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REVIEW

Pseudohypoparathyroidism: one gene, several syndromes

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Abstract Pseudohypoparathyroidism (PHP) and pseudopseudohypoparathyroidism (PPHP) are caused by mutations and/or epigenetic changes at the complex *GNAS* locus on chromosome 20q13.3 that undergoes parent-specific methylation changes at several sites. *GNAS* encodes the alpha-subunit of the stimulatory G protein (Gsα) and several splice variants thereof. Heterozygous inactivating mutations involving the maternal *GNAS* exons 1–13 cause PHP type Ia (PHP1A). Because of much reduced paternal Gsα expression in certain tissues, such as the proximal renal tubules, thyroid, and pituitary, there is little or no Gsα protein in the presence of maternal *GNAS* mutations, thus leading to PTH-resistant hypocalcemia and hyperphosphatemia. When located on the paternal allele, the same or similar *GNAS* mutations are the cause of PPHP. Besides biochemical abnormalities, patients affected by PHP1A show developmental abnormalities, referred to as Albrights hereditary osteodystrophy (AHO). Some, but not all of these AHO features are encountered also in patients affected by PPHP, who typically show no laboratory abnormalities. Autosomal dominant PHP type Ib (AD-PHP1B) is caused by heterozygous maternal deletions within *GNAS* or *STX16*, which are associated with loss-of-methylation (LOM) at exon A/B alone or at all maternally methylated *GNAS* exons. LOM at exon A/B and the resulting biallelic expression of A/B transcripts reduces Gsα expression, thus leading to hormonal resistance. Epigenetic changes at all differentially methylated *GNAS* regions are also observed in sporadic PHP1B, the most frequent disease variant, which remains unresolved at the molecular level, except for rare cases with paternal uniparental isodisomy or heterodisomy of chromosome 20q (patUPD20q).

Keywords Pseudohypoparathyroidism · Pseudopseudohypoparathyroidism · PHP1A · PHP1B · *GNAS* · Stimulatory G protein · Syntaxin 16 · *STX16* · Albrights hereditary osteodystrophy

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The term pseudohypoparathyroidism (PHP) was first coined by Fuller Albright and his colleagues in 1942 to describe three patients, who presented with seizures, hypocalcemia, and hyperphosphatemia consistent with a diagnosis of hypoparathyroidism [1]. Interestingly though, repeated injections of parathyroid extracts failed to improve serum calcium and to induce an increase in urinary phosphate excretion. Due to these findings, Albright and colleagues concluded that their patients were resistant to parathyroid hormone (PTH) rather than PTH-deficient. Additional characteristics of these patients included short stocky build, round face, early-onset obesity, ectopic intramembranous calcifications, brachydactyly, and neurodevelopmental abnormalities; these clinical findings are now referred to as Albright hereditary osteodystrophy (AHO). Albright's hypothesis of hormone resistance rather than deficiency as the underlying basis for the disorder was later confirmed by the first demonstration of elevated serum parathyroid hormone levels in untreated PHP patients [2]. A decade later, Albright et al. [3] described a patient with typical AHO features but normal serum calcium and phosphate. This patient showed physical AHO stigmata similar

to those previously reported for PHP patients, but no evidence for PTH resistance, and he therefore named this disorder pseudopseudohypoparathyroidism (PPHP).

A major step toward understanding further the mechanisms causing this disorder was taken in 1969, when Chase and colleagues demonstrated in PHP patients that infusion of PTH extracts did not cause an increase in urinary cAMP excretion, which was observed when the same PTH preparation was given to healthy controls or PPHP patients [4]. This finding supported the hypothesis of Albright and colleagues that PHP is caused by end-organ resistance to the actions of PTH.

In 1980 two groups showed that the activity of guanine nucleotide regulatory protein (alpha-subunit of the stimulatory G protein, Gsα) in erythrocyte membranes from PHP patients was reduced to approximately 50% of normal controls when tested with Cyc-membranes or turkey erythrocyte membranes [5, 6]. Surprisingly, an indistinguishable reduction in Gsα activity was also reported for red blood cell membranes from PPHP patients, despite lack of hormonal resistance in these patients [7]. PHP patients without evidence for AHO by contrast showed normal Gsα activity. Based on these in vitro findings, patients were classified as either PHP type Ia (PHP1A) or PHP type Ib (PHP1B). Reduced G protein activity reported by two groups of investigators thus independently supported the hypothesis that the deficient activity of the guanine nucleotide regulatory protein is the molecular basis for hormone resistance in this disorder.

