoters are indicated by horizontal arrows in the direction of transcription. The alternative first exons for NESP55 (NESP), XL s, paternal untranslated mRNA transcripts (exon 1A), and G_s (exon 1) are shown splicing onto a common downstream exon (exon 2). The first exon for paternal antisense transcripts are also shown (NESPAS). Common downstream exons 3-13 as well as the downstream exons of the antisense transcript (NESPAS) are not shown. G_s is paternally imprinted in some tissues, indicated by the dashed arrow. The diagram is not drawn to scale.

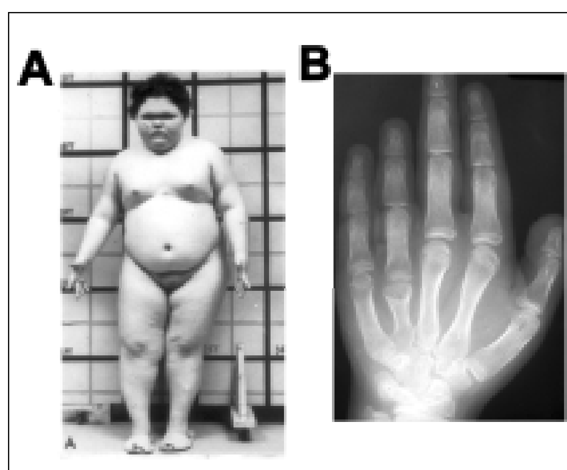

Figure 2 - Features of AHO. A. Photograph of AHO patient showing obesity, rounded face, and short stature. B. Hand radiograph showing brachydactyly of the 4th metacarpal bone.

Most inactivating mutations are frameshift or splice junction mutations that prevent mRNA expression or missense mutations which lead to unstable proteins and reduced protein expression. With few exceptions there is no obvious genotype-phenotype correlation. However some missense mutations lead to specific defects in G_s biochemical function. Various mutations altering carboxy-terminal residues prevent G protein receptor interactions (38, 39). Mutations in Glu^{259} or Arg^{231} within the conformational switch regions lead to a receptor activation defect due to an inability to stabilize the active conformation (40, 41). A mutation at residue Arg^{258} leads to both increased GDP binding in the basal state and an increased rate of GTP hydrolysis in the active state (42, 43). The Ala^{366} to serine mutation leads to an interesting phenotype in which males develop the co-occurrence of PHP type 1a and gonadotropin-independent precocious puberty (44). This mutation promotes GDP release in the absence of hormone receptor stimulation. At core body temperature the resulting protein is thermolabile due to the lack of bound guanine nucleotide, resulting in PHP type 1a. At the slightly lower temperature of the testis, the protein is stable but is constitutively activated as GDP release is the rate-limiting step for G protein activation.

The fact that identical G_s mutations are present in both PHP type 1a and PPHP patients within the same kindred confirms that AHO is an autosomal dominant disorder that probably is the result of G_s haploinsufficiency in most tissues. However this could not explain how a heterozygous mutation could result in multihormone resistance in only a subset of patients. The first clue to this paradox was the observation that whether or not an individual develops hormone resistance (PHP type 1a) is dependent on parental inheritance: maternal inheritance results in PHP type 1a in offspring while paternal inheritance results in PPHP (45). Studies in a G_s knockout model showed that this inheritance pattern is explained by genomic imprinting of G_s (46) (Fig. 3). G_s is primarily expressed from the maternal allele in proximal tubules and therefore mutation of the active maternal allele leads to G_s deficiency in this tissue and renal PTH resistance. In contrast, paternal mutations have little or no effect on G_s expression in proximal tubules or PTH action. Studies have now confirmed that G_s is also imprinted in human pituitary, thyroid, and ovary (47-50) and this likely explains why PHP type 1a patients often present with growth hormone deficiency (51, 52), thyrotropin resistance and hypothyroidism (53, 54) and ovarian dysfunction (55).

