**HYPOPARATHYROIDISM AND PSEUDOHYPOPARATHYROIDISM**

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**ABSTRACT**

In primary hypoparathyroidism with hypocalcemia and hyperphosphatemia, deficient parathyroid hormone (PTH) secretion most commonly occurs from surgical excision of, or damage to, the parathyroid glands. The term idiopathic hypoparathyroidism describes isolated cases when a cause is not obvious, and there is no family history. However, hypoparathyroidism is also a feature common to a variety of hereditable syndromes that may present *de novo*. Familial isolated hypoparathyroidism may show autosomal dominant, autosomal recessive, or X-linked inheritance. Genes involved include *PTH*, *SOX3*, *CASR*, *GNA11* and *GCM2*. Parathyroid hypoplasia is a frequent feature of 22q11.2 deletion syndrome with involvement of the *TBX1* gene. The Hypoparathyroidism, Nerve Deafness, and Renal Dysplasia syndrome is due to haploinsufficiency of the *GATA3* gene. Antibodies against parathyroid tissue are found in isolated hypoparathyroidism or combined with other endocrine deficiencies. Antibodies against the CASR occur in type 1 autoimmune polyglandular syndrome, due to mutations of the *AIRE* gene, or in acquired hypoparathyroidism. Disorders characterized by end-organ resistance to PTH are described collectively by the term pseudohypoparathyroidism (PHP), and PHP1A and PHP1B are caused by maternally-inherited changes at the imprinted *GNAS* complex gene that encodes the Gsα protein. Deleterious mutations of the *PTH1R* gene show resistance to PTH and PTHrP and present as Blomstrand lethal chondrodysplasia, Eiken syndrome, endochondromatosis, and primary failure of tooth eruption. Calcium and vitamin D are the standard therapy for the management of hypoparathyroidism, with hormone replacement [recombinant human PTH(1-84)] therapy recently becoming an option. Calcilytics, PTH analogs, and orally active small molecule PTH1R agonists may, in the future, join the treatment armamentarium.

**PRIMARY HYPOPARATHYROIDISM**

Primary hypoparathyroidism is caused by a group of heterogeneous conditions in which hypocalcemia and hyperphosphatemia occur as a result of deficient parathyroid hormone (PTH) secretion (1). This most commonly results from surgical excision of, or damage to, the parathyroid glands. However, autoimmune disease is also a significant factor in acquired cases, and genetic forms of hypoparathyroidism due to decreased PTH secretion are not rare (Table 1).

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| **Table 1. Forms of Hypoparathyroidism having a Genetic Basis** |
| 1. **Isolated**
	1. 1) Autosomal dominant
		1. *A) PTH* mutation
		2. *B) CASR* activating mutation (ADH1)
			1. a) Bartter Syndrome Type V
		3. *C) GCM2* mutation (dominant negative)
		4. *D) GNA11* activating mutation (ADH2)
	2. 2) Autosomal recessive
		1. *A) PTH* mutation
		2. *B) GCM2* mutation
	3. 3) X-linked
2. **Congenital multi-system syndromes\***
	1. 1) DiGeorge 1 (22q11) & 2 (10p)
	2. 2) Barakat/HDR
	3. 3) Kenny-Caffey 1 & 2 and Sanjad-Sakati
3. **Metabolic disease**
	1. 1) Mitochondrial neuromyopathies
	2. 2) Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency
	3. 3) Heavy-metal storage disorders
4. **Autoimmune disease**
	1. 1) Autoimmune polyendocrine syndrome type I (APS-1 / APECED)
5. **Parathyroid resistance syndromes**
	1. 1) Pseudohypoparathyroidism
	2. 2) Blomstrand chondrodysplasia and related PTH receptor defects
	3. 3) Hypomagnesemia

\* Clarke et al. (2) list other potential syndromic associations with hypoparathyroidism, including: CHARGE (**C**oloboma, **H**eart defect, **A**tresia choanae, **R**etarded growth and development, **G**enital hypoplasia, **E**ar anomalies/deafness), Dubowitz, lymphedema, nephropathy & nerve deafness |

The signs and symptoms of hypoparathyroidism include evidence of latent or overt neuromuscular hyperexcitability due to hypocalcemia (Table 2). The effect may be aggravated by hyperkalemia or hypomagnesemia, but there is wide variation in the severity of symptoms. Patients may complain of circumoral numbness, paresthesias of the distal extremities, or muscle cramping, which can progress to carpopedal spasm or tetany. Laryngospasm or bronchospasm and seizures may also occur. Other less specific manifestations include fatigue, irritability, and personality disturbance. A comprehensive list of features associated with hypocalcemia can be found in the Endotext chapter, “Hypocalcemia: diagnosis and treatment” by Schafer & Shoback (3).

Severe hypocalcemia may be associated with a prolonged QTc interval on electrocardiography, which reverses with treatment. More extensive cardiomyopathic changes may be seen. These include chest pain, elevated enzymes (CPK), left ventricular impairment, and T-wave inversion, suggestive of a myocardial infarction (4, 5) . Patients with chronic hypocalcemia may have calcification of the basal ganglia or more widespread intracranial calcification, detected by skull X-ray or CT scan. Also seen are extrapyramidal neurological symptoms (more often with intracranial calcification), subcapsular cataracts, band keratopathy, and abnormal dentition.

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| **Table 2. Some Clinical Features of Hypocalcemia** |
| * Neuromuscular irritability
* Paresthesias
* Laryngospasm
* Bronchospasm
* Tetany
* Seizures
* Chvostek sign
* Trousseau sign
* Prolonged QT interval on ECG
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Increased neuromuscular irritability may be demonstrated by eliciting a Chvostek or Trousseau sign. A positive Chvostek sign is a prolonged reflex contraction of the facial muscle in response to a digital tap on the cheek just anterior to the ear. As with other hyperreflexias, up to 20% of normal individuals may demonstrate a slight positive reaction. A positive Trousseau sign is carpopedal spasm induced by inflation of a blood pressure cuff covering the upper arm to 20 mm Hg above systolic blood pressure for three minutes. This response reflects the heightened irritability of nerves undergoing pressure ischemia.

In hypoparathyroidism, serum calcium concentrations are decreased and serum phosphate levels are increased. Serum PTH is low or undetectable. (The important exception is PTH resistance, discussed further below.) Usually, serum 1,25-dihydroxyvitamin D (1,25(OH)2D) is low, but alkaline phosphatase activity is normal. Despite an increase in fractional excretion of calcium, intestinal calcium absorption and bone resorption are both suppressed. The renal filtered load of calcium is decreased, and the 24-h urinary calcium excretion is reduced; nephrogenous cyclic AMP excretion is low and renal tubular reabsorption of phosphate is elevated.

The terms idiopathic or isolated hypoparathyroidism have been traditionally used to describe isolated cases of glandular hypofunction when a cause is not obvious and there is no family history. However, hypoparathyroidism is a feature common to a variety of heritable syndromes that may present *de novo*. Hypoparathyroidism can occur because of a congenital hypoplasia/aplasia with or without other congenital anomalies such as dysmorphic facies, immunodeficiency, lymphedema, nephropathy, nerve deafness or cardiac malformation. Thus, in patients with hypoparathyroidism of uncertain onset, a careful examination of craniofacial features and assessment of endocrine, cardiac and renal systems should be performed to exclude a syndromic cause. Similarly, autoimmune hypoparathyroidism can occur as an isolated endocrine condition or with other glandular deficiencies in a pluriglandular autoimmune syndrome, requiring attention to multi-organ endocrine dysfunction.

A significant number of patients with idiopathic hypoparathyroidism and hypercalciuria, but no other anomalies may be found to have *de novo* activating mutations of the CASR gene.

Because of the implications for treatment, CASR molecular screening of patients with this presentation is recommended (6, 7).

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**Familial Isolated Hypoparathyroidism**

Familial isolated hypoparathyroidism (FIH) may show autosomal dominant, autosomal recessive, or X-linked inheritance.

In a few instances of autosomal dominant disease, a mutation in the ***PTH gene*** (MIM# 168450 (8) - <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>) has been found. In one family, a missense mutation (C18R) in the signal sequence of the preproPTH precursor has been identified (9) and the mutant shown to be defective *in vitro* in processing preproPTH to proPTH, although, as patients had one normal gene copy, the autosomal dominant mode of inheritance remained unexplained. Then, further studies in transfected cells showed that the mutant was trapped in the endoplasmic reticulum (ER) promoting ER stress and apoptosis (10). In a family with autosomal recessive hypoparathyroidism, a different, homozygous, signal sequence mutation (S23P) segregates with affected status (11). This mutation may prevent proper cleavage of the signal peptide during processing of the nascent protein. In a girl with isolated hypoparathyroidism, a homozygous S23X signal sequence mutation was found predicting a truncated inactive PTH peptide (12). However, the circulating PTH level was not undetectable, suggesting some translational readthrough of the mutant preproPTH mRNA. A homozygous [Cys25]PTH(1-84) mutation that impairs PTHR1 activation was identified in an idiopathic hypoparathyroid family (13). Elevated circulating PTH levels were found in some (but not all) assays thus defining a novel form of hypoparathyroidism. In another family with autosomal recessive hypoparathyroidism, a donor splice site mutation at the exon 2/intron 2 junction of the PTH gene was identified (14). The mutation leads to exon skipping and loss of exon 2 containing the initiation codon and signal sequence of preproPTH mRNA. The *SOX3* gene encodes a transcriptional factor likely involved in the embryonic development of the parathyroid gland (15). In two multigeneration families with X-linked recessive hypoparathyroidism exhibiting neonatal onset of hypocalcemia and parathyroid agenesis, the trait was mapped to a 906-kb region on distal Xq27 that contains three genes including *SOX3* but no intragenic mutations were found (MIM# 307700). An interstitial deletion-insertion involving chromosomes 2p25.3 and Xq27.1 was found downstream of *SOX3* and was speculated to exert a positional effect on SOX3 expression (16).

Gain-of-function mutations in the ***calcium-sensing receptor (CASR) gene*** (MIM#601199) have been identified in a number of families clinically diagnosed with autosomal dominant hypocalcemia type 1 (ADH1 – MIM#515361) (17, 18). In the parathyroid gland, the activated CASR suppresses PTH secretion, and in the kidney, it induces hypercalciuria that may contribute to the hypocalcemia. In many cases of ADH1, the family history is positive, but *de novo* mutations are quite common (19, 20). Mosaicism for *de novo* mutation in an otherwise healthy parent has been described (21), and may explain some cases of apparently recessive disease. Most importantly, there are implications for counseling parents about the risks of recurrence.

Almost all of the activating mutations are missense and appear almost equally divided between the amino-terminal third of the extracellular domain (ECD) and the transmembrane domain (TMD). Of special interest is the cluster of ECD mutations (A116T to C131W) that cause an increase in receptor sensitivity to extracellular calcium, suggesting that this region is critical for receptor activation. This cluster overlaps the two cysteine residues –cys-129 and cys-131– involved in the interface of the mature protein dimer (22). Further details can be found in the locus-specific database –<http://data.mch.mcgill.ca/casrdb/> (23) and (24).

Although Bartter syndrome subtype V is represented by only a handful of cases with heterozygous severe activating mutations in the *CASR* (MIM#601199), it provides additional insight into the functioning of the CaSR in the thick ascending limb (TAL) of the nephron (25-27). Bartter syndrome encompasses a heterogeneous group of electrolyte homeostasis disorders, the common features of which are hypokalemic alkalosis, hyperreninemia, and hyperaldosteronism. Bartter syndrome subtypes I–IV are autosomal recessive disorders due to inactivating mutations in the following ion transporters or channels active in the TAL: type I, the sodium potassium-chloride cotransporter (NKCC2); type II, the outwardly rectifying potassium channel (ROMK); type III, the voltage-gated chloride channel (CLC-Kb); type IV, Barttin, a chloride channel beta-subunit that is required for trafficking of CLC-Ka and CLC-Kb. Patients with the autosomal dominant Bartter syndrome subtype V have, in addition to the classic features of the syndrome, hypocalcemia, and may exhibit neuromuscular manifestations, seizures, and basal ganglia calcifications. NKCC2 and ROMK in the apical membrane (luminal side) of the TAL have been proposed to generate a transepithelial electrochemical gradient that drives passive paracellular transport of Na+, Mg2+, and Ca2+ from the lumen to blood (28). The CASR is situated in the basolateral membrane (antiluminal side) and, when activated, increases 20-hydroxyeicosatetraenoic acid and decreases cAMP concentrations, both of which would inhibit ROMK and NKCC2 activities (28, 29). Thus, severe activating mutations of the CASR lead to the salt wasting of Bartter syndrome in addition to the hypercalciuric hypocalcemia of ADH1.

Heterozygous gain-of-function missense mutations of *GNA11* have been identified in ADH patients without detectable CASR activating mutations (30-33). The *GNA11* activating mutations increase the sensitivity of the parathyroid gland and renal tubule to extracellular calcium concentrations. Autosomal dominant hypocalcemia and hypoparathyroidism due to *CASR* and *GNA11* mutations are now designated as ADH type 1 (MIM#601198) and type 2 (MIM#615361) respectively. The human Gα11 protein (a Gq family member – MIM#139313) has 359 amino acids with an α-helical domain in the NH2-terminal region, a GTPase domain in the COOH-terminal region, and three switch regions (SR1-3) in the middle portion that change conformation based on whether GTP or GDP is bound (34). The R80C, R181Q, S211W, F341L, and V304M mutations found in hypocalcemic individuals are predicted by 3D modeling to alter the normal Gα11 protein structure. Moreover, cells stably expressing the CASR and transfected with the mutants exhibit increased sensitivity to changes in extracellular calcium (30-33).

Inactivating mutations in the CASR regulator, the adaptor protein 2 sigma subunit encoded by the *AP2S1* gene, cause familial hypocalciuric hypercalcemia type 3 (35). The search for activating mutations in *AP2S1* in familial and sporadic isolated hypoparathyroid patients negative for *CASR* or *GNA11* mutations that would represent an additional genetic cause of ADH has thus far been negative (36, 37).

Recessively inherited FIH may occur with mutations of the ***glial cells missing-2 gene (GCM2;*** *MIM#603716****)***. The *GCM2* gene localizes to chromosome 6p24.2 and encodes a transcription factor. It is expressed in the PTH-secreting cells of the developing parathyroid glands and is critical for their development in terrestrial vertebrates (38-40). A patient with neonatal hypoparathyroidism was found to be homozygous for a partial deletion acquired from both parents (41), and a pair of siblings with homozygous mutations has been reported (42). Additional studies have identified inactivating *GCM2* mutations in cases with autosomal recessive FIH (43, 44). On the other hand, heterozygous mutations that cause dominant-negative *GCM2* mutants have also been identified in patients with autosomal dominant hypoparathyroidism (43, 45, 46). Additional recessive and dominant *GCM2* mutations have been noted in this gene that continues to be expressed in the adult parathyroid [see (47)]. Nevertheless, it appears that the prevalence of genetic defects affecting GCM2 function is not high in isolated hypoparathyroidism, as a recent study investigating 20 unrelated cases with this disorder (10 familial and 10 sporadic) failed to identify any *GCM2* mutations segregating with the disease and/or leading to loss of function (48). Of further interest is that a genetic variant, Y282D that demonstrates significantly enhanced transcriptional activity relative to wild-type GCM2 associates with hyperparathyroidism in some cohorts of the sporadic primary disorder (49). Most recently, novel heterozygous active *GCM2* variants that segregate with affected status in some kindreds with familial isolated ***hyper***parathyroidism have been described (50). Thus, like *CASR* and *GNA11*, both gain-of-function and loss-of-function variants of *GCM2* may contribute to calcemic disorders.

