HHS Public Access

Author manuscript

Curr Opin Endocrinol Diabetes Obes. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2017 February ; 24(1): 33–38. doi:10.1097/MED.0000000000000306.

Non-classic features of pseudohypoparathyroidism type 1A

Ashley H. Shoemaker[1] and **Harald Jüppner**[2]

[1]Division of Pediatric Endocrinology, Vanderbilt University, Nashville, Tennessee, USA

[2]Endocrine Unit and Pediatric Nephrology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Abstract

Purpose of review—To provide readers with a review of contemporary literature describing the evolving understanding of the pseudohypoparathyroidism type 1A (PHP1A) phenotype.

Recent findings—The classic features of PHP1A include multi-hormone resistance and the Albright Hereditary Osteodystrophy phenotype (round facies, short stature, subcutaneous ossifications, brachydactyly, and early-onset obesity. Obesity may be due to a decrease in resting energy expenditure since most patients do not report significant hyperphagia. Patients with PHP1A have an increased risk of type 2 diabetes. In addition to brachydactyly and short stature, orthopedic complications can include spinal stenosis and carpal tunnel syndrome. Hearing loss, both sensorineural and conductive, has been reported in PHP1A. Additionally, ear-nose-throat findings include decreased olfaction and frequent otitis media requiring tympanostomy tubes. Sleep apnea was shown to be 4.4-fold more common in children with PHP1A compared with other obese children; furthermore, asthma-like symptoms have been reported. These new findings are likely multifactorial and further research is needed to better understand these non-classic features of PHP1A.

Summary—Along with the Albright Hereditary Osteodystrophy phenotype and hormone resistance, patients with PHP1A may have additional skeletal, metabolic, ear-nose-throat and pulmonary complications. Understanding these non-classic features will help improve clinical care of PHP1A patients.

Keywords

GNAS; pseudohypoparathyroidism; Albright Hereditary Osteodystrophy; hormone resistance

INTRODUCTION

Pseudohypoparathyroidism type la (PHP1A) is a rare genetic disorder that is characterized by hypocalcemia and hyperphosphatemia despite elevated parathyroid hormone (PTH) levels. These biochemical changes are caused by resistance towards PTH in the proximal renal tubules, which leads to reduced or inappropriately normal synthesis of

Corresponding Author: Ashley Shoemaker, M.D., M.S.C.I., 2200 Children's Way, DOT Room 11133, Nashville, TN 37232-9170, Phone: 615-322-4428, Fax: 615-875-7633, Ashley.H.Shoemaker@vanderbilt.edu.

Conflicts of interest: None

1,25(OH)2vitamin D as well as impaired down-regulation of NPT2a and NPT2c expression, and thus reduced urinary phosphate excretion. Patients affected by PHP1A frequently develop resistance towards several other hormones, particularly thyroid-stimulating hormone (TSH), gonadotropins, and growth hormone-releasing hormone. PHP1A is furthermore characterized by phenotypic findings referred to as Albright Hereditary Osteodystrophy (AHO), which includes short stature, round facies, subcutaneous ossifications and brachydactyly. These patients have early onset obesity, and varying degrees of developmental delays and cognitive impairment. In contrast, most patients affected by pseudohypoparathyroidism type 1B (PHP1B) present with PTH-resistance alone, but they may also show resistance to other hormones, and some have the phenotypic changes classically associated with pseudohypoparathyroidism type 1A (PHP1A). Thus, besides molecular defects in the same genetic locus, there appears to be considerable phenotypical overlap between the two disorders.

The prevalence of PHP1A is not well understood. A recent article from Denmark reported a PHP1A prevalence of 1.1 per 100,000 inhabitants (1). A lower prevalence of 3.4 per million inhabitants was reported in Japan (2). In the United States, we encountered one PHP1A patient per 125,000 patients in a single tertiary medical center, though this likely overestimates the true prevalence due to a referral bias (3).

PHP1A is caused by mutations involving exons 1–13 of *GNAS*, the gene encoding the alpha-subunit of the stimulatory G protein ($G_s\alpha$) and splice variants thereof (Fig. 1). Besides the mRNA encoding $G_s\alpha$, several additional sense and antisense transcripts are derived from the *GNAS* locus that utilize alternative first exons and promoters. These include exon A/B that gives rise to a splice variant that appears to encode an amino-terminally truncated form of $G_s\alpha$, while exon XL allows generation of an extra-large $G_s\alpha$ variant (XLαs). In addition, a non-coding antisense transcript (AS) and the 55-kDa neuroendocrine secretory protein (NESP55) are derived from the *GNAS* locus. Most studies have not found a genotype/phenotype relationship in PHP1A (4), and the AHO phenotype can be seen in patients with molecular defects ranging from point mutations to epigenetic defects at *GNAS* (5). One recent study reported that subcutaneous ossifications were more common in patients harboring truncating versus missense mutations (6).