However G_s imprinting is tissue-specific and therefore G_s is biallelic expressed in most tissues, including the renal medulla and most likely bone. This is consistent with the fact that both maternal and paternal heterozygous G_s mutations (in PHP type 1a and PPHP, respectively) produce G_s haploinsufficiency in most tissues, and this haploinsufficiency is most likely the underlying cause of the AHO syndrome. Tissue-specific G_s imprinting is also the likely explanation for why PHP type 1a patients do not have skeletal PTH resistance (3) and do not lose the ability of PTH to stimulate calcium reabsorption in the distal nephron (7). Likewise it can explain why PHP type 1a patients do not show clinical resistance to other hormones also

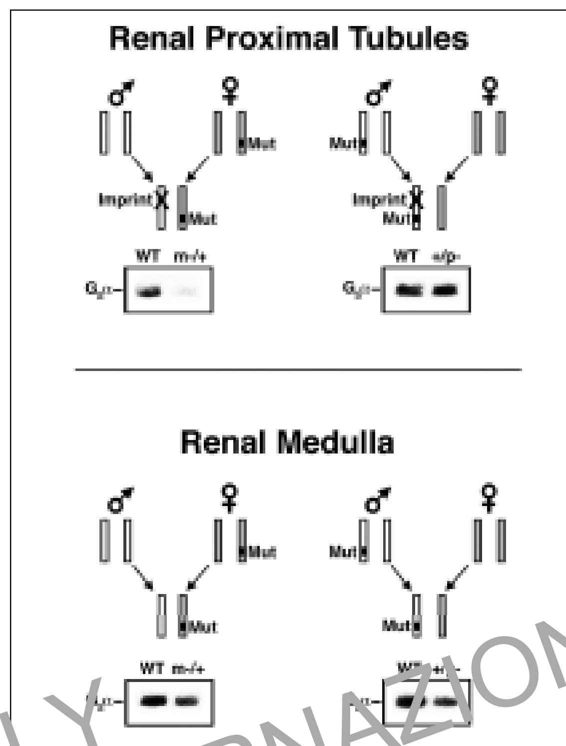

Figure 3 - Tissue-specific G_s imprinting and the effect of heterozygous null mutations. In renal proximal tubules (above) G_s is imprinted on the paternal allele (denoted with X). Mutation (Mut) on the active maternal allele (gray rectangle, left panel) leads to almost total G_s deficiency and PTH resistance while mutation on the paternal allele (right panel) has little effect on G_s expression or PTH sensitivity. This is confirmed by immunoblots of renal cortical membranes isolated from wild type mice (WT) and mice with disruption of the *GNAS* maternal (m-/+) and paternal (+/p-) alleles, respectively (46). In most other tissues (below) G_s is not imprinted and therefore both maternal and paternal mutations lead to ~50% loss of G_s expression, as shown in immunoblots of renal inner medulla membranes from the same mice (46). (Figure adapted from Weinstein, et al. Endocr Rev. 2001; 22:675-705).

Table I - Different forms of pseudohypoparathyroidism (PHP).

	Accompanying Features	Gene Defect
PHP type 1a	AHO, multihormone resistance	Maternal G_s null mutations
PHP type 1b	Borderline TSH resistance in some cases	*GNAS* imprinting defect with maternal *STX16* deletion (familial) *GNAS* imprinting defect (sporadic) Paternal uniparental disomy of 20q Maternal deletion of G_s isoleucine 382
PHP type 1c	AHO, multihormone resistance	No G_s defect; Defect unknown
PHP type 2	Often calcium, vitamin D deficiency	None known; probable secondary physiological defect

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known to work through G_s (e.g. adrenocorticotropin, vasopressin), as G_s is not imprinted in their respective target tissues.
Because of the non-specific nature of many of the features of AHO and the presence of other genetic defects that can mimic AHO [e.g. acrodysostosis (56), AHO-like syndrome mapped to distal chromosome 2 (57)], the diagnosis of AHO should not be made in the absence of a clear family history of PHP type 1a, multihormone resistance, or documented genetic or biochemical G_s defect. While typically AHO is associated with relatively benign subcutaneous ossifications, a few patients with heterozygous G_s mutations develop large plate-like ossifications that invade into deeper tissues such as muscle and cause severe deformity and reduced mobility (referred to as progressive osseous heteroplasia) (58). The mutations in these patients are often identical to those found in more typical AHO patients, so it does not appear that this more severe form of ectopic ossification results from more severe G_s mutations.