### Hypoparathyroidism with Syndromic Features

Hypoparathyroidism due to parathyroid hypoplasia is a frequent feature of ***22q11.2 microdeletions***, the most common cause of ***DiGeorge syndrome 1*** (DS1; MIM#188400) (51, 52) . This syndrome complex arises from a failure of the third and fourth pharyngeal pouches to develop, leading to agenesis or congenital hypoplasia of the parathyroid glands, thymus, and the anterior heart field. Patients with DS1 may typically present with neonatal hypocalcemic seizures due to hypoparathyroidism, severe infections due to thymic hypoplasia, and conotruncal heart defects (53). Because a microdeletion is involved, the identification of novel developmental genes in the 22q11 region has been keenly pursued. One of the genes is *TBX1*, encoding a DNA-binding transcription factor of the T-box family known to have important roles in vertebrate and invertebrate organogenesis and pattern formation (54, 55). Mouse models with Tbx1 haploinsufficiency established the essential contribution of this factor to conotruncal development (56), and placed it in developmental context during organogenesis (57, 58). However, while the *Tbx1* null mutant mice had all the developmental anomalies of DS1 – thymic and parathyroid hypoplasia, abnormal facial structures and cleft palate, skeletal defects and cardiac outflow abnormalities – *Tbx1* haploinsufficiency in mice was associated with only defects of the fourth pharyngeal pouch responsible for the cardiac outflow abnormalities (59). cDNA microarray analyses of mice lacking Tbx1 have identified *Gcm2* as one of the downregulated genes in the pharyngeal region, indicating that Tbx1 is upstream of Gcm2 (60). Furthermore, as Tbx1 is regulated by sonic hedgehog (Shh) (61), a Shh-Tbx1-Gcm2 parathyroid developmental pathway is indicated.

The basis for the phenotypic differences between DGS1 patients who are heterogeneous for *TBX1* loss and the *Tbx1*+/- mice is unclear but could reflect a species-specific gene dosage requirement together with roles of downstream genes regulated by Tbx1. Some patients may have late-onset DGS1 and develop symptomatic hypocalcemia in childhood or later with only subtle phenotypic abnormalities (62, 63). Of note is that the age of diagnosis in rare families with DGS1 patients having *TBX1* inactivating (missense or frameshift) mutations ranged from 7 to 46 years in keeping with late-onset DGS1 (54).

The 22q11.2 deletion syndrome (22q11.2DS) encompasses a wider spectrum of clinical conditions that includes isolated congenital heart disease and velocardiofacial (VCF) syndrome (52). Associated craniofacial abnormalities include cleft palate, pharyngeal insufficiency and mildly dysmorphic facies. In the VCF syndrome, anatomical anomalies of the pharynx are prominent and hypernasal speech due to abnormal pharyngeal musculature with or without cleft palate is typical. In most patients, some degree of intellectual deficit is present and there is strong predisposition to psychiatric illness (schizophrenia or bipolar disorder) in adolescents and adults (64, 65). Further information, both clinical and educational, can be found at web sites specifically devoted to this condition [see (66)].

The 22q11.2DS is due to one of the most common microdeletions (1 in 4000 live births), and it may go clinically unrecognized in its milder or variant forms. Most cases with hypoparathyroidism (~50% of cases) are the result of de novo deletion through meiotic non-allelic homologous recombination, and driven by a unique cluster of low copy repeats designated LCR22 A-H [see (66, 67) ]. Most commonly (~85% of cases), a deletion of ~3 Mb is found, encompassing proximal repeats A to D. Many of the others (~10% of cases) involve atypical nested deletions including those spanning LCR22 A to B. Thus, LSR22 A to B, which includes the *TBX1* gene, is the primary site contributing to parathyroid dysgenesis. Detailed characterization and long-term follow-up for the hypoparathyroid component of this disorder is ongoing.

Although most cases of DiGeorge syndrome are sporadic, as mentioned above autosomal dominant inheritance is not unknown. In utero influences may be important determinants of the clinical picture, since there are instances of monozygotic twins with discordant phenotypes (68-70). Phenocopies occur with diabetic embryopathy, fetal alcohol syndrome, and retinoid embryopathy. In rare instances, it has been shown that a phenotypically normal parent can transmit a microdeletion to an offspring. Such parents have been found to carry a duplication of the 22q11 on the second chromosome, and the combination of duplication and deletion alleles in a parent generates a balanced state, termed “gene dosage compensation” (71, 72).

Although the hypoparathyroidism affects about half of all carriers, it is usually not severe, and frequently treatment following neonatal hypocalcemia can be tapered or stopped in older children. However, the hypoparathyroidism may also remain asymptomatic until adolescence or emerge at times of stress, such as corrective cardiac surgery or severe infection, suggesting that continued surveillance of parathyroid gland reserve is important (73-75).

Traditionally, diagnosis of 22q11.2DS is established with specific cytogenetic studies -- usually with locus-specific fluorescence in-situ hybridization (FISH) testing. These tests will pick up many of the larger common deletions that involve regions of low-copy number repeats (LCRs). However, specific chromosomal array-based and MLPA analyses are now preferred, as they have been shown to have increased sensitivity for smaller deletions (66). Recently, the diagnostic power of next-generation sequencing has been harnessed to identify almost all of the microdeletions underlying sporadic and inherited forms of the disorder (52). Non-invasive prenatal screening and pre-implantation genetic diagnosis) are also clinically available (76). Because the clinical picture is so variable and the prevalence so high, testing for 22q11.2 microdeletion should be considered in the workup for any new hypoparathyroid case for which another cause is not found. Finally, distinct genetic defects can coexist with 22q11.2DS, as exemplified by the finding of concurrence of this syndrome in an adolescent with longstanding ***hyper***calcemia who had familial hypocalciuric hypercalcemia type 3 due to an *AP2S1* mutation (77).

Clinicians will also want to be aware that a small but significant minority (~10%) of patients will have associated autoimmune disease, driven in part, perhaps, by the thymus-based defect in T cell function (64,79). Among the more common (non-endocrine) conditions are arthritis, celiac disease, and autoimmune hematologic disease, particularly idiopathic thrombocytopenic purpura. Autoimmune thyroid disease, with either hypo- or hyperparathyroid states, has been reported (78, 79), and serum TSH assay should be measured regularly. It has been suggested that the later-onset hypoparathyroid disease may be partly autoimmune in origin, not developmental. A survey of 59 Norwegian patients showed discordance of adult onset disease with neonatal hypoparathyroidism, but a significant correlation with parathyroid autoantibodies and the presence of autoimmune disease (78).

The clinical features of DiGeorge syndrome, including hypoparathyroidism, also occur with other cytogenetic abnormalities, notably chromosome 10p haploinsufficiency (80, 81). Deletions of two non-overlapping regions of chromosome 10p contribute to DiGeorge syndrome 2; DS2 at 10p13-14 (82), and the ***Barakat or HDR (Hypoparathyroidism, Nerve Deafness, and Renal Dysplasia) syndrome*** (MIM#146255) (83, 84) at 10p14-10pter (85, 86). The latter is due to haploinsufficiency of *GATA3* (MIM#131320), which encodes a dual zinc finger transcription factor (87) that is essential for normal embryonic development of the parathyroids, auditory system, and kidney. Since the original description, several additional *GATA3* loss-of-function mutations have been described in HDR patients [e.g., (88-91)]. Heterozygous *Gata3*-deficient mice develop parathyroid abnormalities as revealed by challenge with a diet low in calcium and vitamin D that are due to dysregulation of the parathyroid-specific transcription factor, Gcm2. *Gata3*-/- embryos at E12.5 lack Gcm2 expression and have gross defects in the fourth pharyngeal pouches, including absent parathyroid/thymus primordia (92). GATA3 transactivates the *GCM2* promoter and, with GCM2, forms part of a transcriptional cascade essential for the differentiation and survival of parathyroid progenitor cells.

In another congenital disorder, ***Kenny-Caffey syndrome***, hypoparathyroidism is found variably associated with the typical picture of growth retardation, osteosclerosis, cortical thickening of the long bones, and delayed closure of the anterior fontanel (93-96). The original description of the syndrome was of the autosomal dominant form now identified as KCS-2 (MIM#127000) that is caused by heterozygous mutations in the FAM111A gene (97-99). The full functions of FAM111A and how mutations in it cause the disorder are unclear. FAM111A has some homology to peptidases, and is involved with chromatin structure during DNA replication (100). KS-2 is allelic to the lethal disorder, osteocraniostenosis (OCS, MIM#6023611). Hypocalcemia due to hypoparathyroidism was found in some OCS patients who survived the perinatal period (96).

A recessively inherited form of Kenny-Caffey syndrome (KCS-1, MIM#244460) was noted to be similar to the recessive ***Sanjad-Sakati syndrome*** (MIM#241410) characterized by congenital hypoparathyroidism, seizures, growth and developmental retardation and characteristic dysmorphic features, including deep set eyes, depressed nasal bridge with beaked nose, long philtrum, thin upper lip, micrognatia and large, floppy ear lobes. Radiographs showed medullary stenosis reminiscent of Kenny-Caffey syndrome (96, 101). Linkage studies localized the recessive KCS-1 and Sanjad-Sakati syndromes to 1q42-43, and causative mutations in the tubulin chaperone E, *TBCE*, gene were identified in what is now known as ***Hypoparathyroidism, Retardation and Dysmorphism (HRD) syndrome*** (96, 102, 103) . This highlighted the role of TBCE that binds microtubules and proteasomes and protects against misfolded stress (104) in parathyroid development (105).

**Hypoparathyroidism due to Metabolic Disease**

Hypoparathyroidism is also a variable component of the neuromyopathies caused by mitochondrial gene defects (106). Among these are the ***Kearns-Sayre syndrome*** (ophthalmoplegia, retinal degeneration, and cardiac-conduction defects) (MIM#530000), the Pearson marrow pancreas syndrome (lactic acidosis, neutropenia, sideroblastic anemia, and pancreatic exocrine dysfunction) (107) (MIM#557000) and ***mitochondrial encephalomyopathy*** (MIM#540000). The molecular defects range from large deletions and duplications of the mitochondrial genomes in a large number of tissues (108, 109) to single base-pair mutations in one of the transfer RNA genes found only in a restricted range of cell types (MIM#590050). The role of these mitochondrial mutations in the pathogenesis of hypoparathyroidism remains to be clarified. However, mutations in HADHB, that encodes the β-subunit of mitochondrial trifunctional protein, cause infantile onset hypoparathyroidism and peripheral polyneuropathy (110).

Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency (MIM#600890)
is an inborn error of oxidative fatty acid metabolism that may be accompanied by hypoparathyroidism (111). Whether the parathyroid disease is directly related to the enzyme deficiency or secondary to the accompanying mitochondrial disease needs further study.

Parathyroid insufficiency and symptoms of hypocalcemia are occasionally seen in inherited metabolic disorders leading to excess storage of iron (***thalassemia, Diamond-Blackfan anemia, hemochromatosis)*** or copper ***(Wilson disease)*** (112). In most instances, there is similar dysfunction in other endocrine glands, and the parathyroid disease is usually mild. Nonetheless, recognition of the hypoparathyroid state may help explain otherwise non-specific symptoms and aid in overall management of these multisystem diseases.

**Autoimmune Hypoparathyroidism: Acquired and Inherited Disorders**

Antibodies directed against parathyroid tissue have been detected in up to 38% of patients with isolated hypoparathyroid disease, and over 40% of patients having hypoparathyroidism combined with other endocrine deficiencies (113, 114). Subsequently, a survey of a parathyroid expression library led to the identification of one protein selectively associated with the autoimmune process, the NACHT leucine-rich-repeat protein 5 (NALP5). Elevated antibody titers occur in half the patients with autoimmune hypoparathyroidism, with or without another autoimmune disease, but uncommonly in other conditions without hypoparathyroidism (114, 115).

Antibodies against the extracellular domain of the parathyroid CASR were originally reported in more than half of patients with either ***type 1 autoimmune polyglandular syndrome (APS-1, also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy or APECED***), MIM# 240300, (116) or ***acquired hypoparathyroidism*** associated with autoimmune hypothyroidism (117). This finding was confirmed in a subsequent study of 51 cases of idiopathic hypoparathyroidism, but there was a 13% positive rate in controls (118). Other studies of APS-1 patients have also identified elevated CASR antibodies in some cases but at a lower frequency (119-121). Although some have suggested that CASR antibody assays are clinically indicated in acquired hypoparathyroidism (122), it remains to be seen whether the autoantibodies are of primary or secondary importance (114, 123). There is now good evidence that autoantibodies can be functional activators of CASR and thereby could induce hypoparathyroidism. While presently there may not be a convenient clinical test for this, patient sera have been demonstrated to activate the CASR transfected into HEK cells *in vitro* (124). In some hypoparathyroid patients, both autoimmune parathyroid destruction and suppression by CASR activation may co-exist (125).

In APS-1, the most common associated manifestations are hypoparathyroidism with mucocutaneous candidiasis and Addison's disease. Additional features include pernicious anemia, chronic active hepatitis, alopecia, keratitis, gonadal failure, thyroid disease, pancreatic insufficiency, and diabetes mellitus (116). The phenotype is highly variable and patients may not express all elements of the basic triad, leading to the suggestion that the criteria used for molecular screening be relaxed (125, 126). The disease usually presents in infancy with chronic oral thrush, followed by hypoparathyroidism in the first decade, and then adrenocortical failure in the third. Interestingly, there is nearly 100% penetrance of hypoparathyroidism in females, but less than 60% in males, even though the adrenal hypofunction affects both sexes equally (119). Moreover, patients who develop the adrenal hypofunction first are less likely to be male and may never develop hypoparathyroidism. The responsible gene, called the autoimmune regulator (AIRE), maps to chromosome 21q22 and encodes a transcriptional regulator (127-129) . In the absence of AIRE protein, tissue-specific self-antigens are not expressed in the thymus and multiorgan autoimmunity develops, because negative selection of the T cells bearing the autoantigens is disrupted (130). Many patients with APS-1 can be shown to have autosomal recessive inheritance of the AIRE defect. In families with autosomal recessive mutations of AIRE, obligate heterozygotes may also have common autoimmune disorders but APECED is not seen (131). A phenocopy leading to acquired APS-1 may occur when the AIRE gene is silenced by thymic neoplasia (132). APS-1 has been associated with more than 300 mutations of the AIRE gene, and updates can be found in the online mutation database (<https://grenada.lumc.nl/LOVD2/mendelian_genes/home.php?select_db=AIRE>).

**PARATHYROID RESISTANCE SYNDROMES**

**Pseudohypoparathyroidism**

Several clinical disorders characterized by end-organ resistance to PTH have been described collectively by the term pseudohypoparathyroidism (PHP). They are associated with hypocalcemia, hyperphosphatemia, and increased circulating PTH. Target tissue unresponsiveness to the hormone manifests as a lack of increased phosphate excretion and, in some cases, cAMP excretion in response to PTH administration (133). The biochemical characteristics of the different forms of PHP are contrasted with those of hypoparathyroidism in Table 3.