Homozygous mutations in *GNAS* are lethal. Heterozygous mutations involving maternal *GNAS* exons 1–13 cause PHP1A. The same or similar *GNAS* mutations located on the paternal allele are the cause of pseudopseudohypoparathyroidism (PPHP), a disorder characterized by some AHO features, but without the hormonal resistance, obesity, and the other developmental defects encountered in PHP1A. This disorder is frequently only diagnosed after a woman with PPHP has a child affected by PHP1A. The fact that only maternal *GNAS* mutations involving $G_s\alpha$ cause hormonal resistance lead to the hypothesis that the paternal *GNAS* allele is imprinted and does not contribute to the synthesis of this signaling protein in some tissues, such as proximal renal tubules, thyroid, pituitary, brown fat, and certain portions of the CNS, while other tissues such as the distal renal tubules and bone show no evidence for hormonal resistance. However, $G_s\alpha$ protein is not always completely absent, even in tissues with predominantly maternal $G_s\alpha$ expression. For example, paternal $G_s\alpha$ expression in the proximal renal tubules appears to be relatively

normal during infancy and early childhood, and serum calcium and phosphate levels are thus maintained within normal limits (7). These findings suggested that the regulation of paternal $G_s\alpha$ expression occurs in a tissue- and age-dependent manner, and that changes in $G_s\alpha$ protein derived from the paternal *GNAS* allele contribute significantly to the clinical and laboratory variability observed in PHP1A patients. Due to the rarity of the disorder and an incomplete knowledge as to which tissues show preferential maternal $G_s\alpha$ expression, some aspects of PHP1A have not been recognized until recently and are not uniformly present. The current review will be focused on these less well-established abnormalities in PHP1A.

Metabolic Complications

Obesity is typically recognized in the first 2-years of life (8–12), but it is not part of the AHO spectrum as it was shown in 2007 to be a feature specific for PHP1A, but not for PPHP (8). Interestingly, early-onset obesity can be observed also in PHP1B, as recently documented for a patient with PHP1B due to the frequently encountered 3-kb deletion in *STX16*, the gene encoding syntaxin 16 (13). Although increased food-intake through central mechanisms may contribute to weight gain in some children with PHP1A, a reduction in resting energy expenditure is likely the primary mechanism leading to obesity. We found a reduction in resting energy expenditure of 346.4 kcals/day (95% CI −585.5 to −106.9) in children with PHP1A compared with obese controls (14), which was recently confirmed by Roizen et al., who observed a similar reduction of 273.9 kcals/day (SE 60.0 kcals/day) (15). Patients with PHP1A can have increased interest in food, especially in the first two years of life, but older patients do not report increased hunger compared with obese controls (10). These findings are supported by previous studies in murine models of PHP1A (16, 17); for example, mice with a brain-specific maternal *Gnas* exon 1-ablation had increased feed efficiency but normal food intake when the *Gnas* mutation was paternally inherited. In humans affected by PHP1A, obesity occurs despite early and adequate treatment of TSH resistance and growth hormone deficiency.

While decreased resting energy expenditure has been seen in children with PHP1A (14, 15), this finding was not replicated in adults (18). Muniyappa et al. reported an average resting energy expenditure of 1357 ± 84 kcals/day in adults with PHP1A versus 1444 ± 71 kcals/day in matched obese controls. This reduction in energy expenditure was not significant; however, patients were matched by percent body fat, not lean mass. It is therefore possible that the reduction in energy expenditure may become less pronounced in adulthood. Consistent with this conclusion, adults with PHP1A do have less pronounced obesity, with an average BMI of 33.8 and BMI z-score +1.69 vs. BMI z-score +2.58 in children (8).

A leading hypothesis is that abnormalities in hypothalamic melanocortin-4 receptor (MC4R) signaling, a $G_s\alpha$-coupled receptor, leads to energy imbalance and weight gain. There is evidence of reduced paternal $G_s\alpha$ expression in the mouse hypothalamus which would explain why the obese phenotype is specific for PHP1A, not PPHP (17). In contrast to the *Gnas* mouse model, however, the *mc4r* knockout mouse demonstrates both reduction in energy expenditure and significant hyperphagia (19). Severe hyperphagia is also observed patients with *MC4R and POMC* mutations, which is different from most PHP1A patients

(20, 21). Recent studies have revealed that MC4R signals not only through $G_s\alpha$, but also $G_{q11}\alpha$ that couples to the inwardly rectifying potassium channel, Kir7.1 (22, 23). The classic, $G_s\alpha$ coupled signaling pathway of MC4R regulates the increase in sympathetic nervous system tone while the Kir7.1 and $G_{q11}\alpha$ pathways are linked to changes in food intake. Two independent signaling pathways can thus explain the differences in the obesity phenotype seen in PHP1A and MC4R deficiency.

Despite the plateau in weight gain that becomes apparent towards the end of the second decade of life, adults with PHP1A can have reduced insulin sensitivity as measured by oral glucose and mixed meal tolerance tests compared with obese controls (18). Many reports of adults with PHP1A also note glucose intolerance or type 2 diabetes (18, 24, 25), while children with PHP1A showed less insulin resistance than obese controls (14, 26). However, PHP1A children still have an increased risk of impaired glucose tolerance (26), suggesting impaired beta cell function. Changes in insulin action may also be mediated through the central $G_s\alpha$-coupled melanocortin pathway (27). Due to the prevalent obesity and increased risk of diabetes, patients with PHP1A should be monitored for the development of glucose intolerance.

Orthopedic Complications

Brachydactyly is a classic feature of PHP1A (Figure 2) (28), which is also observed in other conditions, for example in patients with acrodysostosis due to heterozygous mutations in PDE4D or the PTH-related peptide (PTHrP) (29, 30). The typical pattern in PHP1A is shortening of the distal phalanx of the thumb and the 3^{rd}–5^{th} metacarpals. The proposed mechanism is insufficient signaling at the PTH/PTHrP receptor, which results in accelerated differentiation of proliferating chondrocytes into hypertrophic cells and thus premature closure of the epiphyses (31–33). Brachydactyly may be more common in patients harboring missense versus truncating mutations (6). Early closure of the epiphyses of other bones most likely contributes to the short stature found in adults with PHP1A. As brachydactyly requires epiphyseal closure, it is not always present at a young age but may instead develop gradually during early childhood (34, 35), which is different from the findings in patients with PDE4D and PRKAR1A mutations (36). Short stature is also a characteristic feature of PPHP thus raising the possibility that $G_s\alpha$ haploinsufficiency, rather than imprinted $G_s\alpha$ expression in the growth plate is responsible for accelerated chondrocyte maturation.