Since Gsα can be found in most tissues, it was conceivable that a defect in this signaling protein could account for PTH resistance in PHP1A patients and would lead to resistance to multiple hormones that act by stimulating adenylate cyclase [8]. In fact, further investigations showed elevated thyroid-stimulating hormone (TSH) levels in affected individuals, consistent with thyroid resistance to this pituitary hormone. Resistance toward other hormones can occur as well. However, resistance to PTH in the proximal renal tubules remains the most prominent hormonal abnormality in PHP1A.

After the identification and characterization of the human gene encoding Gsα [9, 10], now referred to as *GNAS*, two groups independently identified in 1990 heterozygous *GNAS* mutations in PHP1A patients. [11, 12]. By now numerous other heterozygous *GNAS* mutations have been discovered, including missense, truncating, splice site mutations, and small/large deletions or insertions, which lead to disruption of normal RNA processing; these mutant *GNAS* alleles all fail to generate a functional Gαs protein (see Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/all.php) or Leiden Open Variation Database (www.lovd.nl/GNAS)). Surprisingly, the same heterozygous Gαs mutations can be found in either PHP1A or PPHP patients resulting in an equivalent reduction in Gsα activity in both diseases [7, 11]. However, with a few exceptions [13], only PHP1A patients present with clinical manifestations of hormonal resistance. Individuals affected by PHP1A and PPHP can be found in the same kindred, but both disorders never occur in the same sibship. This conundrum was partially explained by Davies and Hughes, and subsequently by Wilson et al., who showed that the parental origin of the mutated allele dictates the clinical phenotype [14, 15]. Thus, patients affected by PHP1A had inherited a *GNAS* mutation from their mother whereas inheritance of such a mutation from a father occurred in patients affected by PPHP. This suggested that Gsα expression from the maternal and paternal *GNAS* allele is not equal in all tissues that mediate their hormonal actions through Gsα-dependent mechanisms.

A subgroup of PHP1A, namely patients with clinical and laboratory findings typical for PHP1A, i.e., multihormonal resistance and AHO features yet normal Gsα activity, is referred to as PHP1C [16]. In some of the patients affected by this disease variant have *GNAS* mutations located near the C-terminal end of the Gsα protein, a region presumably crucial for receptor interaction; these mutations do not lead to detectable changes in the in vitro assays that are used for assessing G protein activity [17, 18]. However, no mutation in the *GNAS* exons encoding Gsα has been identified in most patients with these disease characteristics raising the possibility that intronic variants are the underlying cause or that mutations in another gene are responsible [17].

Progressive osseous heteroplasia (POH) represents another disorder that is caused by inactivating mutations in *GNAS* exons 1–13 [19]. Clinically, POH is characterized by cutaneous ossifications, presenting during childhood that involves subcutaneous or even deep connective tissue, including muscle and fascia. Although few cases with additional AHO characteristics have been described (see below), most of POH patients lack such features.

In 1980, a distinct group of pseudohypoparathyroid patients was described by Winter and Hughes [20]. These authors reported a family in which several members showed PTH-resistant hypocalcemia and hyperphosphatemia without the somatic abnormalities that are typically observed in PHP and PPHP patients (i.e., no AHO features). Similar patients were subsequently shown to have normal Gsα bioactivity [21]. This PHP variant, namely PHP1B, was initially thought to be caused by a genetic defect in the PTH-receptor (PTH/PTHrP receptor), but mutations in all coding exons of PTHR1 gene, its promoter region, and its mRNA were excluded [22–25]. A genome-wide search using genomic DNA from one large kindred with numerous affected individuals subsequently linked the autosomal dominant form of PHP1B (AD-PHP1B) to a region on the telomeric end of chromosome 20q (20q13.3) [26], which was confirmed through the analysis of several additional AD-PHP1B kindreds [27, 28]. Only

obligate female carriers of the mutant allele had affected children, which strongly suggested paternal imprinting, similar to PHP1A and PPHP [14].