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| **Table 3. Biochemical Characteristics of Hypoparathyroidism and Pseudohypoparathyroidism**  |
| **Defects**  | **Serum PO4**  | **PTH**  | **25(OH)D**  | **1,25(OH)2D**  | **UcAMP\***  | **UPO4\***  | **Multiple Endocrine Defects**  |
| Hypoparathyroidism  | ↑  | ↓  | -  | ↓  | -  | -  | Yes/No\*\*  |
| Pseudohypoparathyroidism  |
|      Type 1a  | ↑  | ↑  | -  | ↓  | ↓  | ↓  | Yes  |
|      Type 1b  | ↑  | ↑  | -  | ↓  | ↓  | ↓  | No/Yes#  |
|      Type 1c  | ↑  | ↑  | -  | ↓  | ↓  | ↓  | Yes  |
|      Type 2  | ↑  | ↑  | -  | ↓  | -  | ↓  | No  |

### ↑, increased; ↓, decreased; -, normal;

### \*Response to PTH infusion

### \*\*, depending upon the etiology.

### #, variable, mild defects of the thyroid axis due to TSH resistance may be seen.

**Albright Hereditary Osteodystrophy**

Fuller Albright first recognized that the likely cause of the hypoparathyroid state in PHP is a constitutive absence of target tissue responsiveness (134). In many patients, the end-organ resistance is accompanied by a specific pattern of physical findings, called ***Albright hereditary osteodystrophy (AHO***; MIM#300800). Typically, patients have short stature, round facies, brachydactyly, obesity, and ectopic soft tissue or dermal ossification(s) (osteoma cutis) (Figure 1). In the calvaria, this may manifest as hyperostosis frontalis interna (135). Intracranial calcification(s), cataracts and band keratopathy, subcutaneous calcifications, and dental hypoplasia are also common but are likely the consequences of longstanding hypoparathyroid hypocalcemia (Table 4, see below Figure 1). The brachydactyly may be asymmetric or not, and may involve one or both hands or feet, but the pattern is quite distinctive (136, 137). The shortening tends to involve the first distal phalanx, with a thumbnail (or first toenail) that is wider than it is long. The fourth and fifth metacarpals (or metatarsals) are frequently shortened out of proportion to the others and the second metacarpal is often spared. Radiographic analysis of the hands (pattern profiling) may be helpful in assessment of the brachydactyly (Figure 1) (138).



**Figure 1. Albright’s hereditary osteodystrophy (AHO) and characteristic skeletal abnormalities. A) A child with AHO exhibiting short stature, obesity, and round facies. B) The hand X-ray of a patient with AHO, displaying brachydactyly of the fourth and fifth metacarpal bones. C) Dimpling over the knuckles of a clenched fist (also known as Archibald sign), indicating the short metacarpals. D) Evidence of brachydactyly in the hand, reflecting the shortened fourth and fifth metacarpals and the distal phalanx of the thumb. Images are from: Levine, MA (139).**

|  |
| --- |
| **Table 4. Incidence of signs and symptoms in PHP with AHOa** |
|  | **Percentage**  |
| Short stature  | 80  |
| Obesity  | 50  |
| **Craniofacial**  |
| Round face  | 92  |
| bLenticular opacities  | 44  |
| Strabismus  | 10  |
| bDental hypoplasia  | 51  |
| bBasal ganglia calcification  | 50  |
| Thickened calvaria  | 62  |
| Mental deficit  | 75  |
| **Brachydactyly**  |
| Brachymetacarpia  | 68  |
| Brachymetatarsia  | 43  |
| Brachyphalangia  | 50  |
| **Other connective tissue features**  |
| Decreased bone density  | 15  |
| Ectopic ossification  | 56  |
| bSubcutaneous calcification  | 55  |

a Taken from Drezner and Neelon (1995).

b Features common to other forms of chronic hypoparathyroid hypocalcemia.

Although affected patients are generally short as adults, their bone age as children may be advanced and growth accelerated (138). Patients with AHO may be predisposed to hypertension (140), conductive and sensorineural hearing loss (135, 141), cord compression due to spinal anomalies (142), and movement disorders due to basal ganglia calcification (143). The features of AHO may be subtle in infancy or early childhood; in a few, there is little to see even in adulthood. The round facies, short neck, and low, flat nasal bridge are often accompanied by central obesity (144). A study showed that the obesity phenotype occurs primarily in those patients who also have multiple hormone resistance, i.e., PHP1A (see below), and according to data from mice, a hypothalamic mechanism, rather than hypothyroidism, is the primary underlying cause (145, 146). Interestingly, a study showed that GNAS mutations are not uncommon in severe childhood-onset obesity in the absence of other typical PHP findings (147).

Patients with brachydactyly, mental retardation, and other features closely resembling AHO have been found to carry microdeletions of chromosome 2q37; ***brachydactyly-mental retardation, BDMR***; MIM#600430 (148). Genes important for skeletal and neurological development lie within this region. Haploinsufficiency of *HDAC4* (MIM#605314), encoding a histone deacetylase that regulates gene expression during the development of many tissues including the bone, is responsible for the brachydactyly and the mental retardation in those patients (149). Isolated brachydactyly type E (BDE, MIM#113300) has been associated in sporadic cases with mutations in *HOX13* (MIM#168470) (150) and mutations in the *PTHLH* gene (MIM#168470) on 12p11.2 that encodes PTHrP have been implicated. In one family with autosomal BDE a *cis*-regulatory site downregulates *PTHLH* in translocation t(8;12)(q13;p11.2) and downregulates its targets *ADAMTS-7* and *ADAMTS-12* leading to impaired chondrogenic differentiation (151). Affected individuals of one large family with BDE, short stature, and learning difficulties had an ~900 bp microdeletion encompassing *PTHLH* (152). Additional individuals with BDE and short stature from other different kindreds were found to have *PTHLH* missense, nonstop, and nonsense mutations (152). Different translocations affecting chromosome 12p have also been identified in two families with BDE, leading to increased abundance of a long noncoding RNA on chromosome 12q, which regulates the expression of *PTHLH* in cis and of the *SOX9* gene located on chromosome 17q in trans (153). BDE is associated with hypertension in some cases, in which the disease is inherited in an autosomal dominant manner (termed HTNB). Missense mutations in *PDE3A*, a gene encoding a cAMP/cGMP phosphodiesterase, have been recently found in several unrelated families with HTNB. These mutations cause increased cAMP hydrolytic activity and thus lead to diminished cAMP signaling (154). Some patients with AHO-like features have been described, who also showed platelet Gs hypofunction. Those patients were found to have *IGF2* hypermethylation and *SNURF* hypomethylation, as well as imprinting defects within *GNAS*, the gene encoding the stimulatory G protein alpha-subunit (Gsα; see below) (155).

**PHP1A**

PHP1A patients are characterized by AHO, PTH resistance, and evidence of target organ resistance to other hormones. Patient-derived cells are found to have a reduction in the activity of the Gsα subunit, which is part of the membrane-associated heterotrimeric stimulatory G-protein complex - transducing signals between G-protein coupled receptors and adenylate cyclase (156-158). Adenylyl cyclase catalyzes the synthesis of the second messenger cAMP, and therefore, PHP1A patients tend to have a deficiency in cAMP generation, particularly in certain tissues. As explained above, this deficiency is clear when measuring cAMP excretion in response to PTH administration.

The *GNAS* gene (MIM#168470) encoding the Gsα protein maps to 20q13.2-13.3 and has at least 4 alternative transcriptional start sites (Figure 2) and an antisense transcript, GNAS-AS1 (159). The three upstream exons and the preceding promoter regions are genetically imprinted, i.e., methylated in an allele specific manner. The promoter of the Gsα transcript, which uses exon 1, is unmethylated. Unlike the other alternative *GNAS* products, Gsα expression is biallelic except in a small set of tissues, where Gsα is derived predominantly from the maternal allele (160-164) . This tissue-specific monoallelic Gsα expression affects the penetrance of the PHP phenotype. The maternal transmission of the hormone resistance in PHP1A (165) can be explained by the silencing of the paternal Gsα allele, which would otherwise allow expression of 50% of Gsα protein (166). Thus, the full expression of a coding *GNAS* mutation, which occurs in maternally transmitted cases, leads to AHO plus hormone resistance (PHP1A). On the other hand, if the same mutation is inherited paternally, it causes AHO alone. The latter is termed pseudopseudohypoparathyroidism (PPHP). Thus, PHP1A and PPHP can be found in the same families. Note that a systematic nomenclature and classification, “inactivating PTH/PTHrP signaling disorder” (iPPSD), has been suggested for PHP1A, PPHP, and related disorders arising from abnormal PTH and/or cAMP signaling, accounting for the underlying genetic/epigenetic abnormalities and associated phenotypes (167).

Despite clinical evidence supporting imprinting in portions of the kidney tubule, it has been difficult to confirm this experimentally in humans (168). The imprinting of *GNAS* is complex and involves multiple differentially methylated regions (DMR) (159). Moreover, it is tissue-specific and may vary with developmental stage, although key imprinting of the A/B (also referred to as 1A) DMR is thought to be a primary event that occurs during gametogenesis and is maintained thereafter (169). Ablation of the Gsα ortholog in mice (*Gnas*) has confirmed that maternal, but not paternal, transmission of the deleted allele results in PTH resistance. The homozygous deletion of *Gnas* is embryonic lethal (160). Comparison of Gsα expression in mice with maternally vs paternally disrupted Gsα expression also demonstrated that Gsα expression is predominantly maternal in the renal cortex, but not in renal medulla (160, 170) . PTH resistance is delayed until after infancy in most PHP1A patients, and a study using mice demonstrated that the silencing of the paternal Gsα allele develops postnatally (171).



**Figure 2. Simplified view of the GNAS region and its transcripts. The normal allele-specific methylation and expression patterns of the four alternate first exons of GNAS which splice onto exon 2 to produce transcripts encoding NESP55, XLαs, 1A (referred to as A/B in humans), and Gsα (which uses exon 1). NESP55 and XLαs promoters are oppositely imprinted: NESP55 is expressed from the maternal allele and its promoter region is methylated on the paternal allele, whereas XLαs is expressed from the paternal allele and its promoter is methylated on the maternal allele. Gsα is paternally silenced in some tissues e.g., renal proximal tubule cells, indicated by the dashed arrow. NESP55 protein is unrelated to Gsα, and its entire coding region is located within its first exon. In contrast, XLαs and Gsα proteins have identical COOH-terminal domains (encoded by exons 2-13), while their unique NH2-terminal domains are encoded within their respective first exons. Exon A/B (1A) does not have a translational start site but is transcriptionally active. Loss of exon A/B imprinting (methylation) is associated with decreased Gsα expression in renal proximal tubules and some other hormone-responsive tissues and is the typical cause of PHP1B. (figure from Liu et al., 2000, with permission**).

A variety of inactivating mutations in the Gsα-coding portion of the *GNAS* gene have been identified in PHP1A patients (172, 173). The spectrum includes missense mutations, point mutations impairing efficient and accurate splicing, and small insertion/deletion mutations. The 4-bp deletion in exon 7 (ΔGACT 188/190) has been observed in multiple unrelated cases, suggesting that this may be a hot spot (174, 175). Several other mutations have also been observed in more than one kindred, indicating that additional susceptibility regions may exist. The identification of *de novo* germline mosaicism (176) is consistent with the view that most sporadic cases harbor new mutations, but the separation of such sporadic cases from familial ones, in which there is suppression of phenotype due to imprinting, may be difficult without detailed molecular studies.

PHP1A cases have been described in which no mutations of the *GNAS* gene have been found by nucleotide sequence analysis of exons encoding Gsα. This may be because the mutation is in a regulatory region of the gene not yet examined, or it may be that a large deletion prevents amplification of the mutant allele for subsequent analyses. In cases without identified *GNAS* coding mutations, an assessment of Gsα bioactivity in erythrocytes is helpful in ruling out regulatory region mutations or large deletions. A 35-kb deletion spanning exons 1 through 5 has been identified by using comparative genome hybridization in a patient with PHP1A in whom coding mutations had been ruled out, but a marked reduction of erythrocyte Gsα activity demonstrated (177).

Typically, PHP1A is associated with multiple hormone resistance, including thyroid stimulating hormone (TSH) and gonadotropins, causing hypothyroidism and gonadal failure, respectively. Because the hypothyroidism may express before hypocalcemia is observed (178), early surveillance of thyroid function is warranted. However, thyroid replacement from birth does not appear to prevent the mental deficit typical of PHP1A. In women, the hypogonadism is partial (179), and thus, oral contraceptives may help regulate the menstrual cycle. Estrogen can antagonize bone resorption, leading to an exacerbation of hypocalcemia (180), but placental 1,25-dihydroxyvitamin D synthesis likely obviates this effect altogether in pregnancy so women are frequently normocalcemic at that time (181). Abnormalities of the somatotropin axis have also been reported, with documentation of subnormal growth hormone release following stimulation by L-arginine or growth hormone-releasing hormone (182, 183).

The tissue-specific silencing of the paternal Gsα allele also plays a key role in the development of the additional hormone resistance phenotypes, as monoallelic Gsα expression has been demonstrated in the thyroid, the ovaries, and the pituitary (161-164). Studies have revealed that obesity also develops primarily in patients who inherit the inactivating Gsα mutations from their mothers (184). Gsα is not imprinted in the white adipose tissue (185), but the investigations of mice in which Gsα is ablated conditionally in the brain showed that Gsα is also monoallelic in certain parts of the hypothalamus (145, 146), thus explaining the imprinted mode of inheritance of the obesity phenotype. This likely reflects impaired signaling downstream of the melanocortin receptor type-4 (MC4R), given that it signals via G proteins including Gsα and that inactivating MC4R mutations are causal for dominantly inherited morbid obesity (186, 187). Indeed, almost all GNAS mutations identified in a large cohort of children with severe obesity impaired MCR4 signaling in cell-based assays (147). In mice, ablation of the maternal but not paternal *Gnas* allele in the dorsomedial nucleus of the hypothalamus leads to obesity (145), similar to the findings in mice with the conditional MC4R deficiency in this part of the brain (188). Like obesity, it has been noted that cognitive impairment, a typical AHO feature, also develops primarily after maternal inheritance of the inactivating Gsα mutation (189), although the underlying mechanisms behind the parental-specific inheritance of this phenotype have yet to be defined.

**PHP1B**

PHP1B is typically not associated with AHO or a generalized reduction in Gsα expression (190-192). PHP1B patients show a defect in renal PTH signaling, but an apparently normal response to PTH in bone (193, 194). Affected individuals are therefore functionally hypoparathyroid but show normal skeletal architecture and development. Due to unimpaired PTH responsiveness in bone, however, signs of hyperparathyroid bone disease (osteitis fibrosa cystica) are occasionally observed, complicating the picture (195). Biochemical abnormalities suggestive of thyroid stimulating hormone resistance are also seen in some patients (164). In fact, sometimes, PHP1B cases can present first with hypothyroidism (196, 197). A study also demonstrated short stature and growth hormone deficiency in monozygotic twins with PHP1B (198). Abnormalities of renal uric acid handling have been documented (199, 200). However, clinically significant hormone resistance is restricted to PTH in most cases. Because the hormone resistance is mostly limited to PTH, it was thought at one time that these findings could be explained by a defect in the type-1 parathyroid hormone receptor (PTH1R, MIM#168468). Sequence analyses, however, found no mutations in protein-coding exons or gene promoter regions of the gene (201-203), and studies of PHP1B families show no linkage to *PTHR1* (204, 205).