Possibly due to the brachydactyly, the majorities of children with PHP1A have difficulty with fine motor skills, such as handwriting, and thus should receive occupational therapy services in early childhood (37). Carpal tunnel syndrome is more common in patients with PHP1A with 67% of patients reporting symptoms versus 15% of the general population (37). Symptoms of carpal tunnel syndrome may begin at a young age, even in childhood (37). It is not clear why only some patients with PHP1A develop carpal tunnel syndrome, but brachydactyly or other hand/wrist anthropometric features of AHO, rather than abnormalities in mineral ion homeostasis may contribute to the increased prevalence. This conclusion is supported by the finding of an equally high incidence of carpal tunnel syndrome in PPHP patients, i.e. patients with normal calcium and phosphate homeostasis (37). Since symptoms of carpal tunnel syndrome overlap with symptoms of hypocalcemia

(tingling and numbness), it can be difficult to diagnose carpal tunnel syndrome in PHP1A patients. We recommend that all PHP1A and PPHP patients receive formal evaluation of their fine motor skills and that occupational therapy is offered as early as possible.

Symptomatic spinal stenosis is an increasingly recognized complication of pseudohypoparathyroidism, with more than 10 case reports in the literature (38–48). The classic presentation is a patient with lower extremity weakness that progresses to spastic paraparesis. Symptoms typically begin in early adulthood but have been reported in patients as young as 12 years old. Spinal stenosis appears to affect more men than women with PHP1A (49). The location of the stenosis is most commonly cervical and thoracic. Treatment includes surgical decompression and laminectomy. Approximately half of the patients had residual deficits or progression of disease post-operatively.

Several mechanisms have been proposed to explain spinal stenosis in PHP1A. Most patients have ossification of the ligamentum flavum or the anterior/posterior longitudinal ligaments or hypertrophic bone as the cause of stenosis. Soft tissue ossifications are common in PHP1A and in the spinal column can lead to compression and symptomatic stenosis. Other patients have congenital stenosis from abnormally short pedicles, resulting in a decreased anterior-posterior spinal canal diameter. The shortened pedicles are presumed to be caused by premature closure of the physes due to abnormal PTH signaling. The obesity associated with PHP1A may also contribute to reactive bone formation and ossifications of ligaments by increasing inflammation and by direct biomechanical effects on the spine (50).

Ear, Nose and Throat Complications

There are conflicting reports of sensorineural hearing loss in PHP1A (51, 52). In our retrospective cohort (described previously (3)), only 2 of 18 patients (11%) have sensorineural hearing loss requiring hearing aids. The majority of our pediatric patients affected by this disease (55%), however, have a history of frequent otitis media requiring tympanostomy tubes and 4 of 18 PHP1A patients had chronic perforations and conductive hearing loss requiring tympanoplasty. The round face, skeletal changes and decreased muscle tone characteristic of the AHO phenotype could potentially be associated with eustachian tube dysfunction, as seen in patients with Down syndrome, and an increased risk of otitis media (53). Patients with PHP1A have been described as having abnormal palates and diminished uvular and gag reflexes (54). Dental abnormalities include enamel hypoplasia, blunted roots and delayed tooth eruption (55, 56), though this finding is not associated with increased plasma PTHrP as previously hypothesized (57). Further investigation is needed to better understand the head and neck anatomy of patients with PHP1A.

Patients with PHP1A have Type II hyposmia; they can correctly identify undiluted solutions but not dilute solutions, and they are unaware of any defect in olfaction (51, 54, 58, 59). Patients with PHP1B may also have a mild reduction in olfactory recognition while patients with PPHP have normal olfaction (58, 59) suggesting that PTH resistance and mild hypocalcemia may play a role.

We recently investigated the prevalence of sleep apnea and found a 4.4-fold greater relative risk of sleep apnea in children with PHP1A compared with other obese children (3). In a cohort of 31 children with PHP1A, 52% reported snoring and 45% had been diagnosed with sleep apnea, including central and obstructive apnea, as compared to a prevalence of 5–8% in obese children (60, 61). Obesity alone cannot explain the high rates of sleep apnea in children with PHP1A. It is therefore conceivable that decreased $G_s\alpha$ expression in the central nervous system may directly contribute to abnormal sleep patterns. For example, in the murine disease model changes in $G_s\alpha$ expression is disruptive to normal sleep architecture (62). Neuromuscular and anatomical features could also contribute to sleep apnea in PHP1A, but further research is needed.

Untreated sleep apnea is associated with poor memory and concentration, increased risk of heart disease and even impaired glucose metabolism (63–65). Effective treatment of sleep apnea may mitigate these risks and even improve school performance (66–68). Adenotonsillectomy is first line therapy for children with sleep apnea and adenotonsillar hypertrophy, but was not effective in children with PHP1A, resulting in continued need for CPAP or BiPAP (3). There may also be pulmonary disorders associated with PHP1A, such as an increased prevalence of asthma (3, 15). Asthma has also been reported in patients with PHP1A, PPHP and PHP1B (69–71). One study found a 2.5-fold increased risk of airway infections in PHP1A (1). Due to the high rates of sleep apnea in children with PHP1A, all patients should be questioned for symptoms such as restless sleep, snoring, inattentiveness and daytime somnolence and if symptoms are present, formal evaluation by polysomnography is recommended.