Similar yet often more severe skeletal abnormalities than those reported for AHO are also encountered in other diseases known as acrodysostosis [29–31]. One of these disorders is a rare form of skeletal dysplasia with severe brachydactyly, facial dysostosis, nasal hypoplasia, and short stature (Online Mendelian Inheritance in Man number 101800). Analysis of three unrelated patients affected by acrodysostosis and multihormonal resistance revealed the same heterozygous de novo mutation in *PRKAR1A*, the gene encoding the regulatory subunit of the cAMP-dependent protein kinase A (PKA) [32]. Acrodysostosis can be caused also by heterozygous missense mutations in phosphodiesterase 4D—PDE4D (MIM 600129) [33, 34].

In summary, the current classification of the different PHP variants is based on several of the following criteria: (1) presence or absence of AHO features, (2) presence or absence of hormonal resistance as determined primarily by measurement of elevated PTH and TSH, (3) an inadequate increase in urinary cAMP and phosphate excretion after infusion of exogenous PTH, and (4) by measuring in vitro the activity of the Gsα protein isolated from erythrocyte membranes, an assay that is not widely available. This classification does not encompass Blomstrand's disease, a disorder caused by homozygous or compound heterozygous, inactivating PTH1R mutations [35, 36] or chondrodysplasias caused by heterozygous PTHrP mutations [37, 38] and other forms of acrodysostosis leading to the proposal of a new classification, namely iPPSD, for "inactivating PTH-PTHrP signaling disorders" [39]. The introduction of the major and minor diagnostic criteria would provide helpful guidance for establishing a diagnosis. However, the proposed new classification, just like PHP, does not comprise resistance to other hormones and it does not acknowledge that the mechanisms leading to POH and obesity are largely unknown, thus making either term unsatisfactory.

GNAS locus

GNAS is located on the long arm of chromosome 20 in human (20q13.3); the structurally very similar murine homolog is on chromosome 2 [9, 40–43]. In both species, *GNAS* gives rise to at least five different mRNAs that are transcribed either in sense or antisense orientation (Fig. 1). The alpha-subunit of the stimulatory guanine-binding nucleotide (Gsα) is the most abundant and best characterized gene product. In humans, Gsα is encoded by exons 1–13 [10], whereas its homologue in mice is encoded by 12 exons [40]. Studies in rodents have shown that the promoter and the first exon of Gsα lie in a CpG-rich island, but show no methylation marks on either allele [44], explaining why Gsα is biallelically expressed in most tissues [45]. However, in few tissues like renal proximal tubule, thyroid, gonads, pituitary, various areas in the central nervous system, and brown adipose tissue, Gsα is derived predominantly from the maternal allele; the paternal allele is silenced through yet undefined mechanisms [45–47]. Silencing of paternal Gsα expression would explain why multihormone resistance is observed when inactivating mutations are carried on the maternal allele [8]. The *GNAS* locus gives rise to four additional transcripts, including an antisense transcript (AS), the neuroendocrine secretory protein 55 (NESP55), the extra-large form of Gsα (XLαs), and the A/B transcript (1A in mice). Unlike Gsα, the promoters of these transcripts are located in differentially methylated regions (DMR) and show parent-specific methylation, thus allowing transcription only from the unmethylated allele. Promoters giving rise to the XLαs, A/B, and AS transcripts are methylated on the maternal allele and, thus, are transcribed exclusively from the paternal allele. The NESP55 promoter, on the other hand, is paternally methylated, and transcripts are derived exclusively from the maternal allele. NESP55, XLαs, and A/B transcripts are each encoded by a unique first exon that splices onto exon 2–13 of *GNAS*; note that the NESP exon comprises an in-frame termination codon, the mRNA portion derived from exons 2–13 is therefore located in the 3′ untranslated region [48–50]. XLαs is an isoform of Gsα with a long amino-terminal portion [49, 50]. Like Gsα, XLαs can activate adenylyl cyclase to generate cAMP although further investigations are required to elucidate its biological roles [51, 52]. Both NESP55 and XLαs are highly expressed in neuroendocrine tissues [53, 54]. A third promoter located approximately 2.5 kb upstream of Gsα gives rise to the widely expressed A/B transcript [55–57], which may encode an amino-terminally truncated form of Gsα [58]. The A/B promoter is methylated on the maternal allele and transcribed exclusively from the paternal allele. Patients affected by PHP1B show a loss-of-methylation (LOM) at the maternal exon A/B and thus biallelic A/B expression, which reduces Gsα transcript levels leading to hormonal resistance (discussed below) [27]. In mice, methylation at the exon 1A DMR is established during oogenesis and maintained throughout the pre- and post-implantation period [57]. Immediately upstream of the XLαs promoter lies *GNAS* exon AS, which gives rise to an antisense transcript (AS) (Nespas in mice) [59, 60]. Like XLαs and A/B, the AS promoter is methylated on the maternal allele and its mRNA is exclusively transcribed from the paternal allele in most tissues except for adrenal and testes where biallelic expression has been reported [54]. Like the exon 1A DMR, maternal methylation at the promoter of the first antisense exon is established during oogenesis [61].