Most cases of PHP1B are sporadic, but a familial form of PHP1B with an apparent autosomal dominant mode of inheritance also exists (AD-PHP1B). In four AD-PHP1B kindreds, linkage to chromosome 20q13.3 was established, the same region which includes the *GNAS* locus (204). In these families, the pattern of transmission suggested paternal imprinting, and inheritance is therefore the same as for PHP1A. A further 13 PHP1B subjects were studied, some of whom had bone responsiveness to PTH (166). All lacked methylation of the alternate exon A/B, an epigenetic defect that is postulated to inhibit expression of the functional exon 1-containing Gsα transcript in renal tissues only (Figure 2). Thus, the loss of methylation of the maternal exon A/B allele leads to the silencing of the maternal as well as paternal Gsα allele, causing PTH resistance specifically in renal proximal tubule cells. A genetic analysis indicated that mutations in a regulatory region some distance from the *GNAS* coding exons were likely to account for the unique imprinting defect(s) associated with PHP1B (206). A search for the mutation revealed the presence of a 3 kb microdeletion that segregated with the disease in 12 kindreds with AD-PHP1B and also occurred in 4 sporadic cases (207). The deletion, flanked by direct repeats, removes 3 exons of the *STX16* gene, which encodes syntaxin-16. Two other deletions within *STX16* and larger deletions spanning both STX16 and its telomeric neighbor NPEPL1 have been identified in AD-PHP1B kindreds (208-211). In all these cases, maternal, but not paternal, inheritance of the *STX16* deletion led to PTH resistance. Because *STX16* is apparently not imprinted (208), loss of one copy of this gene is not predicted to underlie the PHP1B pathogenesis. Interestingly, two large deletions ablating *NESP55* without any overlap with *STX16* as the cause of PHP1B in families in whom affected individuals showed isolated loss of A/B methylation (211, 212). Note that the *NESP55* region showed an apparent gain of methylation due to the deletion of the maternal allele.

In two other PHP1B kindreds, nearly identical deletions of the *NESP55* DMR including exons 3 and 4 of the antisense transcript segregated with the disease (213). In this instance, however, the A/B DMR was not the only region to lose the differential methylation required to allow maternal expression of Gsα in the kidney. Maternal methylation was also lost in the regions of the *XLαs* and *GNAS-AS1* promoters. Another kindred with these widespread epigenetic defects of *GNAS* has been described (214). The affected individuals in this kindred carried a maternally inherited deletion that removed antisense exons 3 and 4 with flanking intronic regions but not the *NESP55* exon. Additional genomic deletions or rearrangements in the chromosomal regions comprising *GNAS* have also been identified and proposed to underlie the *GNAS* methylation abnormalities in some AD-PHP-Ib cases (215-219).

These PHP1B deletions point to two different imprinting control regions (ICRs) for the GNAS complex locus: one within the STX16 gene and the other at the NESP55 DMR. The ICR defined by the deletion at the neighboring STX16 gene seems to be in a different location in the mouse, because the targeted ablation of the region homologous to the 3-kb deletion caused neither *Gnas* methylation defects nor PTH resistance in mice (220). Recently, genome-wide methylation analysis of embryonic stem cells indicated that the A/B region is modestly hypomethylated compared to differentiated cells (221, 222), suggesting that this imprinted region differs from most other imprinted loci and is regulated critically in the early embryo. Subsequently, a study showed that deleting either the maternal STX16-ICR or the maternal NESP55-ICR results in significant further A/B hypomethylation in human embryonic stem cells (hESCs) (223). Moreover, while wild-type hESCs recovered their methylation following a transient inhibition of the maintenance DNA methyltransferase DNMT1 (mimicking the global demethylation process in the preimplantation embryo), the cells with maternally deleted STX16- or NESP55-ICR failed to regain methylation (223). This study also showed that the shortest region of overlap among the PHP1B-causing STX16 deletions was shown to harbor a pluripotent cell-specific enhancer element for the NESP55 promoter on the maternal allele (223). Taken together with a mouse study implicating NESP55 transcription in the regulation of maternal GNAS imprints (224), these findings strongly suggest that the GNAS exon A/B imprint is controlled, at least partly, in the early embryo by the NESP55 transcript that relies on the long-range enhancer within STX16. Thus, perturbation of this mechanism appears to be the underlying cause of the GNAS methylation defects observed in familial PHP1B cases.

Sporadic PHP1B cases also show broad *GNAS* epigenetic defects that involve A/B. In some of these cases, paternal uniparental disomy of different chromosome 20 segments have been reported as the likely cause of PHP1B in several such cases (225-229). The cause of the epigenetic defects and PTH resistance, however, remains unknown for most cases of sporadic PHP1B. *GNAS* methylation defects have been identified in some cases with hypomethylation at multiple maternally methylated imprinted regions (230-233). In fact, some of those cases show both PTH resistance and the clinical features resulting from the methylation changes of the other loci, such as Beckwith-Wiedemann Syndrome.

A recent study revealed that, in addition to the exon A/B DMR, methylation at a new *GNAS* region close to the *GNAS-AS1* promoter (termed *GNAS-AS2*), is lost in patients who carry *STX16* deletions (234). Note that this region is also affected in those cases that display broad *GNAS* methylation changes. Recently, two distinct subdomains with the GNAS-AS2 region have been identified, and a patient with partial loss of A/B methylation showed gain-of-methylation in one subdomain and no alteration in the other (235). The effect of methylation changes at *GNAS-AS2* has yet to be determined at the level of gene expression, and their pathophysiologic significance is unclear. Two distinct PHP1B families have been recently described to carry maternal retrotransposon insertions in the large intron between exon XL and A/B of the maternal GNAS allele (236, 237). These cases had apparently normal levels of GNAS-AS2 methylation (235, 237), reflecting, perhaps, that the deleterious genetic alteration is located downstream of this DMR. The mechanism by which these retrotransposons cause A/B hypomethylation may entail perturbation of NESP55 transcription. The inserted sequence comprises multiple polyadenylation signals (AAUAAA), which may truncate the transcript prematurely, and one of the studies showed that the level of NESP55 transcript was reduced in patient-derived induced pluripotent cells (236).

A study compared the clinical phenotypes of PHP1B patients who show isolated A/B loss of methylation to those with broad GNAS methylation defects (238). No clinical differences could be established according to the pattern of *GNAS* epigenetic defects, although serum PTH levels were significantly higher in females with broad *GNAS* methylation defects than females with isolated loss of 1A methylation. Another study also found an intrauterine growth advantage for both AD-PHP-1b and sporadic PHP-1b cases, but the results indicate that the sporadic cases are not as markedly growth accelerated as AD-PHP-1b cases at birth (239).

Contrary to the classical understanding that AHO features are unique to PHP1A, some studies have identified patients with PTH resistance and AHO features who show *GNAS* epigenetic defects rather than Gsα coding mutations (200, 240-242). Thus, there may be some overlap between the clinical and molecular features of PHP1A and PHP1B. It is possible that the AHO features observed in patients with *GNAS* epigenetic defects result from a genetic mechanism that is similar to the mechanism underlying the hormone resistance in PHP1A patients, i.e., due to monoallelic Gsα expression in additional tissues.

A PHP1B family with a novel Gsα mutation, deletion of isoleucine-382 in the carboxyl terminus has been described (243). In transfected cells this mutation led to uncoupling from the PTHR1 and isolated PTH resistance but not from other receptors, including TSH receptor. However, the same mutation showed uncoupling from multiple receptors, questioning the role of this mutation in the pathogenesis of PHP1B in this family. Such mutations within Gsα coding exons are likely to be a rare cause of PHP1B (166).

**PHP1c and PHP2**

Patients with PHP1c have multiple hormone resistance but normal Gsα activity. The defect may be in other components of the receptor-adenylate cyclase system, such as the catalytic unit, but some PHP1c cases have been reported to carry Gsα coding mutations (244). These mutations render the Gsα protein unable to mediate cAMP generation in response to receptor activation but do not affect basal adenylate cyclase stimulating activity or the ability to be activated by non-hydrolyzable GTP analogs (244-246). Thus, some forms of PHP1c appear to be an allelic variant of PHP1A. Finally, patients with PHP2 have a normal urinary cAMP response to PTH but an impaired phosphaturic response (247). The defect could be in the cAMP-dependent protein kinase (PKA), one of its substrates or targets, or in a component of the PTH-PKC signaling pathway.

Impaired PTH-induced phosphaturia with normal nephrogenous cAMP formation (i.e., PHP2) appears as the least common form of PHP. PHP2 is a sporadic disorder, but a familial form of PHP2 has been reported (248). In addition, a self-limited form of this disease in newborns has also been described, suggesting that it is transient in nature (249-251). The etiology and pathophysiological mechanisms behind this PHP variant remain unknown. Because patients show adequate nephrogenous cAMP generation in response to exogenous PTH, molecular defects downstream of cAMP production are implicated, such as protein kinase A (247). Accordingly, a study (252) has discovered a heterozygous mutation of the gene encoding the regulatory subunit of PKA (*PRKAR1A*) in three patients with ***multiple hormone resistance and acrodysostosis***, a form of skeletal dysplasia that includes severe brachydactyly type-E and other skeletal findings that resemble AHO (also known as Maroteaux-Malamut syndrome (253, 254). Several other variants of *PRKAR1A* have also been identified in other patients with a similar phenotype (255-258). These mutations, including the recurrent mutation R368X leading to the truncation of the C-terminal 14 residues, impair cAMP binding to the regulatory subunit, thereby blocking the activation of PKA (252, 259-261). In addition to acrodysostosis, patients carrying this mutation display evidence for target organ resistance to PTH, thyrotropin, growth hormone-releasing hormone, and gonadotropins, but these findings are accompanied by elevated basal plasma and urinary cAMP levels and with an apparently normal cAMP response to exogenous PTH administration. In certain other patients with acrodysostosis, but mostly without hormone resistance, it has been shown that the disease is caused by missense mutations in *PDE4D*, which encodes a cAMP phosphodiesterase (258, 262, 263). Given that PDE4D is an enzyme that reduces the intracellular cAMP concentration, the *PDE4D* mutations are likely to be gain-of-function (264). The type of acrodysostosis caused by *PRKAR1A* mutations has been termed **acrodysostosis-1** (MIM#101800), while the one caused by *PDE4D* mutations **acrodysostosis-2** (MIM#614613). In addition, another subtype of cAMP phosphodiesterase, PDE3A, is affected in another disorder characterized by severe hypertension and brachydactyly type-E with short stature (154, 265), underscoring the importance of cAMP signaling in skeletal development and the regulation of vascular tone.

**Other Phenotypes Associated with *GNAS* Mutations**

In contrast to the PHP phenotype associated with inactivating *GNAS* mutations, a different form of sporadic bone disease, (***polyostotic fibrous dysplasia)*** results from *de novo GNAS* mutations that cause constitutive Gsα activity (266). A more severe form of this disease (***panostotic fibrous dysplasia***) with hyperphosphatasia and hyperphosphaturic rickets has also been described (267, 268) . Patients carrying these activating mutations are mosaic for mutant and wild-type cells, indicating that the mutation is acquired during postzygotic development. These mutations affect the arginine residue at position 201 (exon 8) and, rarely, the glutamine at 227 (exon 9), and inhibit the intrinsic GTP hydrolase activity of Gsα, thereby leading to constitutive activity. Such constitutively activating mutations of GNAS are also found in a variety of endocrine and non-endocrine tumors, such as growth hormone-secreting adenomas (269) . A missense mutation in exon 13 (A366S) results in a Gsα protein that is unstable at 37°C, but constitutively active at lower temperatures (270, 271). Affected patients have PHP due to PTH resistance and precocious puberty (testotoxicosis) due to hormone-independent constitutive activation of luteinizing hormone receptors at lower ambient temperatures in the testes. Another Gsα mutant carrying Ala-Val-Asp-Thr amino acid repeats in the guanine-binding domain has been described in a patient with neonatal diarrhea and PTH resistance (272). In this instance, the mutant protein is unstable and localized to the cytoplasm rather than plasma membrane, which explains the hormone resistance. On the other hand, this mutation increases the rate of GDP-GTP exchange and, thus, confers overactivity. The increased activity of Gsα seems to be evident during the neonatal period in the gut, where the mutant localizes to the plasma membrane, thus explaining the diarrhea phenotype. Additional cases with missense Gsα mutations have been reported, presenting with clinical findings that likely reflect both gain and loss of Gsα function (273, 274).

Inactivating *GNAS* mutations have also been identified in patients with ***congenital osteoma cutis*** and ***progressive osseous heteroplasia (POH***), suggesting that these connective tissue conditions are another variant in the phenotypic spectrum of *GNAS*-related disease (275-278). No genotype-phenotype correlation has been revealed regarding these disorders, as the same mutation can be associated with either typical AHO features or severe ossifications that involve deep connective tissues and skeletal muscle (279). Nonetheless, patients with POH inherit the *GNAS* mutation from their fathers or acquire this mutation *de novo* on the paternal *GNAS* allele. This parent-of-origin specific inheritance of POH was established by analyzing 18 unrelated kindreds with this disorder (280). In a single, three generation, kindred, the inheritance of the mutation from males led to POH, while the inheritance of the same mutation from females led to typical AHO. It thus appears likely that alterations in the activity of a paternally expressed *GNAS* product, such as XLαs, contribute to the pathogenesis of POH. However, POH-like features have also been seen in some patients with maternally inherited *GNAS* mutations (281). A study revealed that the distribution of POH lesions follows dermomyotomes and shows a tendency for one-sidedness, suggesting that post-zygotic second hits may contribute to the development of these lesions on top of the inherited heterozygous mutations of *GNAS* (282).

**Differential Diagnosis and Genetic Counseling**

Patients with dysmorphic features resembling AHO may require careful endocrinologic work-up to confirm and delineate the form of PHP that is present. Similar studies of family members may also be warranted, since the biochemical and clinical features vary within families. If PHP1A with AHO is established, genetic counseling may aid in understanding the multisystemic nature of the disorder, particularly in relation to the patient's growth and development, and later-onset connective tissue complications. For either PHP1A or PHP1B, extensive counseling may be required to adequately explain the various implications of paternal imprinting for the parent-specific recurrence risks in offspring. Germline mosaicism has been reported (176) , which is clearly important in assessing risks for recurrence in future sibs of a singleton family. Given the recently described complexities in the molecular, biochemical, and physical features of PHP1A and PHP1B, molecular testing is critical for achieving a clear diagnosis and validating the inheritance pattern in any given family.