CONCLUSION

Recent efforts to characterize the non-classic features of PHP1A have improved our understanding of this complex disorder. Many of these findings have not been studied in patients with PPHP and PHP1B; further study in these related disorders will help elucidate the role of *GNAS* imprinting in the non-classic features. In particular, a better understanding of the impact of $G_s\alpha$ mutations on head and neck anatomy is needed. Longitudinal assessments could help address differences between the pediatric and adult phenotypes and the risk of long-term non-classical complications in PHP1A.

Acknowledgments

None

Financial support: This work was supported by NIH grants K23DK101689 (AHS) and RO1 DK46718 (HJ) from the National Institute of Diabetes, Digestive and Kidney Diseases.

References

1*. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Pseudohypoparathyroidism — epidemiology, mortality and risk of complications. Clin Endocrinol (Oxf). 2015 This article provides country level data from Denmark on prevalence and mortality in PHP.

2. Nakamura Y, Matsumoto T, Tamakoshi A, Kawamura T, Seino Y, Kasuga M, et al. Prevalence of idiopathic hypoparathyroidism and pseudohypoparathyroidism in Japan. Journal of epidemiology / Japan Epidemiological Association. 2000; 10(1):29–33.

3**. Landreth H, Malow BA, Shoemaker AH. Increased Prevalence of Sleep Apnea in Children with Pseudohypoparathyroidism Type 1a. Hormone research in paediatrics. 2015 This is the first study to examine the prevalence of sleep apnea in PHP1A.

4. Elli FM, de Sanctis L, Bollati V, Tarantini L, Filopanti M, Barbieri AM, et al. Quantitative analysis of methylation defects and correlation with clinical characteristics in patients with Pseudohypoparathyroidism type I and GNAS epigenetic alterations. J Clin Endocrinol Metab. 2013:jc20133086.

5**. Elli FM, Linglart A, Garin I, de Sanctis L, Bordogna P, Grybek V, et al. The prevalence of GNAS deficiency-related diseases in a large cohort of patients characterized by the EuroPHP network. J Clin Endocrinol Metab. 2016:jc20154310. This article is important because it provided further evidence of phenotypic overlap between the different types of pseudohypoparathyroidism.

6*. Thiele S, Werner R, Grotzinger J, Brix B, Staedt P, Struve D, et al. A positive genotype-phenotype correlation in a large cohort of patients with Pseudohypoparathyroidism Type 1a and Pseudo-pseudohypoparathyroidism and 33 newly identified mutations in the GNAS gene. Molecular genetics & genomic medicine. 2015; 3(2):111–20. This is the only study to have found a genotype-phenotype correlation in PHP1A. [PubMed: 25802881]

7. Turan S, Fernandez-Rebollo E, Aydin C, Zoto T, Reyes M, Bounoutas G, et al. Postnatal establishment of allelic Galphas silencing as a plausible explanation for delayed onset of parathyroid hormone resistance owing to heterozygous Galphas disruption. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2014; 29(3):749–60.

8. Long DN, McGuire S, Levine MA, Weinstein LS, Germain-Lee EL. Body mass index differences in pseudohypoparathyroidism type 1a versus pseudopseudohypoparathyroidism may implicate paternal imprinting of Galpha(s) in the development of human obesity. J Clin Endocrinol Metab. 2007; 92(3):1073. [PubMed: 17164301]

9. Ong KK, Amin R, Dunger DB. Pseudohypoparathyroidism—another monogenic obesity syndrome. Clin Endocrinol (Oxf). 2000; 52(3):389–91. [PubMed: 10718839]

10. Wang L, Shoemaker AH. Eating behaviors in obese children with pseudohypoparathyroidism type 1a: a cross-sectional study. International journal of pediatric endocrinology. 2014; 2014(1):21. [PubMed: 25337124]

11. Nwosu BU, Lee MM. Pseudohypoparathyroidism type 1a and insulin resistance in a child. Nat Rev Endocrinol. 2009; 5(6):345–50. [PubMed: 19465898]

12. Dekelbab BH, Aughton DJ, Levine MA. Pseudohypoparathyroidism type 1A and morbid obesity in infancy. Endocr Pract. 2009; 15(3):249–53. [PubMed: 19364695]

13. de Lange IM, Verrijn Stuart AA, van der Luijt RB, Ploos van Amstel HK, van Haelst MM. Macrosomia, obesity, and macrocephaly as first clinical presentation of PHP1b caused by STX16 deletion. Am J Med Genet A. 2016

14. Shoemaker AH, Lomenick JP, Saville BR, Wang W, Buchowski MS, Cone RD. Energy expenditure in obese children with pseudohypoparathyroidism type 1a. Int J Obes (Lond). 2013; 37(8):1147–53. [PubMed: 23229731]

15**. Roizen JD, Danzig J, Groleau V, McCormack S, Casella A, Harrington J, et al. Resting Energy Expenditure is Decreased in Pseudohypoparathyroidism Type 1A. J Clin Endocrinol Metab. 2015:jc20153895. This article was the first to replicate the previously reported finding of decreased energy expenditure in PHP1A.