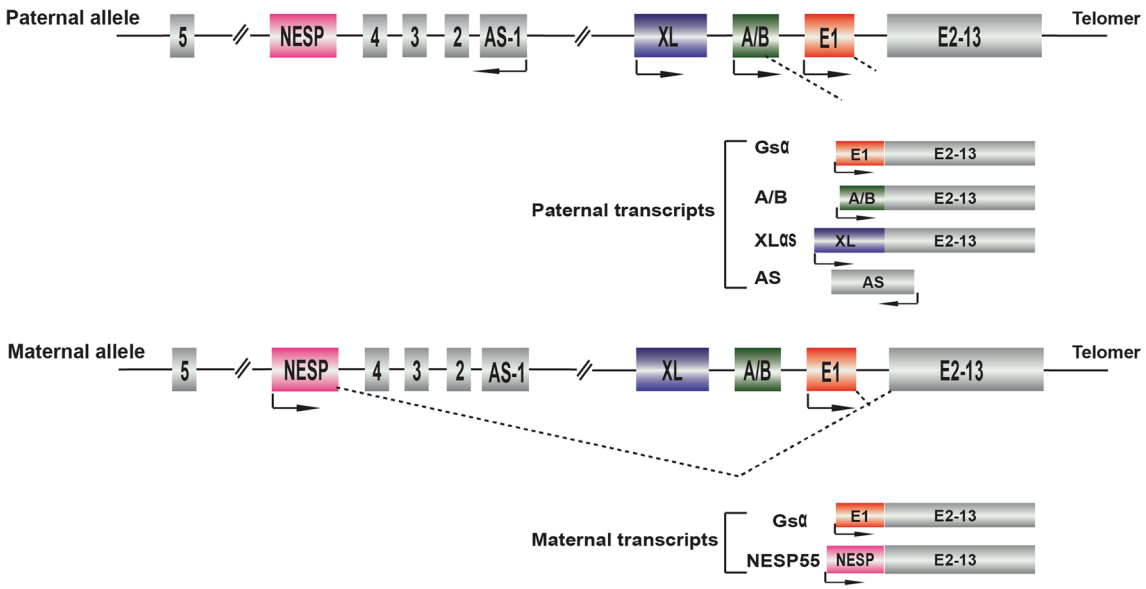

Fig. 1 Organization of the *GNAS* locus. The *GNAS* complex gives rise to several imprinted sense and antisense transcripts. Gsα, the most abundant product derived from this locus, is encoded by exons 1–13. This transcript is biallelically expressed in most tissues, except for few tissues like renal proximal tubule, thyroid, pituitary, brown adipose tissue, gonads, and various nuclei in the brain where paternal Gsα expression is reduced through yet undefined mechanisms. The *GNAS* locus gives rise to four other transcripts, including the antisense transcript (AS), the neuroendocrine secretory protein 55 (NESP55), as well as an extra-large form of Gsα, named XLαs, and the A/B transcript (1A in mice) that may give rise to an amino-terminally truncated Gsα. Promoters for XLαs, A/B, and AS transcripts are methylated on the maternal allele and, thus, transcribed exclusively from the paternal allele. The NESP55 promoter, on the other hand, is paternally methylated and transcribed exclusively from the maternal allele. The NESP55, XLαs, and A/B transcripts contain their own unique first exons that splice onto *GNAS* exon 2–13. Immediately upstream of the XLαs promoter lies the first exon encoding the antisense transcript AS. Maternal and paternal *GNAS*-derived mRNAs are shown above and below the gene structure. *Boxes* indicate exons, and splicing patterns are represented by *broken lines*. *Arrows* indicate direction of transcription. ** indicates promoter methylation either on the maternal (XL, A/B, and AS) or the paternal allele (NESP)

Loss-of-function mutations involving Gsα—PHP1A and PPHP/POH

Heterozygous inactivating mutations involving those *GNAS* exons encoding Gsα cause different disorders (Fig. 2). When one of these heterozygous mutations is located on the maternal allele patients will present with multihormonal resistance, in addition to AHO features (see above); this disorder is known as PHP1A [11, 12]. On the other hand, if a heterozygous inactivating mutation