**THE PARATHYROID HORMONE RECEPTOR AND SKELETAL DYSPLASIAS**

PTHR1 is a family B G protein-coupled receptor that signals through multiple different G proteins including Gsα (283). It responds to two ligands, PTH and the PTH-related peptide (PTHrP). It would thus be predicted that deleterious mutations might show resistance to PTH, as well as evidence for a defect of PTHrP action. Functional polymorphisms in the *PTHR1* are associated with adult height and bone mineral density (284), emphasizing the role that the receptor and its ligands play in endochondral bone formation. Inactivating or loss-of-function mutations in the *PTHR1* have been implicated in the molecular pathogenesis of ***Blomstrand lethal chondrodysplasia*** ***(BLC***; MIM#215045), and other skeletal dysplasias and dental abnormalities (285). The rare, recessive BLC is characterized by short-limbed dwarfism with craniofacial malformations, hydrops, hypoplastic lungs and aortic coarctation (286-290). The bones show accelerated endochondral ossification and deficient remodeling. The Blomstrand disease has been subdivided into ***type I***, which refers to the severe (classical) form, and ***type II***, which refers to a relatively milder variant, and the difference between severity is attributed to complete or incomplete inactivation of the PTHR1, respectively (291, 292). A milder form of recessively inherited skeletal dysplasia, known as ***Eiken syndrome*** (MIM#600002), has also been linked to mutations of *PTHR1* (293). Dominantly acting *PTHR1* mutations have been identified in endochondromas of patients with ***enchondromatosis (Ollier's disease*** - MIM#166000), a familial disorder with evidence of autosomal dominance characterized by multiple benign cartilage tumors, and a predisposition to malignant osteocarcinomas (294, 295). As many patients with Ollier’s disease do not have *PTHR1* mutations, it is likely that the condition is genetically heterogeneous (296). Dominantly inherited ***symmetrical enchondromatosis*** is associated with duplication of 12p11.23 to 12p11.22 that includes the *PTHLH* gene encoding PTHrP suggesting that abnormal PTHR1 signaling may underlie this unusual form of endochondromatosis (297). In addition, some cases of autosomal dominant nonsyndromic ***primary failure of tooth eruption (PFE***) are due to loss-of-function mutations in the PTHR1 that are dominantly acting, leading to haploinsufficiency of the receptor (298-302) .

##

**HYPOMAGNESEMIA**

In humans, hypomagnesemia leads to a suppression of parathyroid hormone release and some degree of peripheral resistance. Although the exact molecular mechanism underlying the suppression of the parathyroid gland in hypomagnesemia is unknown, it is important to recognize that laboratory testing in cases of hypocalcemia with reduced PTH should include measurement of serum magnesium, particularly in newborns (303). Primary hypomagnesemia with secondary hypocalcemia (HSH) is an autosomal recessive disorder characterized by neuromuscular symptoms in infancy due to extremely low levels of serum magnesium and moderate to severe hypocalcemia. Homozygous mutations in the magnesium transporter gene transient receptor potential cation channel member 6 (TRPM6) cause the disease. HSH, a potentially lethal condition, can be misdiagnosed as primary hypoparathyroidism (304). Long-term prognosis after treatment with high dose of oral magnesium supplementation is good. Hypomagnesemia is also associated with long-term use of proton-pump inhibitors that decrease the luminal pH of the intestine by acting on the enterocyte apical TRPM6/7 channels (305, 306).

**MANAGEMENT OF HYPOPARATHYROIDISM**

**Calcium and Vitamin D**.

The goal of treatment in hypoparathyroid states is to raise the serum calcium sufficiently to alleviate acute symptoms of hypocalcemia and prevent the chronic complications (307, 308). The calcium concentration required for this purpose is generally in the low-normal range. It is equally important to ensure that treatment does not result in hypercalcemia, as even transient hypercalcemia could lead to nephrocalcinosis and renal failure. Acute or severe symptomatic hypocalcemia is best treated with intravenous calcium infusion. Initial doses of 2 to 5 millimoles of elemental calcium as the gluconate salt can be given over a 10 to 20 minute period, followed by 2 millimoles elemental calcium per hour as a maintenance dose, to be adjusted according to symptoms and biochemical response. Care must be taken to ensure that the infusion does not extravasate, as this can lead to severe tissue damage. Where possible treatment through central access is preferred. Ionized or total calcium levels should be monitored frequently. Doses in children 5 to 14 years of age need to be adjusted for body weight, while neonates and infants require age-specific dosing. If present, hyperphosphatemia, alkalosis and hypomagnesemia should be corrected concomitantly. Post-surgical hypocalcemia after thyroid or parathyroid surgery is now rarely severe and usually transient with appropriate management (309). However, the occasional patient can represent a significant problem, particularly if the indication for surgery is chronic hyperparathyroidism, and the post-operative hypoparathyroid state is permanent (310). The long-term effects of standard therapy, hypercalciuria, nephrolithiasis, nephrocalcinosis, ectopic tissue calcification and mood changes, remain a concern (311).

The mainstay of chronic treatment is oral calcium and activated vitamin D (calcitriol), which should be started as soon as possible to allow reduction and discontinuation of the intravenous calcium. Oral calcium comes in several forms, but calcium carbonate is generally the least expensive. A total of 20 to 80 millimoles elemental calcium daily (2 to 8 g calcium carbonate per day) is generally effective, but should be given in divided doses and adjusted on the basis of gastro-intestinal tolerance, relief of hypocalcemic symptoms, and appropriate biochemical response. Vitamin D is preferably administered as calcitriol (0.25 to 1.0 micrograms per day), but, with some conditions, pharmacological doses of cholecalciferol or ergocalciferol or calcidiol may be less expensive and equally efficacious (312). Cholecalciferol and ergocalciferol doses are more difficult to titrate, and given their long duration of action, any overdoses can result in sustained toxicity. It is, therefore, appropriate to institute a starting dose of 25,000 IU/day and titrate upwards (to 100,000 IU/daily) with an assessment of serum and urinary parameters afterward with follow-up at 6 and 12 months, even if the patient is relatively asymptomatic. However, the use of active vitamin D (calcitriol or alphacalcidol) is recommended given that the lack of PTH along with the accompanying hyperphosphatemia reduces renal conversion of 25-hydroxyvitamin D to active vitamin D (307, 308). Serum calcium and 24-hour urinary excretion should be carefully monitored when therapy is started and continued until the dosing is stabilized. Hypercalciuria that occurs as treatment is initiated, even prior to the normalization of the serum calcium, may warrant an assessment of nephrocalcinosis by renal ultrasound. Consequently, only a low-normal serum calcium concentration may be attainable, but many patients feel well enough that there is no need to entirely normalize the serum calcium. In this way, the risk of renal failure due to chronic hypercalciuria − especially problematic in patients with *CASR* activating mutations (6, 7) − is minimized. Even after normalization or near-normalization of serum calcium, a significant number of patients report problems with fatigue, exhaustion, and mood disturbances (e.g., depression, anxiety, hostility, and paranoid ideation) not in keeping with the degree of hypocalcemia, suggesting that there may be non-calcitropic effects of PTH not remedied by maintenance of normocalcemia alone (311). In an epidemiological and health-related quality of life study from Norway, postsurgical hypoparathyroid patients scored worse than those with nonsurgical hypoparathyroidism or pseudohypoparathyroidism (313), providing further support for the notion of direct effects of PTH on mood.

In pseudohypoparathyroidism, calcitriol (and not other forms of vitamin D) should be used for the treatment, because the PTH resistance in the proximal tubule does not allow for the efficient synthesis of 1,25(OH)2D from 25-hydroxyvitamin D. In pseudohypoparathyroidism type 1A, there is also a degree of PTH resistance in the bone due to haploinsufficiency of Gsα. However, in pseudohypothyroidism type 1B, the bone is fully sensitive to PTH, so monitoring serum PTH levels during treatment is critical with the aim of normalizing or reducing PTH levels as much as possible (314, 315). Hypercalciuria as a result of the calcitriol and calcium treatment is a lesser concern in pseudohypoparathyroidism because PTH actions in the distal tubule are still functional, preventing excess loss of calcium in the urine and providing greater protection against nephrocalcinosis.

**Hormone Replacement Therapy**

Hormone replacement has been advocated as a potentially superior form of treatment for decades but only recently have preparations of recombinant human hormone –– teriparatide (PTH 1-34), full-length parathyroid hormone (PTH 1-84), and abaloparatide (PTHrP analog) — become available. In 2015, the U.S. Food and Drug Administration (FDA) approved recombinant human (rh) PTH (1-84) for the management of hypoparathyroidism (316). This provided an additional therapeutic option for the management of those patients who demonstrate poor control with the standard calcium and active vitamin D supplemental therapy. The FDA indication was for subjects with hypoparathyroidism of any etiology, except ADH, but including postsurgical cases. The FDA did not limit the duration of its use but approved rhPTH(1-84) with a “black box” warning because of the history of rat osteosarcoma and PTH use (317). However, no evidence for this in primates or in clinical use has been forthcoming (318), and the ‘black box’ warning has since been withdrawn (319).

The use of PTH in hypoparathyroidism was demonstrated initially with the amino-terminal fragment of PTH, teriparatide [PTH(1–34)] (320). Beneficial control in children and in adults occurred when teriparatide was administered daily, with better control when the peptide was administered in twice-daily dosing regimens (320-324). With a pump delivery system by which teriparatide could be administered continuously (325, 326), urinary calcium excretion fell, and markers of bone turnover normalized. A smaller daily dose was required with pump delivery vs multiple daily dosing regimens. An open-label trial of PTH(1–34) in adult subjects with postsurgical hypoparathyroidism showed improvement in quality of life (327). Beneficial effects on calcium homeostasis have also been demonstrated in specific ADH cases with activating CaSR mutations (328, 329).

The full-length PTH (1-84) mimics the secreted product of the parathyroid gland, and its longer biological half-life (than PTH(1-34) makes once-daily dosing feasible in the treatment of hypoparathyroidism (330-332). Studies by several groups have noted a substantial reduction in the requirement for calcium and active vitamin D (333-335); only transient reductions in urinary calcium excretion (331); a tendency for lumbar spine bone mineral density (BMD) to increase and that of the distal one-third radius to fall (334); a rapid increase in bone turnover, assessed by circulating markers and dynamic histomorphometric analyses of bone that achieves a new steady state that is higher than baseline values within 2–3 years (336); and improvements in quality of life in some studies (333, 337).

In a placebo-controlled 24-week clinical trial of rhPTH (1-84) in 130 hypoparathyroid patients the primary endpoints of a reduction by 50% in calcium supplements and in active vitamin D along with maintenance of the serum calcium were met in over half of the study subjects (338). There was a greater percentage of subjects in whom active vitamin D could be eliminated entirely while taking no more than 500 mg of oral calcium daily. The drug was titrated from 50 to 100 μg/d, with just over half of the subjects needing the highest dose. The rhPTH(1-84) reduced serum phosphate levels, improved the calcium-phosphate product, and maintained 1,25(OH)2D and serum calcium levels in the normal range (339). In addition, therapy with a long-acting prodrug of PTH(1-34), TransCon PTH (palopegteriparatide), in hypoparathyroidism has been shown to improve scores in quality-of-life measures (340). However, despite these early positive results, the inconvenient route of administration, daily or twice daily subcutaneous injection, leads to most patients opting for conventional treatment with oral calcium and calcitriol.

The manufacturer of rhPTH(1-34) has recently decided to discontinue this product at the end of 2024 due to an unresolved supply issue (<https://www.takeda.com/newsroom/statements/2022/discontinue-manufacturing-natpar-natpara/>). In addition, the use of teriparatide or aboloparatide for hypoparathyroidism has not been approved by the FDA. Therefore, no available FDA-approved hormone replacement therapies currently exist for the management of this disorder.

**Calcilytics**

Calcilytics are small molecule allosteric modulators of the CASR that antagonize the calcium-sensing receptor and promote PTH secretion and are a promising alternative for disorders with intact but hypofunctioning parathyroid glands (341). Calcilytics inhibit the activation of the CASR in both the parathyroid and renal tubule, and thus, they not only promote PTH secretion but also increase renal calcium reabsorption and are, therefore, of potential interest for the treatment of ADH1. In contrast, clinical studies in patients with ADH1 treated with PTH(1-34) led to better control of blood calcium levels (324), but the effects of the activated CASR in the kidney led to continued increases in urinary calcium excretion, different from patients with postsurgical hypoparathyroidism (326, 329). Thus, while FDA approval was given for PTH treatment of hypoparathyroidism, ADH1 was excluded from the indication.

In cell culture experiments studying activating CASR mutants, calcilytics normalize the left-ward shift of the calcium response curve (342, 343). The utility of calcilytics was further demonstrated in studies of mice harboring activating *Casr* mutations. In one study, two knock-in mouse models of ADH1 with activating mutations in the *Casr* were generated. Daily oral administration of the calcilytic JTT-305/MK-3442 to these mice increased serum PTH and calcium levels and reduced urinary calcium excretion (310). Intraperitoneal injection of the calcilytic NPS2143 in the *nuf* mouse model of ADH1, transiently increased circulating PTH and calcium levels without increasing urinary calcium levels (342). In a preliminary clinical study, IV administration of the calcilytic NPSP795 to five patients with ADH1 increased their plasma PTH levels and decreased their fractional urinary calcium excretion (344). Calcilytics comprise two main classes of compounds; the amino alcohols (e.g., NPS2143, NPSP795, JTT-305/MK-5442) and the quinazolinones (e.g., ATF936 and AXT914) (341). While both classes of compounds corrected the gain-of-function properties of several of the ADH1 CASR mutations tested *in vitro*, a subset of mutations involving NPS2143 binding sites within the transmembrane domain of the CASR are not fully corrected with NPS2143 but are normalized with the quinazolinone drugs (ATF936 and AXT914) (345-347). Whether this is reflected in mouse model studies and clinical situations remains to be determined.

Cases of hypoparathyroidism presenting as ADH but without *CASR* mutations have been found to have activating mutations of the gene encoding Gα11, the alpha-subunit of the heterotrimeric G protein that couples the CASR to signaling pathways (348, 349). The syndrome has been designated ADH2. Even though Gα11 is downstream of the CASR, *in vitro* studies showed that the calcilytic NPS2143 rectifies the altered Ca2+ signaling of the overactive mutants (350). Knock-in mice harboring an ADH2 Gα11 activating mutation faithfully replicate ADH2 (351). Treatment with the calcilytic NPS2143 or a Gα11/q-specific inhibitor, YM-254890 (352), increased circulating PTH and calcium levels in the heterozygous mutant mice (351). Thus, calcilytics, by blocking the renal CASR, may have potential use for treating ADH1 and ADH2, as well as other forms of hypoparathyroidism.

**Other Therapies**

If the serum calcium attainable with oral calcium and calcitriol is below the normal range and the patient remains symptomatic, then a trial of a thiazide diuretic may be considered, with the aim of reducing the hypercalciuria to raise the serum calcium further. The argument for efficacy seems greatest for responsive forms of autosomal dominant hypocalcemia due to activating CaSR mutations, since the thiazide-sensitive transporter, SLC12A3 (MIM#600968), is a downstream target of and is suppressed by activated CaSR in the kidney. For reasons that are not clear, however, thiazides work well in only a subset of patients (353). It is critical to monitor serum potassium and magnesium levels, as thiazide use can increase renal losses of these cations with resulting hypokalemia and hypomagnesemia. Some authorities suggest thiazides should not be used in APS1 patients with adrenal insufficiency and in ADH1 patients with Bartter syndrome type V (307, 308).

As the serum calcium is normalized, elevated serum phosphate concentrations generally decline, but phosphate-binding gels such as aluminum hydroxide are occasionally helpful in reducing hyperphosphatemia at the beginning of therapy or in cases where there is persistent hyperphosphatemia. Patients who develop intracranial calcifications may experience seizures related to chronic neuropathic changes, and it may be necessary to add appropriate anti-epileptic medication(s). In all chronically hypocalcemic patients, ocular assessments should be performed periodically.

In cases with documented abnormalities of the somatotropin axis, the growth hormone replacement therapy is effective but has to be initiated as soon as possible (315, 354, 355).

**REFERENCES**

1. Shoback DM, Bilezikian JP, Costa AG, Dempster D, Dralle H, Khan AA, et al. Presentation of Hypoparathyroidism: Etiologies and Clinical Features. The Journal of Clinical Endocrinology &amp; Metabolism. 2016;101(6):2300-12.