16. Chen WJ, Wu ZY, Wang N, Lin MT, Mu-rong SX. Quantitative studies on SMN1 gene and carrier testing of spinal muscular atrophy. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2005; 22(6):559–602. [PubMed: 16331551]

17. Chen M, Wang J, Dickerson KE, Kelleher J, Xie T, Gupta D, et al. Central nervous system imprinting of the G protein G(s)alpha and its role in metabolic regulation. Cell Metab. 2009; 9(6): 548–55. [PubMed: 19490909]

18. Muniyappa R, Warren MA, Zhao X, Aney SC, Courville AB, Chen KY, et al. Reduced insulin sensitivity in adults with pseudohypoparathyroidism type 1a. The Journal of clinical endocrinology and metabolism. 2013; 98(11):E1796–801. [PubMed: 24030943]

19. Huszar D, Lynch CA, Fairchild-Huntress V, Dunmore JH, Fang Q, Berkemeier LR, et al. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. Cell. 1997; 88(1):131–41. [PubMed: 9019399]
20. Farooqi IS, Yeo GS, Keogh JM, Aminian S, Jebb SA, Butler G, et al. Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency. J Clin Invest. 2000; 106(2):271–9. [PubMed: 10903343]
21. Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T, O'Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med. 2003; 348(12):1085–95. [PubMed: 12646665]
22. Ghamari-Langroudi M, Digby GJ, Sebag JA, Millhauser GL, Palomino R, Matthews R, et al. G-protein-independent coupling of MC4R to Kir7.1 in hypothalamic neurons. Nature. 2015; 520(7545):94–8. [PubMed: 25600267]
23. Li YQ, Shrestha Y, Pandey M, Chen M, Kablan A, Gavrilova O, et al. G(q/11)alpha and G(s)alpha mediate distinct physiological responses to central melanocortins. J Clin Invest. 2016; 126(1):40–9. [PubMed: 26595811]
24. Moehlig RC, Gerisch RA. Pseudohypoparathyroidism with decreased glucose tolerance; report of a case. J Clin Endocrinol Metab. 1950; 10(12):1609–15. [PubMed: 14803549]
25. Smulyan H, Raisz LG. Pseudo-pseudohypoparathyroidism with unusual features. J Clin Endocrinol Metab. 1959; 19(4):478–84. [PubMed: 13654478]
26. Shoemaker, AH., Perez, KP. Fasting glucose and hemoglobin A1c are poor measures of glucose homeostasis in children with pseudohypoparathyroidism type 1a. Endocrine Society's 98th Annual Meeting; Boston, MA. 2016;
27. Obici S, Feng Z, Tan J, Liu L, Karkanias G, Rossetti L. Central melanocortin receptors regulate insulin action. J Clin Invest. 2001; 108(7):1079–85. [PubMed: 11581309]
28. Albright FBCH, Smith PH, Parson W. Pseudo-hypoparathyroidism — an example of "Seabright-bantam syndrome": report of three cases. Endocrinology. 1942; 30:922–32.
29. Lee H, Graham JM Jr, Rimoin DL, Lachman RS, Krejci P, Tompson SW, et al. Exome sequencing identifies PDE4D mutations in acrodysostosis. Am J Hum Genet. 2012; 90(4):746–51. [PubMed: 22464252]
30. Klopocki E, Hennig BP, Dathe K, Koll R, de Ravel T, Baten E, et al. Deletion and point mutations of PTHLH cause brachydactyly type E. Am J Hum Genet. 2010; 86(3):434–9. [PubMed: 20170896]
31. Kobayashi T, Chung UI, Schipani E, Starbuck M, Karsenty G, Katagiri T, et al. PTHrP and Indian hedgehog control differentiation of growth plate chondrocytes at multiple steps. Development. 2002; 129(12):2977–86. [PubMed: 12050144]
32. Bastepe M, Weinstein LS, Ogata N, Kawaguchi H, Juppner H, Kronenberg HM, et al. Stimulatory G protein directly regulates hypertrophic differentiation of growth plate cartilage in vivo. Proc Natl Acad Sci U S A. 2004; 101(41):14794–9. [PubMed: 15459318]
33. Sakamoto A, Chen M, Kobayashi T, Kronenberg HM, Weinstein LS. Chondrocyte-specific knockout of the G protein G(s)alpha leads to epiphyseal and growth plate abnormalities and ectopic chondrocyte formation. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2005; 20(4):663–71.
34. Viragh K, Toke J, Sallai A, Jakab Z, Racz K, Toth M. Gradual development of brachydactyly in pseudohypoparathyroidism. J Clin Endocrinol Metab. 2014; 99(6):1945–6. [PubMed: 24684469]
35. Puzhko S, Goodyer CG, Kerachian MA, Canaff L, Misra M, Juppner H, et al. Parathyroid hormone signaling via Galphas is selectively inhibited by an NH(2)-terminally truncated Galphas: implications for pseudohypoparathyroidism. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2011; 26(10):2473–85.
36. Linglart A, Fryssira H, Hiort O, Holterhus PM, Perez de Nanclares G, Argente J, et al. PRKAR1A and PDE4D mutations cause acrodysostosis but two distinct syndromes with or without GPCR-signaling hormone resistance. J Clin Endocrinol Metab. 2012; 97(12):E2328–38. [PubMed: 23043190]

37. Joseph AW, Shoemaker AH, Germain-Lee EL. Increased prevalence of carpal tunnel syndrome in albright hereditary osteodystrophy. J Clin Endocrinol Metab. 2011; 96(7):2065–73. [PubMed: 21525160]

38. Roberts TT, Khasnavis S, Papaliodis DN, Citone I, Carl AL. Spinal cord compression in pseudohypoparathyroidism. The spine journal : official journal of the North American Spine Society. 2013; 13(12):e15–9.