is located on the paternal allele, patients will present with most of the AHO features, but they show no obesity, no neurocognitive impairment, and usually no hormonal resistance [62, 63]; this condition is referred to as PPHP. Assays measuring Gsα bioactivity in erythrocyte membrane show an approximately 50% reduction for both disorders [5, 6]. Gsα haploinsufficiency could explain the AHO features observed in PHP1A and PPHP. Hormonal resistance occurs only in PHP1A patients, although one recent study revealed mild PTH resistance in a PPHP patient [13]. Presence of hormonal resistance, and possibly obesity and cognitive impairment in PHP1A, but not in PPHP, is most likely explained by the fact that some tissues, like renal proximal tubules, thyroid, pituitary, and gonads, express Gsα predominantly from the maternal allele (see above), while the paternal allele is silenced through yet unknown mechanisms. Thus, inactivating mutations on the maternal allele will result in little or no Gsα protein being produced. As a result, hormone resistance will occur only in tissues in which paternal Gsα expression is constitutively reduced, while hormone responsiveness does not seem to be impaired in tissues that normally show biallelic Gsα expression, although only half of the Gsα protein is detected.

In PHP1A, PTH resistance in renal proximal tubule is the most frequently encountered hormonal resistance; thus, patients will present with hypocalcemia, hyperphosphatemia, elevated PTH and decreased 1,25-dihydroxyvitamin D levels. Despite being the most prominent laboratory finding in PHP1A, hypocalcemia due to PTH resistance in renal proximal tubule does not develop until after infancy. Delayed onset of hormonal resistance may be explained by a delay in reducing paternal Gsα expression in renal proximal tubules as shown in recent studies using mice with ablation of *Gnas* exon 1 on either the maternal or the paternal allele [64]. PHP1A patients frequently present with resistance to other hormones that signal through