Pseudohypoparathyroidism type 1b

PHP type 1b patients have renal PTH resistance that is similar to that in PHP type 1a patients, but lack the features of the AHO phenotype. As in PHP type 1a, the urinary cAMP response to administered PTH is markedly reduced in these patients, indicating a proximal signaling defect (53). Several lines of evidence have ruled out PTH/PTHrP receptor defects as the cause of PHP type 1b (59, 60). In contrast to PHP type 1a, PHP type 1b is associated with normal G_s expression and bioactivity in erythrocyte membranes (53, 61), ruling out typical loss-of-function mutations within or surrounding the G_s coding exons as the underlying defect. Lack of G_s haploinsufficiency may likely explain why these patients do not develop AHO.
While in most cases PHP type 1b is an apparently sporadic disease, in some instances the disease occurs in a familial manner. The first evidence that PHP type 1b is due to a *GNAS* defect came from a study showing that familial PHP type 1b genetically mapped to 20q13 in the vicinity of the *GNAS* gene (62). Moreover in the families that were studied PTH resistance only occurred when an individual inherited the trait from his or her mother, similar to the inheritance pattern of PTH resistance present in AHO/PHP type 1a. Subsequently it has been shown that virtually all cases of PHP type 1b (both familial and sporadic) are associated with a *GNAS* imprinting defect in which both parental alleles have a paternal imprinting pattern, or epigenotype (25, 63, 64). In proximal tubules, where G_s is normally expressed primarily from the maternal allele, the presence of a paternal epigenotype on both parental alleles should lead to G_s deficiency and PTH resistance. In most other tissues where G_s is normally expressed equally from both parental alleles, the imprinting defect should have no effect on G_s expression.
In most cases familial PHP type 1b is associated with both a 3 kilobase deletion within the linked *STX16* gene located upstream of *GNAS* and loss of maternal-specific imprinting (methylation) of the exon 1A differentially methylated region (DMR) (65) (L.S.W., J.L., unpublished results). Presumably the deleted region contains one or more *cis*-acting elements that are critical for establishing the methylation of the exon 1A DMR during oogenesis, but that are not important for establishing the imprinting of the intervening NESP55 and XL s regions. When the deletion is inherited from the mother it appears to result in loss of maternal-specific exon 1A DMR methylation and PTH resistance. When the deletion is inherited from the father it has no effect on exon 1A DMR methylation (as the paternal allele is normally unmethylated) or on PTH action. Sporadic cases of PHP type 1b are not associated with the *STX16* deletion mutation but are associated with *GNAS* imprinting defects (25, 65) (L.S.W., J.L., unpublished results). Some patients have imprinting defects involving only the exon 1A DMR while most have more global *GNAS* imprinting defects which involve either the whole locus or the exon 1A, NESP55, and XL s/antisense promoters, but not XL s exon 1 (25) (L.S.W., J.L., unpublished results). In one patient PTH resistance was associated with paternal uniparental disomy of the long arm of chromosome 20 (66). It is unclear whether the imprinting defects in sporadic PHP type 1b result from underlying genetic mutations or are the result of a failure in the imprinting mechanism that may rarely occur in a random manner.
In both familial and sporadic PHP type 1b, the loss of maternal-specific exon 1A DMR methylation is the epigenetic defect that is consistently associated with renal PTH resistance. We have proposed a model in which the exon 1A DMR has a *cis*-acting regulatory element (silencer or insulator) for the G_s promoter that is both methylation-sensitive and tissue-specific (16, 25). In the example shown in Fig. 4 a silencer within the exon 1A DMR binds a tissue-specific repressor on the paternal allele in proximal tubules, which suppresses G_s expression from the paternal allele. The repressor fails to bind to the maternal allele because the silencer is methylated, allowing the G_s promoter to remain active in the maternal allele. In most other tissues the repressor is not expressed, and therefore G_s is biallelically expressed. In PHP type 1b the exon 1A methylation on the maternal allele is absent. This allows the repressor to bind to both alleles in proximal tubules, leading to G_s deficiency and renal PTH resistance. In most other tissues G_s expression is unaffected because the repressor is absent. This model is supported by results in mice with deletion of the exon 1A DMR (L.S.W., J.L., unpublished results). Paternal deletion of the exon 1A DMR resulted in G_s overexpression in renal proximal tubules and lower levels of circulating PTH (consistent with