39. Li P, Huang L, Zhao Z, Ye X, Liu Z. Spinal-cord compression related to pseudohypoparathyroidism. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2011; 18(1):143–5. [PubMed: 20851612]

40. Jiang Y, Hu H, Ye X, Peng J, He H, Xu G, et al. Multilevel myelopathy associated with pseudohypoparathyroidism simulating diffuse skeletal hyperostosis: a case report and literature review. Spine. 2010; 35(23):E1355–8. [PubMed: 20938388]

41. van Lindert EJ, Bartels RH, Noordam K. Spinal stenosis with paraparesis in albright hereditary osteodystrophy. Case report and review of the literature. Pediatric neurosurgery. 2008; 44(4):337–40. [PubMed: 18552518]

42. Okada K, Iida K, Sakusabe N, Saitoh H, Abe E, Sato K. Pseudohypoparathyroidism-associated spinal stenosis. Spine. 1994; 19(10):1186–9. [PubMed: 8059279]

43. Alam SM, Kelly W. Spinal cord compression associated with pseudohypoparathyroidism. Journal of the Royal Society of Medicine. 1990; 83(1):50–1. [PubMed: 2304055]

44. Firooznia H, Golimbu C, Rafii M. Case report 312. Diagnosis: progressive paraparesis in a woman with pseudohypoparathyroidism (PHP) with ossification of the posterior longitudinal ligament from C4 to T5. Skeletal radiology. 1985; 13(4):310–3. [PubMed: 4001976]

45. Cullen DR, Pearce JM. Spinal Cord Compression in Pseudohypoparathyroidism. J Neurol Neurosurg Psychiatry. 1964; 27:459–62. [PubMed: 14213476]

46. Chen H, Tseng F, Su D, Tsai K. Multiple intracranial calcifications and spinal compressions: rare complications of type la pseudohypoparathyroidism. J Endocrinol Invest. 2005; 28(7):646–50. [PubMed: 16218049]

47. Lee SH, Mun SH, Cho SY, Kim YJ, Jin DK, Ki CS, et al. Spinal Stenosis with Paraparesis in a Korean Boy with Albright's Hereditary Osteodystrophy: Identification of a Novel Nonsense Mutation in the GNAS. Ann Clin Lab Sci. 2015; 45(3):344–7. [PubMed: 26116601]

48. Tam VH, Chen SP, Mak CM, Fung LM, Lee CY, Chan AY. A novel mutation in pseudohypoparathyroidism type 1a in a Chinese woman and her son with hypocalcaemia. Hong Kong Med J. 2014; 20(3):258–60. [PubMed: 24914079]

49. Martinelli TA, Wiesel SW. Epidemiology of spinal stenosis. Instructional course lectures. 1992; 41:179–81. [PubMed: 1588062]

50. Knutsson B, Sanden B, Sjoden G, Jarvholm B, Michaelsson K. Body mass index and risk for clinical lumbar spinal stenosis: A cohort study. Spine. 2015

51. Ikeda K, Sakurada T, Sasaki Y, Takasaka T, Furukawa Y. Clinical investigation of olfactory and auditory function in type I pseudohypoparathyroidism: participation of adenylate cyclase system. The Journal of laryngology and otology. 1988; 102(12):1111–4. [PubMed: 3147312]

52. Koch T, Lehnhardt E, Bottinger H, Pfeuffer T, Palm D, Fischer B, et al. Sensorineural hearing loss owing to deficient G proteins in patients with pseudohypoparathyroidism: results of a multicentre study. Eur J Clin Invest. 1990; 20(4):416–21. [PubMed: 2121501]

53. Ramia M, Musharrafieh U, Khaddage W, Sabri A. Revisiting Down syndrome from the ENT perspective: review of literature and recommendations. Eur Arch Otorhinolaryngol. 2014; 271(5): 863–9. [PubMed: 23689804]

54. Henkin RI. Impairment of olfaction and of the tastes of sour and bitter in pseudohypoparathyroidism. J Clin Endocrinol Metab. 1968; 28(5):624–8. [PubMed: 5653198]

55. Wesley RK, Cullen CL, Golnick AL. Pseudohypoparathyroidism: report of case with systemic and oral manifestations. Pediatric Denistry. 1986; 8(1):48–52.

56. Ritchie GM. Dental manifestations of pseudohypoparathyroidism. Arch Dis Child. 1965; 40(213): 565–72. [PubMed: 5830003]

57*. Reis MT, Matias DT, Faria ME, Martin RM. Failure of tooth eruption and brachydactyly in pseudohypoparathyroidism are not related to plasma parathyroid hormone-related protein levels.

Bone. 2016; 85:138–41. This is the first study to look at the underlying mechanism of failure of tooth eruption and brachydactyly in PHP1A. [PubMed: 26855372]