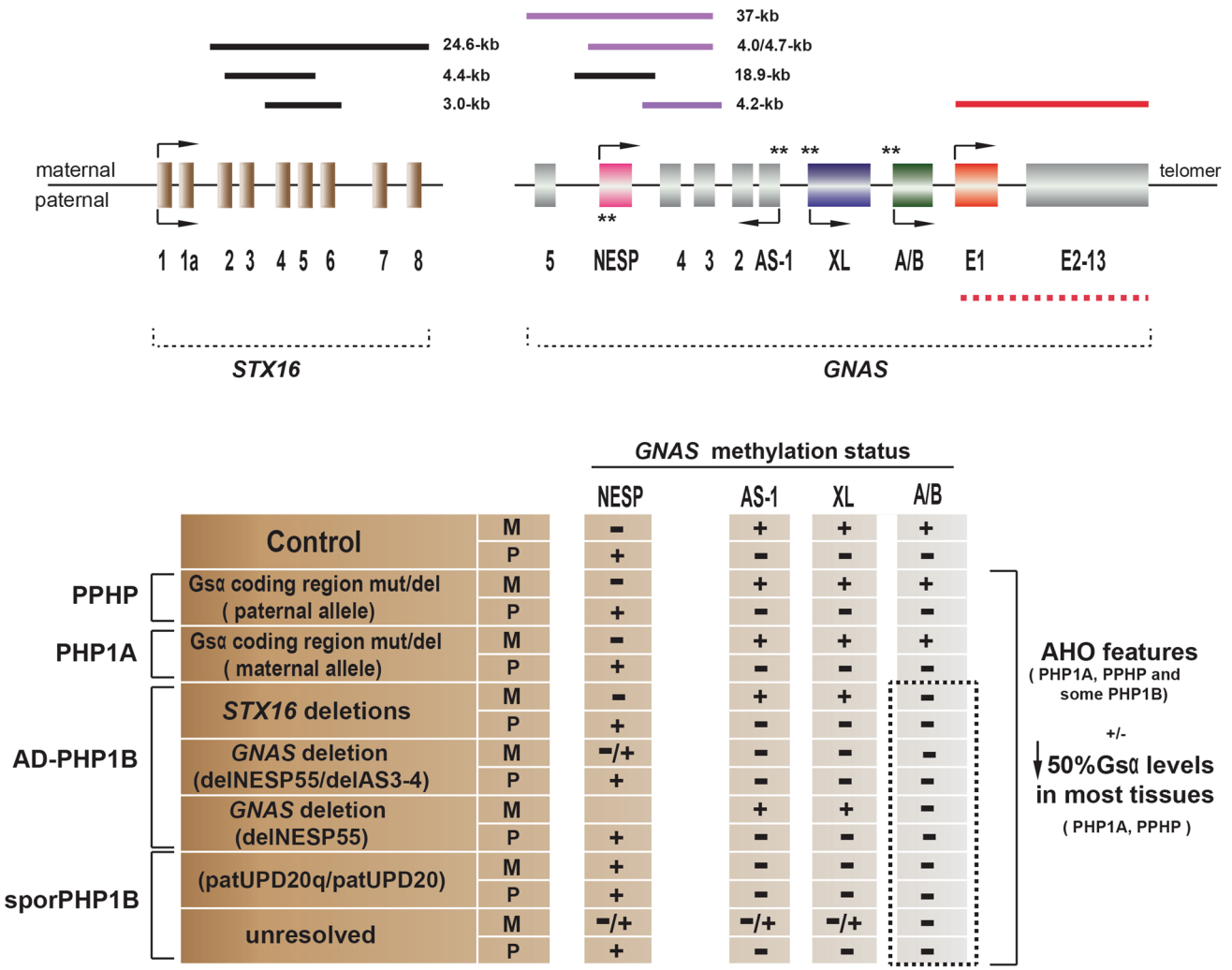

Fig. 2 Classification of pseudohypoparathyroidism and underlying genetic defects. Mutations involving any of the thirteen *GNAS* exons encoding Gsα are associated with AHO (Albright's hereditary osteodystrophy) with or without hormone resistance based on which parental allele is affected, i.e., pseudohypoparathyroidism 1A (PHP1A), if a mutation is present on the maternal allele (*horizontal red line*), or pseudopseudohypoparathyroidism (PPHP), and progressive osseus heteroplasia (POH), if a mutation is present on the paternal allele (*horizontal red dashed line*). AD-PHP1B results from deletions upstream of the Gsα-coding region and is associated with loss-of-methylation in one or more regions. Maternal *STX16* deletions and a maternal exon NESP deletion (*black lines*) lead to isolated loss-of-methylation at *GNAS* exon A/B [97–100]. Maternal deletions that include *GNAS* exons AS3-4 alone or combined with exon NESP (delNESP/AS3-4) (*purple lines*) result in loss-of-methylation in all maternal *GNAS* DMRs [85, 101, 102]. Patients with sporadic PHP1B (sporPHP1B) show loss-of-methylation at all maternal *GNAS* DMRs and a gain-of-methylation at exon NESP; these epigenetic changes can be incomplete [27, 89, 90]. Except for patients affected by paternal uniparental disomy involving the long arm of chromosome 20q (patUPD20q), the genetic defect leading to sporPHP1B remains unknown [92]. *Boxes* and *connecting lines* represent exons and introns, respectively. *Arrows* indicate direction of transcription