2. Clarke BL, Brown EM, Collins MT, J√ºppner H, Lakatos P, Levine MA, et al. Epidemiology and Diagnosis of Hypoparathyroidism. The Journal of clinical endocrinology and metabolism. 2016;101(6):2284-99.

3. Schafer AL, and Shoback DM. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al. eds. Endotext. South Dartmouth (MA); 2000.

4. Fisher NG, Armitage A, McGonigle RJ, and Gilbert TJ. Hypocalcaemic Cardiomyopathy; the relationship between myocardial damage, left ventricular function, calcium and ECG changes in a patient with idiopathic hypocalcaemia. European Journal of Heart Failure. 2001;3(3):373-6.

5. Tziomalos K, Kakavas N, Kountana E, Harsoulis F, and Basayannis E. Reversible dilated hypocalcaemic cardiomyopathy in a patient with primary hypoparathyroidism. Clinical endocrinology. 2006;64(6):717-8.

6. Lienhardt A, Bai M, Lagarde J-P, Rigaud M, Zhang Z, Jiang Y, et al. Activating Mutations of the Calcium-Sensing Receptor: Management of Hypocalcemia. The Journal of Clinical Endocrinology &amp; Metabolism. 2001;86(11):5313-23.

7. Obermannova B, Sumnik Z, Dusatkova P, Cinek O, Grant M, Lebl J, et al. Novel calcium-sensing receptor cytoplasmic tail deletion mutation causing autosomal dominant hypocalcemia: molecular and clinical study. European Journal of Endocrinology. 2016;174(4):K1-K11.

8. McKusick VA. Mendelian Inheritance in Man and its online version, OMIM. Am J Hum Genet. 2007;80(4):588-604.

9. Arnold A, Horst SA, Gardella TJ, Baba H, Levine MA, and Kronenberg HM. Mutation of the signal peptide-encoding region of the preproparathyroid hormone gene in familial isolated hypoparathyroidism. J Clin Invest. 1990;86:1084-7.

10. Datta R, Waheed A, Shah GN, and Sly WS. Signal sequence mutation in autosomal dominant form of hypoparathyroidism induces apoptosis that is corrected by a chemical chaperone. Proceedings of the National Academy of Sciences of the United States of America. 2007;104(50):19989-94.

11. Sunthornthepvarakul T, Churesigaew S, and Ngowngarmratana S. A Novel Mutation of the Signal Peptide of the Preproparathyroid Hormone Gene Associated with Autosomal Recessive Familial Isolated Hypoparathyroidism\*. The Journal of Clinical Endocrinology &amp; Metabolism. 1999;84(10):3792-6.

12. Ertl D-A, Stary S, Streubel B, Raimann A, and Haeusler G. A novel homozygous mutation in the parathyroid hormone gene (PTH) in a girl with isolated hypoparathyroidism. Bone. 2012;51(3):629-32.

13. Lee S, Mannstadt M, Guo J, Kim SM, Yi H-S, Khatri A, et al. A Homozygous [Cys25]PTH(1-84) Mutation That Impairs PTH/PTHrP Receptor Activation Defines a Novel Form of Hypoparathyroidism. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2015;30(10):1803-13.

14. Parkinson DB, and Thakker RV. A donor splice site mutation in the parathyroid hormone gene is associated with autosomal recessive hypoparathyroidism. Nature Genetics. 1992;1(2):149-52.

15. Grigorieva IV, and Thakker RV. Transcription factors in parathyroid development: lessons from hypoparathyroid disorders. Annals of the New York Academy of Sciences. 2011;1237(1):24-38.

16. Bowl MR, Nesbit MA, Harding B, Levy E, Jefferson A, Volpi E, et al. An interstitial deletion-insertion involving chromosomes 2p25.3 and Xq27.1, near SOX3, causes X-linked recessive hypoparathyroidism. The Journal of clinical investigation. 2005;115(10):2822-31.

17. Pollak MR, Brown EM, Estep HL, McLaine PN, Kifor O, Park J, et al. Autosomal dominant hypocalcaemia caused by a Ca2+-sensing receptor gene mutation. Nature Genetics. 1994;8:303-7.

18. Hendy GN, D'Souza-Li L, Yang B, Canaff L, and Cole DEC. Mutations of the calcium-sensing receptor (CASR) in familial hypocalciuric hypercalcemia, neonatal severe hyperparathyroidism, and autosomal dominant hypocalcemia. Human Mutation. 2000;16(4):281-96.

19. Cole DEC, Yun FHJ, Wong BYL, Shuen AY, Booth RA, Scillitani A, et al. Calcium-sensing receptor mutations and denaturing high performance liquid chromatography. Journal of Molecular Endocrinology. 2009;42(4):331-9.

20. Hendy GN, Guarnieri V, and Canaff L. Progress in Molecular Biology and Translational Science. Elsevier; 2009:31-95.

21. Hendy GN, Minutti C, Canaff L, Pidasheva S, Yang B, Nouhi Z, et al. Recurrent Familial Hypocalcemia Due to Germline Mosaicism for an Activating Mutation of the Calcium-Sensing Receptor Gene. The Journal of Clinical Endocrinology &amp; Metabolism. 2003;88(8):3674-81.

22. Ray K, Hauschild BC, Steinbach PJ, Goldsmith PK, Hauache O, and Spiegel AM. Identification of the Cysteine Residues in the Amino-terminal Extracellular Domain of the Human Ca2+ Receptor Critical for Dimerization. Journal of Biological Chemistry. 1999;274(39):27642-50.

23. Pidasheva S, D'Souza-Li L, Canaff L, Cole DEC, and Hendy GN. CASRdb: calcium-sensing receptor locus-specific database for mutations causing familial (benign) hypocalciuric hypercalcemia, neonatal severe hyperparathyroidism, and autosomal dominant hypocalcemia. Human Mutation. 2004;24(2):107-11.

24. Hannan FM, Nesbit MA, Zhang C, Cranston T, Curley AJ, Harding B, et al. Identification of 70 calcium-sensing receptor mutations in hyper- and hypo-calcaemic patients: evidence for clustering of extracellular domain mutations at calcium-binding sites. Human Molecular Genetics. 2012;21(12):2768-78.

25. Vargas-Poussou R, Huang C, Hulin P, Houillier P, Jeunemaitre X, Paillard M, et al. Functional Characterization of a Calcium-Sensing Receptor Mutation in Severe Autosomal Dominant Hypocalcemia with a Bartter-Like Syndrome. Journal of the American Society of Nephrology. 2002;13(9):2259-66.

26. Watanabe S, Fukumoto S, Chang H, Takeuchi Y, Hasegawa Y, Okazaki R, et al. Association between activating mutations of calcium-sensing receptor and Bartter's syndrome. The Lancet. 2002;360(9334):692-4.

27. Vezzoli G, Arcidiacono T, Paloschi V, Terranegra A, Biasion R, Weber G, et al. Autosomal dominant hypocalcemia with mild type 5 Bartter syndrome. J Nephrol. 2006;19(4):525-8.

28. Hebert SC. Bartter syndrome. Current opinion in nephrology and hypertension. 2003;12(5):527-32.

29. Carmosino M, Gerbino A, Hendy GN, Torretta S, Rizzo F, Debellis L, et al. NKCC2 activity is inhibited by the Bartter's syndrome type 5 gain-of-function CaR-A843E mutant in renal cells. Biol Cell. 2015;107(4):98-110.

30. Nesbit MA, Hannan FM, Howles SA, Babinsky VN, Head RA, Cranston T, et al. Mutations affecting G-protein subunit alpha11 in hypercalcemia and hypocalcemia. N Engl J Med. 2013;368(26):2476-86.

31. Mannstadt M, Harris M, Bravenboer B, Chitturi S, Dreijerink KM, Lambright DG, et al. Germline mutations affecting Galpha11 in hypoparathyroidism. N Engl J Med. 2013;368(26):2532-4.

32. Li D, Opas EE, Tuluc F, Metzger DL, Hou C, Hakonarson H, et al. Autosomal dominant hypoparathyroidism caused by germline mutation in GNA11: phenotypic and molecular characterization. J Clin Endocrinol Metab. 2014;99(9):E1774-83.

33. Piret SE, Gorvin CM, Pagnamenta AT, Howles SA, Cranston T, Rust N, et al. Identification of a G-Protein Subunit-Œ±11 Gain-of-Function Mutation, Val340Met, in a Family With Autosomal Dominant Hypocalcemia Type 2 (ADH2). Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2016;31(6):1207-14.

34. Mizuno N, and Itoh H. Functions and regulatory mechanisms of Gq-signaling pathways. Neurosignals. 2009;17(1):42-54.

35. Hendy GN, and Cole DE. Ruling in a suspect: the role of AP2S1 mutations in familial hypocalciuric hypercalcemia type 3. J Clin Endocrinol Metab. 2013;98(12):4666-9.

36. Lambert AS, Grybek V, Francou B, Esterle L, Bertrand G, Bouligand J, et al. Analysis of AP2S1, a calcium-sensing receptor regulator, in familial and sporadic isolated hypoparathyroidism. J Clin Endocrinol Metab. 2014;99(3):E469-73.

37. Rogers A, Nesbit MA, Hannan FM, Howles SA, Gorvin CM, Cranston T, et al. Mutational analysis of the adaptor protein 2 sigma subunit (AP2S1) gene: search for autosomal dominant hypocalcemia type 3 (ADH3). J Clin Endocrinol Metab. 2014;99(7):E1300-5.

38. Kanemura Y, Hiraga S, Arita N, Ohnishi T, Izumoto S, Mori K, et al. Isolation and expression analysis of a novel human homologue of the <i>Drosophila glial cells missing</i> (<i>gcm</i>) gene. FEBS Letters. 1999;442(2-3):151-6.

39. Gunther T, Chen Z-F, Kim J, Priemel M, Rueger JM, Amling M, et al. Genetic ablation of parathyroid glands reveals another source of parathyroid hormone. Nature. 2000;406(6792):199-203.

40. Okabe M, and Graham A. The origin of the parathyroid gland. Proceedings of the National Academy of Sciences of the United States of America. 2004;101(51):17716-9.

41. Ding C, Buckingham B, and Levine MA. Familial isolated hypoparathyroidism caused by a mutation in the gene for the transcription factor GCMB. Journal of Clinical Investigation. 2001;108(8):1215-20.

42. Thomee C, Schubert SW, Parma J, L√™ PQ, Hashemolhosseini S, Wegner M, et al. GCMB Mutation in Familial Isolated Hypoparathyroidism with Residual Secretion of Parathyroid Hormone. The Journal of Clinical Endocrinology & Metabolism. 2005;90(5):2487-92.

43. Canaff L, Zhou X, Mosesova I, Cole DEC, and Hendy GN. Glial Cells Missing-2 (GCM2) transactivates the calcium-sensing receptor gene: effect of a dominant-negative GCM2 mutant associated with autosomal dominant hypoparathyroidism. Human Mutation. 2009;30(1):85-92.

44. Bowl MR, Mirczuk SM, Grigorieva IV, Piret SE, Cranston T, Southam L, et al. Identification and characterization of novel parathyroid-specific transcription factor Glial Cells Missing Homolog B (GCMB) mutations in eight families with autosomal recessive hypoparathyroidism. Hum Mol Genet. 2010;19(10):2028-38.

45. Mannstadt M, Bertrand G, Muresan M, Weryha G, Leheup B, Pulusani SR, et al. Dominant-negative GCMB mutations cause an autosomal dominant form of hypoparathyroidism. The Journal of clinical endocrinology and metabolism. 2008;93(9):3568-76.

46. Mirczuk SM, Bowl MR, Nesbit MA, Cranston T, Fratter C, Allgrove J, et al. A Missense<i>Glial Cells Missing Homolog B</i>(<i>GCMB</i>) Mutation, Asn502His, Causes Autosomal Dominant Hypoparathyroidism. The Journal of Clinical Endocrinology &amp; Metabolism. 2010;95(7):3512-6.

47. Hendy GN, and Cole DEC. Hypoparathyroidism. Springer Milan; 2015:167-75.

48. Maret A, Ding C, Kornfield SL, and Levine MA. Analysis of the<i>GCM2</i>Gene in Isolated Hypoparathyroidism: A Molecular and Biochemical Study. The Journal of Clinical Endocrinology &amp; Metabolism. 2008;93(4):1426-32.

49. D'Agruma L, Coco M, Guarnieri V, Battista C, Canaff L, Salcuni AS, et al. Increased Prevalence of the<i>GCM2</i>Polymorphism, Y282D, in Primary Hyperparathyroidism: Analysis of Three Italian Cohorts. The Journal of Clinical Endocrinology &amp; Metabolism. 2014;99(12):E2794-E8.

50. Guan B, Welch JM, Sapp JC, Ling H, Li Y, Johnston JJ, et al. GCM2-Activating Mutations in Familial Isolated Hyperparathyroidism. American journal of human genetics. 2016;99(5):1034-44.

51. Lackey AE, and Muzio MR. StatPearls. Treasure Island (FL); 2023.

52. McDonald-McGinn DM, Sullivan KE, Marino B, Philip N, Swillen A, Vorstman JAS, et al. 22q11.2 deletion syndrome. Nat Rev Dis Primers. 2015;1:15071-.

53. Botto LD, May K, Fernhoff PM, Correa A, Coleman K, Rasmussen SA, et al. A Population-Based Study of the 22q11.2 Deletion: Phenotype, Incidence, and Contribution to Major Birth Defects in the Population. Pediatrics. 2003;112(1):101-7.

54. Yagi H, Furutani Y, Hamada H, Sasaki T, Asakawa S, Minoshima S, et al. Role of TBX1 in human del22q11.2 syndrome. The Lancet. 2003;362(9393):1366-73.

55. Baldini A, Fulcoli FG, and Illingworth E. Current Topics in Developmental Biology. Elsevier; 2017:223-43.

56. Scambler PJ. 22q11 Deletion Syndrome: A Role for TBX1 in Pharyngeal and Cardiovascular Development. Pediatric Cardiology. 2010;31(3):378-90.

57. Guo C, Sun Y, Zhou B, Adam RM, Li X, Pu WT, et al. A Tbx1-Six1/Eya1-Fgf8 genetic pathway controls mammalian cardiovascular and craniofacial morphogenesis. The Journal of clinical investigation. 2011;121(4):1585-95.

58. Huh S-H, and Ornitz DM. Beta-catenin deficiency causes DiGeorge syndrome-like phenotypes through regulation of Tbx1. Development (Cambridge, England). 2010;137(7):1137-47.

59. Jerome LA, and Papaioannou VE. DiGeorge syndrome phenotype in mice mutant for the T-box gene, Tbx1. Nature Genetics. 2001;27(3):286-91.

60. Ivins S, Lammerts van Beuren K, Roberts C, James C, Lindsay E, Baldini A, et al. Microarray analysis detects differentially expressed genes in the pharyngeal region of mice lacking Tbx1. Developmental Biology. 2005;285(2):554-69.

61. Garg V, Yamagishi C, Hu T, Kathiriya IS, Yamagishi H, and Srivastava D. Tbx1, a DiGeorge Syndrome Candidate Gene, Is Regulated by Sonic Hedgehog during Pharyngeal Arch Development. Developmental Biology. 2001;235(1):62-73.

62. Scire G, Dallapiccola B, Iannetti P, Bonaiuto F, Galasso C, Mingarelli R, et al. Hypoparathyroidism as the major manifestation in two patients with 22q11 deletions. American journal of medical genetics. 1994;52(4):478-82.