58. Weinstock RS, Wright HN, Spiegel AM, Levine MA, Moses AM. Olfactory dysfunction in humans with deficient guanine nucleotide-binding protein. Nature. 1986; 322(6080):635–6. [PubMed: 3018580]
59. Doty RL, Fernandez AD, Levine MA, Moses A, McKeown DA. Olfactory dysfunction in type I pseudohypoparathyroidism: dissociation from Gs alpha protein deficiency. J Clin Endocrinol Metab. 1997; 82(1):247–50. [PubMed: 8989268]
60. Verhulst SL, Schrauwen N, Haentjens D, Suys B, Rooman RP, Van Gaal L, et al. Sleep-disordered breathing in overweight and obese children and adolescents: prevalence, characteristics and the role of fat distribution. Arch Dis Child. 2007; 92(3):205–8. [PubMed: 17041010]
61. Alonso-Alvarez ML, Cordero-Guevara JA, Teran-Santos J, Gonzalez-Martinez M, Jurado-Luque MJ, Corral-Penafiel J, et al. Obstructive sleep apnea in obese community-dwelling children: the NANOS study. Sleep. 2014; 37(5):943–9. [PubMed: 24790273]
62. Lassi G, Ball ST, Maggi S, Colonna G, Nieus T, Cero C, et al. Loss of Gnas imprinting differentially affects REM/NREM sleep and cognition in mice. PLoS Genet. 2012; 8(5):e1002706. [PubMed: 22589743]
63. Djonlagic I, Guo M, Matteis P, Carusona A, Stickgold R, Malhotra A. Untreated sleep-disordered breathing: links to aging-related decline in sleep-dependent memory consolidation. PloS one. 2014; 9(1):e85918. [PubMed: 24489679]
64. Attal P, Chanson P. Endocrine aspects of obstructive sleep apnea. J Clin Endocrinol Metab. 2010; 95(2):483–95. [PubMed: 20061419]
65. Bucks RS, Olaithe M, Eastwood P. Neurocognitive function in obstructive sleep apnoea: a metareview. Respirology. 2013; 18(1):61–70. [PubMed: 22913604]
66. Biggs SN, Vlahandonis A, Anderson V, Bourke R, Nixon GM, Davey MJ, et al. Long-term changes in neurocognition and behavior following treatment of sleep disordered breathing in school-aged children. Sleep. 2014; 37(1):77–84. [PubMed: 24470698]
67. Kushida CA, Nichols DA, Holmes TH, Quan SF, Walsh JK, Gottlieb DJ, et al. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: The Apnea Positive Pressure Long-term Efficacy Study (APPLES). Sleep. 2012; 35(12):1593–602. [PubMed: 23204602]
68. Kylstra WA, Aaronson JA, Hofman WF, Schmand BA. Neuropsychological functioning after CPAP treatment in obstructive sleep apnea: a meta-analysis. Sleep medicine reviews. 2013; 17(5):341–7. [PubMed: 23063416]
69. Alexander SB, Tucker HS Jr. Pseudohypoparathyroidism; report of a case with late manifestations. J Clin Endocrinol Metab. 1949; 9(9):862–73. [PubMed: 18139328]
70. Rahmat N, Venables P. Sinus pauses and high-grade atrioventricular block in Albright's hereditary osteodystrophy with pseudopseudohypoparathyroidism. BMJ case reports. 2013; 2013
71. Romanet P, Osei L, Netchine I, Pertuit M, Enjalbert A, Reynaud R, et al. Case report of GNAS epigenetic defect revealed by a congenital hypothyroidism. Pediatrics. 2015; 135(4):e1079–83. [PubMed: 25802348]

KEY POINTS

- Reduced resting energy expenditure likely contributes to the early-onset obesity seen in PHP1A and adults may be at increased risk of type 2 diabetes.
- Orthopedic complications, including brachydactyly, spinal stenosis and carpal tunnel, are common in PHP1A
- Patients with PHP1A may have ear-nose-throat complications including dental anomalies, hearing loss, frequent otitis media and decreased olfaction.
- Sleep apnea is at least 4-times more common in children with PHP1A than similarly obese controls and polysomnography should be performed in patients with a history of snoring, daytime somnolence or inattention.

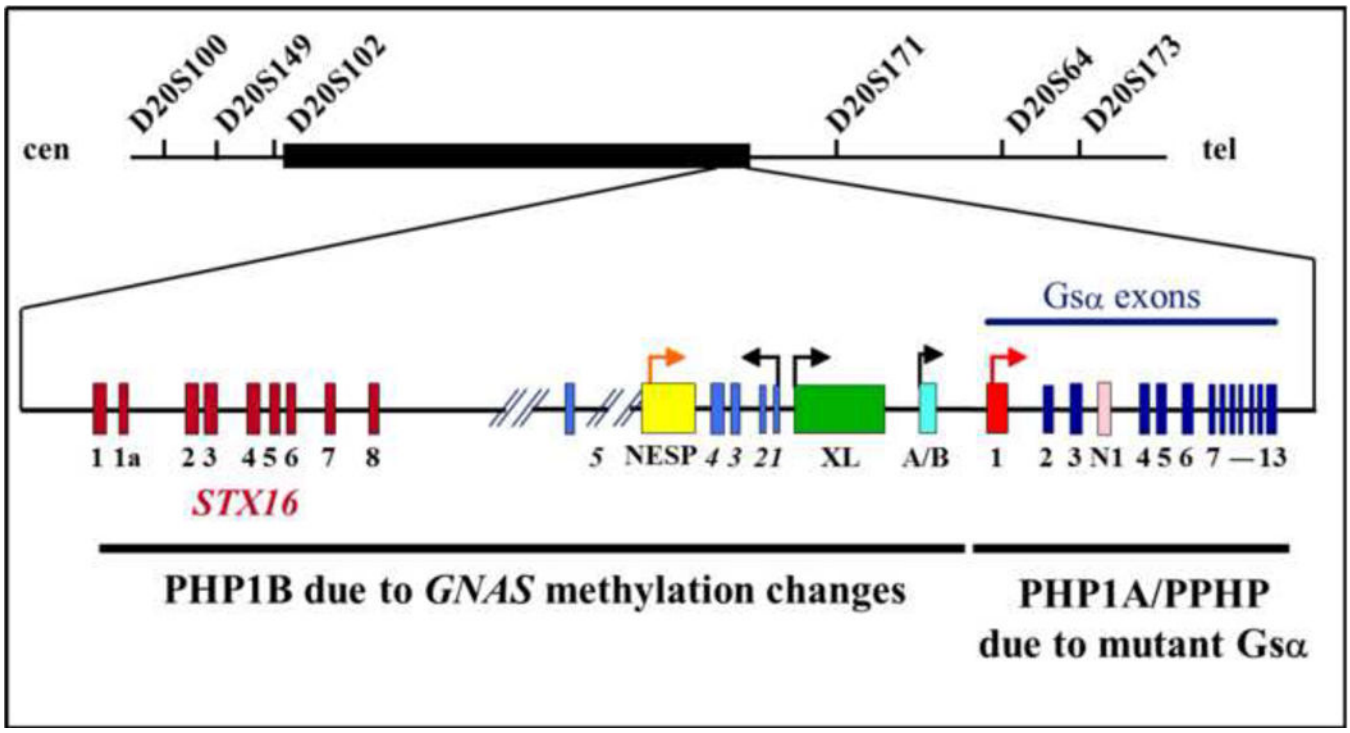

Figure 1.