Gsα-coupled receptors, such as the receptors for thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and growth hormone-releasing hormone (GHRH) [65–67]. TSH levels can be elevated at birth in PHP1A and may subsequently normalize for 9–20 months before increasing again [68]; however, most patients affected by this disease show a rise in TSH before PTH levels increase [64]. Note that not all hormones that signal through Gsα-coupled receptors manifest end-organ resistance. Such examples include vasopressin or hormones in the hypothalamo-pituitary-adrenal axis, which could be explained by biallelic Gsα expression in those cells mediating the actions of these hormones [69, 70].

Heterozygous inactivating mutations involving those *GNAS* regions encoding Gsα have been identified also in patients affected by progressive osseous heteroplasia (POH), which appears to be the most severe form of PPHP. POH is characterized by ectopic intramembranous bone

formation that affects not only the subcutaneous tissue, but can extend into the skeletal muscle and deep connective tissue [19, 71–73]. In contrast to PPHP, POH patients rarely show additional AHO features or hormonal resistance [19, 74] even though some studies report mild AHO and hormonal resistance in POH patients [75]. It remains unclear why paternal inheritance of a *GNAS* mutation should lead to PPHP in some individuals and POH in others. It is furthermore unclear why phenotypic expression is variable among patients with the same mutations, even within a single family. This heterogeneity of clinical presentation hints toward additional regulatory elements or environmental factors that may modify a patient's clinical presentation.

The inactivating mutations reported to involve Gsα are scattered throughout the entire *GNAS* region encoding this signaling protein, with one mutation hotspot in exon 7 (c.565_568delGACT) accounting for 17.8% of the cases [34, 76, 77]. There appears to be no correlation between type or location of the Gsα mutation, and onset of the disease, severity of endocrine resistance, or number of AHO signs in PHP1A/PPHP [78]. However, recent genotype–phenotype studies have shown that the birth weights for PPHO/POH patients were particularly reduced when the *GNAS* mutations involved exons 2 through 13, while mutations in exon1/intron 1 had somewhat higher birth parameters. The lower birth weights with paternal mutations in exons 2–13 could suggest that XLαs may have an important role during fetal development [79].

GNAS methylation abnormalities resulting in reduced Gsα expression—PHP1B

Unlike individuals affected by PHP1A, most PHP1B patients show isolated PTH resistance in renal proximal tubules, which leads to elevated plasma PTH levels, hypocalcemia, and hyperphosphatemia, but usually no AHO features [16, 21, 27]. However, mild TSH resistance as well as mild AHO features have been described in several PHP1B patients [80–85]; some patients even show bone abnormalities that are indistinguishable from those encountered in PHP1A or PPHP [86]. Although, erythrocyte membranes analyses typically revealed no reduction in Gsα bioactivity similar to that seen in PHP1A and PPHP, one report demonstrated a small reduction in erythrocyte Gsα activity in several PHP1B patients, which was more apparent in PHP1B patients with some AHO features indicating that a "threshold" for Gsα activity is required for development of the AHO phenotype [87]. Unlike PHP1A, genetic analysis performed on PHP1B patients revealed no inactivating mutations in the *GNAS* exons encoding Gsα, instead epigenetic defects at one or more *GNAS* DMRs were identified [27, 28, 88]. Most PHP1B cases are sporadic and these show loss-of-methylation at *GNAS* exons A/B, XL, and AS, which is typically associated with a gain-of-methylation at the exon NESP DMR (see Fig. 2). Most familial cases show an autosomal dominant mode of inheritance (AD-PHP1B) with loss-of-methylation (LOM) at the maternal *GNAS* exon A/B alone; few familial cases show additional maternal methylation changes, including LOM at the DMRs of *GNAS* exons AS and XL, and an apparent gain-of-methylation (GOM) at the NESP55 DMR. For the sporadic, but not the familial cases, the *GNAS* methylation changes can be complete or partial; however, the DMR comprising the promoter of the A/B transcript is always affected. Incomplete *GNAS* methylation changes, which are observed in some sporadic PHP1B patients, could suggest that somatic mosaicism as all cells should be affected if an epimutation had occurred during gametogenesis [27, 82, 89, 90].