63. Sykes K, Bachrach L, Siegel-Bartelt J, Ipp M, Kooh S, and Cytrynbaum C. Velocardiofacial syndrome presenting as hypocalcemia in early adolescence. Arch Pediatr Adolesc Med. 1997;151:745-7.

64. Kapadia RK, and Bassett AS. Recognizing a common genetic syndrome: 22q11.2 deletion syndrome. CMAJ. 2008;178(4):391-3.

65. Liu H, Abecasis GR, Heath SC, Knowles A, Demars S, Chen Y-J, et al. Genetic variation in the 22q11 locus and susceptibility to schizophrenia. Proceedings of the National Academy of Sciences of the United States of America. 2002;99(26):16859-64.

66. McDonald-McGinn DM, Hain HS, Emanuel BS, and Zackai EH. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, et al. eds. GeneReviews((R)). Seattle (WA); 1993.

67. Burnside RD. 22q11.21 Deletion Syndromes: A Review of Proximal, Central, and Distal Deletions and Their Associated Features. Cytogenetic and Genome Research. 2015;146(2):89-99.

68. Goodship J, Cross I, Scambler P, and Burn J. Monozygotic twins with chromosome 22q11 deletion and discordant phenotype. Journal of medical genetics. 1995;32(9):746-8.

69. Hillebrand G, Siebert R, Simeoni E, and Santer R. DiGeorge syndrome with discordant phenotype in monozygotic twins. J Med Genet. 2000;37(9):E23-E.

70. Miller JD, Bowker BM, Cole DE, and Guyda HJ. DiGeorge's syndrome in monozygotic twins. Treatment with calcitriol. Am J Dis Child. 1983;137(5):438-40.

71. Alkalay AA, Guo T, Montagna C, Digilio MC, Dallapiccola B, Marino B, et al. Genetic dosage compensation in a family with velo-cardio-facial/DiGeorge/22q11.2 deletion syndrome. American journal of medical genetics Part A. 2011;155A(3):548-54.

72. Carelle-Calmels N, Saugier-Veber P, Girard-Lemaire F, Rudolf G, Doray B, Guerin E, et al. Genetic Compensation in a Human Genomic Disorder. New England Journal of Medicine. 2009;360(12):1211-6.

73. Jatana V, Gillis J, Webster BH, and Ad√®s LC. Deletion 22q11.2 syndrome‚ÄîImplications for the intensive care physician\*. Pediatric Critical Care Medicine. 2007;8(5):459-63.

74. Nagasaki K, Iwasaki Y, Ogawa Y, Kikuchi T, and Uchiyama M. Evaluation of parathyroid gland function using sodium bicarbonate infusion test for 22q11.2 deletion syndrome. Hormone research in paediatrics. 2011;75(1):14-8.

75. Weinzimer SA. Endocrine aspects of the 22q11.2 deletion syndrome. Genetics in Medicine. 2001;3(1):19-22.

76. Jensen TJ, Dzakula Z, Deciu C, van den Boom D, and Ehrich M. Detection of Microdeletion 22q11.2 in a Fetus by Next-Generation Sequencing of Maternal Plasma. Clinical Chemistry. 2012;58(7):1148-51.

77. Tenhola S, Hendy GN, Valta H, Canaff L, Lee BSP, Wong BYL, et al. Cinacalcet Treatment in an Adolescent With Concurrent 22q11.2 Deletion Syndrome and Familial Hypocalciuric Hypercalcemia Type 3 Caused by<i>AP2S1</i>Mutation. The Journal of Clinical Endocrinology &amp; Metabolism. 2015;100(7):2515-8.

78. Lima K, Abrahamsen TG, Wolff ABe, Husebye E, Alimohammadi M, K√§mpe O, et al. Hypoparathyroidism and autoimmunity in the 22q11.2 deletion syndrome. European Journal of Endocrinology. 2011;165(2):345-52.

79. Meek CL, Kaplan F, Pereira RS, and Viljoen A. Hypocalcemia following Treatment for Hyperthyroidism. Clinical Chemistry. 2011;57(6):811-4.

80. Daw SCM, Taylor C, Kraman M, Call K, Mao J-i, Schuffenhauer S, et al. A common region of 10p deleted in DiGeorge and velocardiofacial syndromes. Nature Genetics. 1996;13(4):458-60.

81. Gottlieb S, Driscoll DA, Punnett HH, Sellinger B, Emanuel BS, and Budarf ML. Characterization of 10p deletions suggests two nonoverlapping regions contribute to the DiGeorge syndrome phenotype. American journal of human genetics. 1998;62(2):495-8.

82. Schuffenhauer S, Lichtner P, Peykar-Derakhshandeh P, Murken J, Haas OA, Back E, et al. Deletion mapping on chromosome 10p and definition of a critical region for the second DiGeorge syndrome locus (DGS2). European Journal of Human Genetics. 1998;6(3):213-25.

83. Barakat AY, D'Albora JB, Martin MM, and Jose PA. Familial nephrosis, nerve deafness, andhypoparathyroidism. The Journal of Pediatrics. 1977;91(1):61-4.

84. Bilous RW, Murty G, Parkinson DB, Thakker RV, Coulthard MG, Burn J, et al. Autosomal Dominant Familial Hypoparathyroidism, Sensorineural Deafness, and Renal Dysplasia. New England Journal of Medicine. 1992;327(15):1069-74.

85. Lichtner P, Konig R, Hasegawa T, Van Esch H, Meitinger T, and Schuffenhauer S. An HDR (hypoparathyroidism, deafness, renal dysplasia) syndrome locus maps distal to the DiGeorge syndrome region on 10p13/14. Journal of medical genetics. 2000;37(1):33-7.

86. Van Esch H, Groenen P, Daw S, Poffyn A, Holvoet M, Scambler P, et al. Partial DiGeorge syndrome in two patients with a 10p rearrangement. Clinical genetics. 1999;55(4):269-76.

87. Van Esch H, Groenen P, Nesbit MA, Schuffenhauer S, Lichtner P, Vanderlinden G, et al. GATA3 haplo-insufficiency causes human HDR syndrome. Nature. 2000;406(6794):419-22.

88. Ali A, Christie PT, Grigorieva IV, Harding B, Van Esch H, Ahmed SF, et al. Functional characterization of GATA3 mutations causing the hypoparathyroidism-deafness-renal (HDR) dysplasia syndrome: insight into mechanisms of DNA binding by the GATA3 transcription factor. Human Molecular Genetics. 2006;16(3):265-75.

89. Nesbit MA. Hypoparathyroidism. Springer Milan; 2015:199-213.

90. Nesbit MA, Bowl MR, Harding B, Ali A, Ayala A, Crowe C, et al. Characterization of GATA3 Mutations in the Hypoparathyroidism, Deafness, and Renal Dysplasia (HDR) Syndrome. Journal of Biological Chemistry. 2004;279(21):22624-34.

91. Zahirieh A, Nesbit MA, Ali A, Wang K, He N, Stangou M, et al. Functional analysis of a novel GATA3 mutation in a family with the hypoparathyroidism, deafness, and renal dysplasia syndrome. J Clin Endocrinol Metab. 2005;90(4):2445-50.

92. Grigorieva IV, Mirczuk S, Gaynor KU, Nesbit MA, Grigorieva EF, Wei Q, et al. Gata3-deficient mice develop parathyroid abnormalities due to dysregulation of the parathyroid-specific transcription factor Gcm2. The Journal of clinical investigation. 2010;120(6):2144-55.

93. Kenny FM, and Linarelli L. Dwarfism and cortical thickening of tubular bones. Transient hypocalcemia in a mother and son. Am J Dis Child. 1966;111(2):201-7.

94. Bergada I, Schiffrin A, Abu Srair H, Kaplan P, Dornan J, Goltzman D, et al. Kenny syndrome: description of additional abnormalities and molecular studies. Human Genetics. 1988;80(1):39-42.

95. Caffey J. CONGENITAL STENOSIS OF MEDULLARY SPACES IN TUBULAR BONES AND CALVARIA IN TWO PROPORTIONATE DWARFS‚ÄîMOTHER AND SON; COUPLED WITH TRANSITORY HYPOCALCEMIC TETANY. American Journal of Roentgenology. 1967;100(1):1-11.

96. Hershkovitz E, and Parvari R. Hypoparathyroidism. Springer Milan; 2015:215-24.

97. Abraham MB, Li D, Tang D, O'Connell SM, McKenzie F, Lim EM, et al. Short stature and hypoparathyroidism in a child with Kenny-Caffey syndrome type 2 due to a novel mutation in FAM111A gene. Int J Pediatr Endocrinol. 2017;2017:1.

98. Isojima T, Doi K, Mitsui J, Oda Y, Tokuhiro E, Yasoda A, et al. A recurrent de novo <i>FAM111A</i> mutation causes kenny‚Äìcaffey syndrome type 2. Journal of Bone and Mineral Research. 2014;29(4):992-8.

99. Unger S, Gorna MW, Le Bechec A, Do Vale-Pereira S, Bedeschi MF, Geiberger S, et al. FAM111A mutations result in hypoparathyroidism and impaired skeletal development. American journal of human genetics. 2013;92(6):990-5.

100. Alabert C, Bukowski-Wills J-C, Lee S-B, Kustatscher G, Nakamura K, de Lima Alves F, et al. Nascent chromatin capture proteomics determines chromatin dynamics during DNA replication and identifies unknown fork components. Nature cell biology. 2014;16(3):281-93.

101. Teebi AS. Hypoparathyroidism, retarded growth and development, and dysmorphism or Sanjad-Sakati syndrome: an Arab disease reminiscent of Kenny-Caffey syndrome. J Med Genet. 2000;37(2):145.

102. Parvari R, Hershkovitz E, Kanis A, Gorodischer R, Shalitin S, Sheffield VC, et al. Homozygosity and linkage-disequilibrium mapping of the syndrome of congenital hypoparathyroidism, growth and mental retardation, and dysmorphism to a 1-cM interval on chromosome 1q42-43. American journal of human genetics. 1998;63(1):163-9.

103. Parvari R, Hershkovitz E, Grossman N, Gorodischer R, Loeys B, Zecic A, et al. Mutation of TBCE causes hypoparathyroidism-retardation-dysmorphism and autosomal recessive Kenny-Caffey syndrome. Nat Genet. 2002;32(3):448-52.

104. Voloshin O, Gocheva Y, Gutnick M, Movshovich N, Bakhrat A, Baranes-Bachar K, et al. Tubulin chaperone E binds microtubules and proteasomes and protects against misfolded protein stress. Cellular and Molecular Life Sciences. 2010;67(12):2025-38.

105. Parvari R, Diaz GA, and Hershkovitz E. Parathyroid Development and the Role of Tubulin Chaperone E. Hormone research in paediatrics. 2006;67(1):12-21.

106. Chow J, Rahman J, Achermann JC, Dattani MT, and Rahman S. Mitochondrial disease and endocrine dysfunction. Nature Reviews Endocrinology. 2016;13(2):92-104.

107. Seneca S, Meirleir LD, Scbepper JD, Balduck N, Jochmans K, Liebaers I, et al. Pearson marrow pancreas syndrome: a molecular study and clinical management. Clinical genetics. 1997;51(5):338-42.

108. Tengan CH. Mitochondrial Encephalomyopathy and Hypoparathyrodism Associated with a Duplication and a Deletion of Mitochondrial Deoxyribonucleic Acid. Journal of Clinical Endocrinology &amp; Metabolism. 1998;83(1):125-9.

109. Wilichowski E, Gruters A, Kruse K, Rating D, Beetz R, Korenke GC, et al. Hypoparathyroidism and Deafness Associated with Pleioplasmic Large Scale Rearrangements of the Mitochondrial DNA: A Clinical and Molecular Genetic Study of Four Children with Kearns-Sayre Syndrome. Pediatric Research. 1997;41(2):193-200.

110. Naiki M, Ochi N, Kato YS, Purevsuren J, Yamada K, Kimura R, et al. Mutations in <i>HADHB</i>, which encodes the Œ≤‚Äêsubunit of mitochondrial trifunctional protein, cause infantile onset hypoparathyroidism and peripheral polyneuropathy. American Journal of Medical Genetics Part A. 2014;164(5):1180-7.

111. Tyni T, Rapola J, Palotie A, and Pihko H. Hypoparathyroidism in a patient with long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency caused by the G1528C mutation. The Journal of Pediatrics. 1997;131(5):766-8.

112. Carpenter TO, Carnes DL, and Anast CS. Hypoparathyroidism in Wilson's Disease. New England Journal of Medicine. 1983;309(15):873-7.

113. Brown EM. Anti-parathyroid and anti-calcium sensing receptor antibodies in autoimmune hypoparathyroidism. Endocrinol Metab Clin North Am. 2009;38(2):437-45, x.

114. Kemp EH, and Weetman AP. Hypoparathyroidism. Springer Milan; 2015:177-88.

115. Alimohammadi M, Bjorklund P, Hallgren A, Pontynen N, Szinnai G, Shikama N, et al. Autoimmune Polyendocrine Syndrome Type 1 and NALP5, a Parathyroid Autoantigen. New England Journal of Medicine. 2008;358(10):1018-28.

116. Eisenbarth GS, and Gottlieb PA. Autoimmune Polyendocrine Syndromes. New England Journal of Medicine. 2004;350(20):2068-79.

117. Li Y, Song YH, Rais N, Connor E, Schatz D, Muir A, et al. Autoantibodies to the extracellular domain of the calcium sensing receptor in patients with acquired hypoparathyroidism. The Journal of clinical investigation. 1996;97(4):910-4.

118. Goswami R, Brown EM, Kochupillai N, Gupta N, Rani R, Kifor O, et al. Prevalence of calcium sensing receptor autoantibodies in patients with sporadic idiopathic hypoparathyroidism. European Journal of Endocrinology. 2004:9-18.

119. Gylling M, Kääriäinen E, Väisänen R, Kerosuo L, Solin M-L, Halme L, et al. The Hypoparathyroidism of Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy Protective Effect of Male Sex. The Journal of Clinical Endocrinology &amp; Metabolism. 2003;88(10):4602-8.

120. Kemp EH, Gavalas NG, Krohn KJE, Brown EM, Watson PF, and Weetman AP. Activating autoantibodies against the calcium-sensing receptor detected in two patients with autoimmune polyendocrine syndrome type 1. The Journal of clinical endocrinology and metabolism. 2009;94(12):4749-56.

121. Soderbergh A, Myhre AG, Ekwall O, Gebre-Medhin G, Hedstrand H, Landgren E, et al. Prevalence and Clinical Associations of 10 Defined Autoantibodies in Autoimmune Polyendocrine Syndrome Type I. The Journal of Clinical Endocrinology &amp; Metabolism. 2004;89(2):557-62.

122. Mayer A, Ploix C, Orgiazzi J, Desbos A, Moreira A, Vidal H, et al. Calcium-Sensing Receptor Autoantibodies Are Relevant Markers of Acquired Hypoparathyroidism. The Journal of Clinical Endocrinology &amp; Metabolism. 2004;89(9):4484-8.

123. Schott M, and Scherbaum WA. Hypoparathyroidism and autoimmune polyendocrine syndromes. N Engl J Med. 2004;351(10):1032-3; author reply -3.

124. Kifor O, McElduff A, LeBoff MS, Moore FD, Butters R, Gao P, et al. Activating Antibodies to the Calcium-Sensing Receptor in Two Patients with Autoimmune Hypoparathyroidism. The Journal of Clinical Endocrinology &amp; Metabolism. 2004;89(2):548-56.