The *GNAS* gene complex on chromosome 20. PHP1A is caused by mutations involving exons 1–13 of *GNAS*, the gene encoding the alpha-subunit of the stimulatory G protein ($G_s\alpha$) and multiple splice variants. Additional sense and antisense transcripts are derived from the *GNAS* locus and the alternate first exons A/B, $XL_{\alpha s}$ and Nesp55. In some tissues, $G_s\alpha$ transcripts are preferentially expressed from the maternal allele, due to tissue-specific paternal imprinting. Mutations in the gene *GNAS* give rise to the disease pseudohypoparathyroidism type 1A (PHP1A) when inherited on the maternal allele or the less severe disease pseudopseudohypoparathyroidism (PPHP) when inherited on the paternal allele. Loss of the normal methylation pattern results in pseudohypoparathyroidism type 1B (PHP1B).

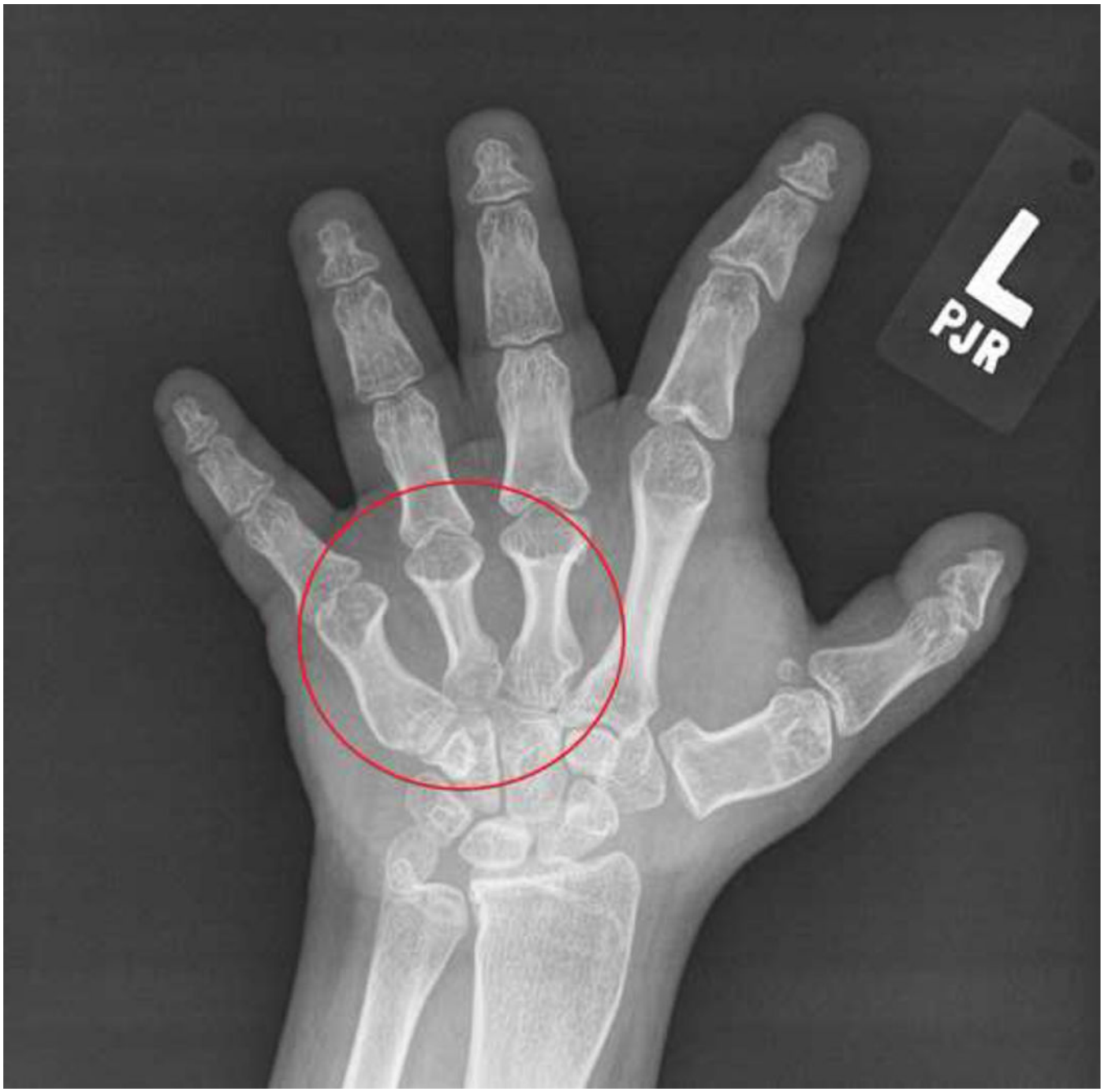

Figure 2.

Left hand film of a female child with pseudohypoparathyroidism type 1a (PHP1A). The red circle highlights brachydactyly, the shortening of the 3rd–5th metacarpals.