In addition to the established methylation alterations, a recent genome-wide methylation study in PHP1B patients revealed a novel DMR within the *GNAS* locus, referred to as GNAS-AS2 that appears to be hypomethylated in familial and sporadic PHP1B patients [91]. Further studies though are needed to better understand the functional and clinical impact of methylation changes in this region. Although the underlying genetic mechanisms are yet undefined in most sporadic PHP1B patients, *GNAS* methylation abnormalities were shown to be caused in some of these cases by uniparental paternal disomy (isodisomy or less frequently heterodisomy) involving the entire chromosome 20q or portions thereof [92–96]. Most AD-PHP1B cases on the other hand are secondary to deletions on the maternal allele of which the most frequent is a 3-kb deletion that removes exons 4–6 of *STX16*, the gene encoding syntaxin 16 located approximately 250 kb centromeric of *GNAS* [97]. Other reported deletions within *STX16* gene include a 4.4-kb and a 26-kb deletions [98, 99]. These *STX16* deletions are all associated with isolated LOM at *GNAS* exon A/B, which leads to a reduction in Gsα transcription through yet undefined mechanisms. Isolated LOM at *GNAS* exon A/B occurs also with a maternal deletion comprising exon NESP55 and the upstream region [100]. As all of the above reported deletions result in isolated LOM at *GNAS* exon A/B, it is conceivable that these two distinct regions may be required for establishing the methylation imprint at this DMR. Only few unrelated AD-PHP1B families revealed LOM at all three maternal *GNAS* DMRs, which are caused by deletions that include exon NESP55, as well exons AS 3–4 [85, 101]. Broad LOM at the three maternal *GNAS* DMRs was also reported for deletions restricted to maternal exons AS 3–4 [102]. Lack of these exons is obviously sufficient to cause a loss of the maternal *GNAS* methylation imprints indicating that this region might be interacting with a cis-acting element involved in establishing or maintaining the maternal *GNAS* methylation imprints.

AD-PHP1B as well as sporadic PH1B patients manifest similar clinical and laboratory findings despite different epigenetic changes at the *GNAS* locus [103]. Nonetheless, based on a recent study, body weight and length of both cohorts of PHP1B patients show some differences. Patients with epimutations alone, rather than genetic and methylation changes at the *GNAS* locus showed some acceleration of fetal growth resulting in significantly higher weights and increased lengths at birth [104]. The increase in birth weights was particularly pronounced in AD-PHP1B patients, who had inherited the 3-kb *STX16* deletion from a healthy carrier mother; these newborns were almost 4.5 SDS heavier than those, who were later diagnosed with PPHP/POH due to *GNAS* mutations involving exons E2-13 [105]. These differences in birth parameters suggest a complex interplay between the different *GNAS*-derived transcripts.

In conclusion, the *GNAS* locus on chromosome 20q13.3, which encodes the alpha-subunit of the stimulatory G protein (Gsα) and several different splice variants thereof, is subject to complex regulatory mechanisms that include parent-specific methylation of several exons/promoters and a tissue-/cell-specific reduction in paternal Gsα expression through as-yet unknown mechanisms. Three distinct yet related diseases are caused by mutations in this genetic locus. Maternal mutations involving those *GNAS* exons that encode Gsα cause pseudohypoparathyroidism type Ia (PHP1A), while the same or similar mutations on the paternal allele lead to pseudopseudohypoparathyroidism (PPHP). The autosomal dominant form of pseudohypoparathyroidism type Ib (AD-PHP1B) is caused by maternal deletions in *GNAS* or *STX16*, which are associated with distinct methylation changes involving different *GNAS* exons. With the exception of patients with patUPD20q, most sporadic PHP1B cases remain unresolved.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this review article no studies with human participants or animal experimentation were performed by the two authors.

Informed consent For this type of study formal consent is not required.

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