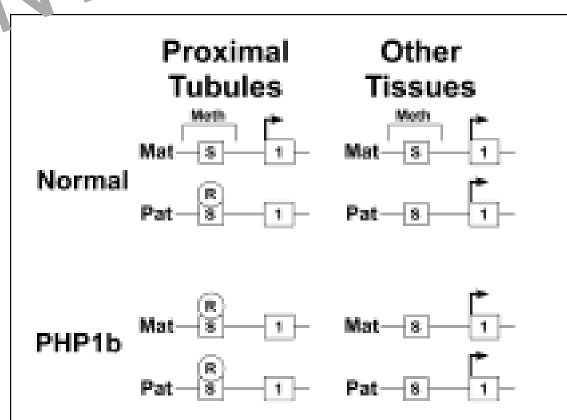

Figure 4 - Proposed model for tissue-specific G_s imprinting and pathogenesis of PHP type 1b. In each panel the maternal (Mat) and paternal (Pat) alleles are depicted with a *cis*-acting silencer element (S) within the exon 1A differentially methylated region and G_s exon 1 (1). In normal subjects (upper panels) the region containing the silencer is methylated (Meth) on the maternal allele. In proximal tubules (left hand panel) a tissue-specific repressor protein (R) binds to the silencer on the paternal allele and suppresses expression from the G_s promoter on this allele. Methylation of the silencer on the maternal allele prevents binding of the repressor, allowing the maternal G_s promoter to remain active. In most other tissues (right hand panel) the repressor is absent and therefore G_s is biallelically expressed. In PHP type 1b (lower panels) methylation is absent, allowing the repressor to bind to both alleles in proximal tubules, resulting in G_s deficiency. Methylation has no effect on G_s expression in other tissues because the repressor is absent.

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higher PTH sensitivity), presumably due to the absence of the *cis*-acting negative regulatory element on the paternal allele. In contrast, the maternal deletion had no effect.
One family has been reported in which PHP type 1b resulted from a inherited G_s missense mutation (deletion of isoleucine 382) within the carboxyl terminal region of G_s (39). Biochemical analysis of the mutant protein showed it to be unable to be activated by the PTH/PTHrP receptor, although it could be activated by other G_s receptors. Because of this selective receptor coupling defect the affected patients developed PTH resistance without developing AHO or other hormonal defects. Consistent with the paternal imprinting of G_s, the mutation only resulted in PTH resistance when it was inherited maternally.
Because G_s is also partially imprinted in thyroid cells (48-50), one might expect that PHP type 1b patients may also have evidence for TSH resistance. Although it was originally reported that TSH resistance is not a feature of PHP type 1b, it has been more recently shown that almost 50% of PHP type 1b patients confirmed to have the exon 1A methylation defect have evidence for borderline or mild TSH resistance as well (50, 66).

Conclusions

PHP is a genetically heterogeneous group of disorders which is defined by the presence of renal PTH resistance. Because G_s is normally expressed primarily from the maternal allele in renal proximal tubules, G_s deficiency and PTH resistance may result from either loss-of function genetic mutations (PHP type 1a) or epigenetic changes (PHP type 1b) in the *GNAS* maternal allele which lead to loss of G_s expression or expression of a bioinactive protein. Mutations on the maternal allele in PHP type 1a also lead to mild to moderate hormone resistance in other organs where G_s is imprinted. In addition these mutations lead to G_s haploinsufficiency in most other tissues where G_s is normally not imprinted, and this probably is the underlying cause of the AHO phenotype. Patients who inherit these mutations paternally only develop the AHO phenotype. Familial PHP type 1b is usually associated with a deletion mutation in a closely linked gene that presumably leads to a specific *GNAS* imprinting defect by unknown mechanisms. Almost all PHP type 1b patients have lost the maternal-specific imprinting of the exon 1A DMR located just upstream of the G_s promoter region, and this epigenetic change presumably leads to G_s deficiency in tissues, such as proximal tubules, where G_s is normally expressed primarily from the maternal allele.

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