125. Buzi F, Badolato R, Mazza C, Giliani S, Notarangelo LD, Radetti G, et al. Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy Syndrome: Time to Review Diagnostic Criteria? The Journal of Clinical Endocrinology &amp; Metabolism. 2003;88(7):3146-8.

126. Ferre EM, Rose SR, Rosenzweig SD, Burbelo PD, Romito KR, Niemela JE, et al. Redefined clinical features and diagnostic criteria in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. JCI Insight. 2016;1(13).

127. Halonen M, Kangas H, Rüppell T, Ilmarinen T, Ollila J, Kolmer M, et al. APECED-causing mutations in AIRE reveal the functional domains of the protein. Human Mutation. 2004;23(3):245-57.

128. Nagamine K, Peterson P, Scott HS, Kudoh J, Minoshima S, Heino M, et al. Positional cloning of the APECED gene. Nature Genetics. 1997;17(4):393-8.

129. Aaltonen J, Bjorses P, Perheentupa J, Horelli‚ÄìKuitunen N, Palotie A, Peltonen L, et al. An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. Nature Genetics. 1997;17(4):399-403.

130. Akirav EM, Ruddle NH, and Herold KC. The role of AIRE in human autoimmune disease. Nature Reviews Endocrinology. 2010;7(1):25-33.

131. Cervato S, Mariniello B, Lazzarotto F, Morlin L, Zanchetta R, Radetti G, et al. Evaluation of the autoimmune regulator (AIRE) gene mutations in a cohort of Italian patients with autoimmune-polyendocrinopathy-candidiasis-ectodermal-dystrophy (APECED) and in their relatives. Clinical endocrinology. 2009;70(3):421-8.

132. Cheng MH, Fan U, Grewal N, Barnes M, Mehta A, Taylor S, et al. Acquired autoimmune polyglandular syndrome, thymoma, and an AIRE defect. The New England journal of medicine. 2010;362(8):764-6.

133. Chase LR, Melson GL, and Aurbach GD. Pseudohypoparathyroidism: defective excretion of 3',5'-AMP in response to parathyroid hormone. J Clin Invest. 1969;48:1832-44.

134. Albright F, Burnett CH, Smith PH, and Parson W. Pseudohypoparathyroidism - an example of "Seabright-Bantam syndrome". Endocrinology. 1942;30:922-32.

135. Wilson LC, and Trembath RC. Albright's hereditary osteodystrophy. J Med Genet. 1994;31(10):779-84.

136. de Sanctis L, Vai S, Andreo MR, Romagnolo D, Silvestro L, and de Sanctis C. Brachydactyly in 14 genetically characterized pseudohypoparathyroidism type Ia patients. J Clin Endocrinol Metab. 2004;89(4):1650-5.

137. Puzhko S, Goodyer CG, Mohammad AK, Canaff L, Misra M, Jüppner H, et al. Parathyroid hormone signaling via Galphas is selectively inhibited by an NH(2) -terminally truncated Galphas: Implications for pseudohypoparathyroidism. J Bone Miner Res. 2011;26(10):2473-85.

138. Poznanski AK, Werder EA, Giedion A, Martin A, and Shaw H. The pattern of shortening of the bones of the hand in PHP and PPHP--A comparison with brachydactyly E, Turner Syndrome, and acrodysostosis. Radiology. 1977;123(3):707-18.

139. Levine MA. Clinical spectrum and pathogenesis of pseudohypoparathyroidism. Reviews in endocrine & metabolic disorders. 2000;1(4):265-74.

140. Brickman AS, Stern N, and Sowers JR. Hypertension in pseudohypoparathyroidism type I. Am J Med. 1988;85(6):785-92.

141. 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.

142. Goadsby PJ, Lollin Y, and Kocen RS. Pseudopseudohypoparathyroidism and spinal cord compression. J Neurol Neurosurg Psychiatry. 1991;54(10):929-31.

143. Maeda SS, Fortes EM, Oliveira UM, Borba VC, and Lazaretti-Castro M. Hypoparathyroidism and pseudohypoparathyroidism. Arq Bras Endocrinol Metabol. 2006;50(4):664-73.

144. Ong KK, Amin R, and Dunger DB. Pseudohypoparathyroidism--another monogenic obesity syndrome. Clinical endocrinology. 2000;52(3):389-91.

145. Chen M, Shrestha YB, Podyma B, Cui Z, Naglieri B, Sun H, et al. Gsalpha deficiency in the dorsomedial hypothalamus underlies obesity associated with Gsalpha mutations. J Clin Invest. 2017;127(2):500-10.

146. 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.

147. Mendes de Oliveira E, Keogh JM, Talbot F, Henning E, Ahmed R, Perdikari A, et al. Obesity-Associated GNAS Mutations and the Melanocortin Pathway. N Engl J Med. 2021;385(17):1581-92.

148. Phelan MC, Rogers RC, Clarkson KB, Bowyer FP, Levine MA, Estabrooks LL, et al. Albright hereditary osteodystrophy and del(2) (q37.3) in four unrelated individuals. American journal of medical genetics. 1995;58(1):1-7.

149. Williams SR, Aldred MA, Der Kaloustian VM, Halal F, Gowans G, McLeod DR, et al. Haploinsufficiency of HDAC4 causes brachydactyly mental retardation syndrome, with brachydactyly type E, developmental delays, and behavioral problems. Am J Hum Genet. 2010;87(2):219-28.

150. Johnson D, Kan SH, Oldridge M, Trembath RC, Roche P, Esnouf RM, et al. Missense mutations in the homeodomain of HOXD13 are associated with brachydactyly types D and E. Am J Hum Genet. 2003;72(4):984-97.

151. Maass PG, Wirth J, Aydin A, Rump A, Stricker S, Tinschert S, et al. A cis-regulatory site downregulates PTHLH in translocation t(8;12)(q13;p11.2) and leads to Brachydactyly Type E. Hum Mol Genet. 2010;19(5):848-60.

152. 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.

153. Maass PG, Rump A, Schulz H, Stricker S, Schulze L, Platzer K, et al. A misplaced lncRNA causes brachydactyly in humans. J Clin Invest. 2012;122(11):3990-4002.

154. Maass PG, Aydin A, Luft FC, Schachterle C, Weise A, Stricker S, et al. PDE3A mutations cause autosomal dominant hypertension with brachydactyly. Nat Genet. 2015;47(6):647-53.

155. Izzi B, Francois I, Labarque V, Thys C, Wittevrongel C, Devriendt K, et al. Methylation defect in imprinted genes detected in patients with an Albright's hereditary osteodystrophy like phenotype and platelet Gs hypofunction. PLoS One. 2012;7(6):e38579.

156. Farfel Z, Brickman AS, Kaslow HR, Brothers VM, and Bourne HR. Defect of receptor-cyclase coupling protein in pseudohypoparathyroidism. N Engl J Med. 1980;303:237-42.

157. Levine MA, Downs RW, Jr., Singer M, Marx SJ, Aurbach GD, and Spiegel AM. Deficient activity of guanine nucleotide regulatory protein in erythrocytes from patients with pseudohypoparathyroidism. Biochem Biophys Res Commun. 1980;94:1319-24.

158. Levine MA, Jap TS, Mauseth RS, R.S. Downs J, and Spiegel AM. Activity of the stimulatory guanine nucleotide-binding protein is reduced in erythrocytes from patients with pseudohypoparathyroidism and pseudohypoparathyroidism: Biochemical, endocrine, and genetic analysis of Albright's hereditary osteodystrophy in six kindreds. J Clin Endocrinol Metab. 1986;62:497-502.

159. Beaudet AL. Complex imprinting. Nat Genet. 2004;36(8):793-5.

160. Yu S, Yu D, Lee E, Eckhaus M, Lee R, Corria Z, et al. Variable and tissue-specific hormone resistance in heterotrimeric Gs protein a-subunit (Gsa) knockout mice is due to tissue-specific imprinting of the Gsa gene. Proc Natl Acad Sci USA. 1998;95:8715-20.

161. Hayward BE, Barlier A, Korbonits M, Grossman AB, Jacquet P, Enjalbert A, et al. Imprinting of the G(s)alpha gene GNAS1 in the pathogenesis of acromegaly. J Clin Invest. 2001;107(6):R31-6.

162. Mantovani G, Ballare E, Giammona E, Beck-Peccoz P, and Spada A. The Gsalpha Gene: Predominant Maternal Origin of Transcription in Human Thyroid Gland and Gonads. J Clin Endocrinol Metab. 2002;87(10):4736-40.

163. Germain-Lee EL, Ding CL, Deng Z, Crane JL, Saji M, Ringel MD, et al. Paternal imprinting of Galpha(s) in the human thyroid as the basis of TSH resistance in pseudohypoparathyroidism type 1a. Biochem Biophys Res Commun. 2002;296(1):67-72.

164. Liu J, Erlichman B, and Weinstein LS. The stimulatory G protein a-subunit Gsa is imprinted in human thyroid glands: implications for thyroid function in pseudohypoparathyroidism types 1A and 1B. J Clin Endocrinol Metabol. 2003;88(9):4336-41.

165. Davies AJ, and Hughes HE. Imprinting in Albright's hereditary osteodystrophy. J Med Genet. 1993;30:101-3.

166. Liu J, Litman D, Rosenberg M, Yu S, Biesecker L, and Weinstein L. A GNAS1 imprinting defect in pseudohypoparathyroidism type IB. J Clin Invest. 2000;106:1167-74.

167. Thiele S, Mantovani G, Barlier A, Boldrin V, Bordogna P, De Sanctis L, et al. From pseudohypoparathyroidism to inactivating PTH/PTHrP signalling disorder (iPPSD), a novel classification proposed by the EuroPHP network. Eur J Endocrinol. 2016;175(6):P1-P17.

168. Zheng H, Radeva G, McCann JA, Hendy GN, and Goodyer CG. Gas transcripts are biallelically expressed in the human kidney cortex: implications for pseudohypoparathyroidism type Ib. J Clin Endocrinol Metab. 2001;86(10):4627-9.

169. Weinstein LS, Liu J, Sakamoto A, Xie T, and Chen M. Minireview: GNAS: normal and abnormal functions. Endocrinology. 2004;145(12):5459-64.

170. Weinstein LS, Yu S, and Ecelbarger CA. Variable imprinting of the heterotrimeric G protein G(s) alpha-subunit within different segments of the nephron. Am J Physiol Renal Physiol. 2000;278(4):F507-14.

171. 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. J Bone Miner Res. 2014;29(3):749-60.

172. Weinstein LS, Gejman PV, Friedman E, Kadowaki T, Collins RM, Gershon ES, et al. Mutations of the Gs alpha-subunit gene in Albright hereditary osteodystrophy detected by denaturing gradient gel electrophoresis. Proc Natl Acad Sci U S A. 1990;87(21):8287-90.

173. Patten JL, Johns DR, Valle D, Eil C, Gruppuso PA, Steele G, et al. Mutation in the gene encoding the stimulatory G protein of adenylate cyclase in Albright's hereditary osteodystrophy. New Engl J Med. 1990;322:1412-9.

174. Weinstein LS, Gejman PV, de Mazancourt P, American N, and Spiegel AM. A heterozygous 4-bp deletion mutation in the Gs alpha gene (GNAS1) in a patient with Albright hereditary osteodystrophy. Genomics. 1992;13(4):1319-21.

175. Ahrens W, Hiort O, Staedt P, Kirschner T, Marschke C, and Kruse K. Analysis of the GNAS1 gene in Albright's hereditary osteodystrophy. J Clin Endocrinol Metab. 2001;86(10):4630-4.

176. Aldred MA, Bagshaw RJ, Macdermot K, Casson D, Murch SH, Walker-Smith JA, et al. Germline mosaicism for a GNAS1 mutation and Albright hereditary osteodystrophy. J Med Genet. 2000;37(11):E35.

177. Fernandez-Rebollo E, Garcia-Cuartero B, Garin I, Largo C, Martinez F, Garcia-Lacalle C, et al. Intragenic GNAS deletion involving exon A/B in pseudohypoparathyroidism type 1A resulting in an apparent loss of exon A/B methylation: potential for misdiagnosis of pseudohypoparathyroidism type 1B. J Clin Endocrinol Metab. 2010;95(2):765-71.

178. Levine MA. An update on the clinical and molecular characteristics of pseudohypoparathyroidism. Current opinion in endocrinology, diabetes, and obesity. 2012;19(6):443-51.

179. Namnoum AB, Merriam GR, Moses AM, and Levine MA. Reproductive dysfunction in women with Albright's hereditary osteodystrophy. J Clin Endocrinol Metab. 1998;83:824-9.

180. McIlroy J, Dryburgh F, Hinnie J, Dargie R, and Al-Rawi A. Oestrogen and calcium homeostasis in women with hypoparathyroidism. BMJ. 1999;319(7219):1252-3.

181. Breslau NA, and Zerwekh JE. Relationship of estrogen and pregnancy to calcium homeostasis in pseudohypoparathyroidism. J Clin Endocrinol Metab. 1986;62(1):45-51.

182. Germain-Lee EL, Groman J, Crane JL, Jan de Beur SM, and Levine MA. Growth hormone deficiency in pseudohypoparathyroidism type 1a: another manifestation of multihormone resistance. J Clin Endocrinol Metab. 2003;88(9):4059-69.

183. Mantovani G, Maghnie M, Weber G, De Menis E, Brunelli V, Cappa M, et al. Growth hormone-releasing hormone resistance in pseudohypoparathyroidism type ia: new evidence for imprinting of the Gs alpha gene. J Clin Endocrinol Metab. 2003;88(9):4070-4.

184. Long DN, McGuire S, Levine MA, Weinstein LS, and 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):1073-9.

185. Mantovani G, Bondioni S, Locatelli M, Pedroni C, Lania AG, Ferrante E, et al. Biallelic expression of the Gsalpha gene in human bone and adipose tissue. J Clin Endocrinol Metab. 2004;89(12):6316-9.

186. Yeo GS, Farooqi IS, Aminian S, Halsall DJ, Stanhope RG, and O'Rahilly S. A frameshift mutation in MC4R associated with dominantly inherited human obesity. Nat Genet. 1998;20(2):111-2.

187. Vaisse C, Clement K, Guy-Grand B, and Froguel P. A frameshift mutation in human MC4R is associated with a dominant form of obesity. Nat Genet. 1998;20(2):113-4.

188. 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.

189. Mouallem M, Shaharabany M, Weintrob N, Shalitin S, Nagelberg N, Shapira H, et al. Cognitive impairment is prevalent in pseudohypoparathyroidism type Ia, but not in pseudopseudohypoparathyroidism: possible cerebral imprinting of Gsalpha. Clinical endocrinology. 2008;68(2):233-9.

190. Peterman MG, and Garvey JL. Pseudohypoparathyroidsim; case report. Pediatrics. 1949;4(6):790-7, illust.

191. Reynolds TB, Jacobson G, Edmondson HA, Martin HE, and Nelson CH. Pseudohypoparathyroidism; report of a case showing bony demineralization. J Clin Endocrinol Metab. 1952;12(5):560-73.

192. Farfel Z, Brothers VM, Brickman AS, Conte F, Neer R, and Bourne HR. Pseudohypoparathyroidism: inheritance of deficient receptor-cyclase coupling activity. Proc Natl Acad Sci U S A. 1981;78(5):3098-102.

193. Ish-Shalom S, Rao LG, Levine MA, Fraser D, Kooh SW, Josse RG, et al. Normal parathyroid hormone responsiveness of bone-derived cells from a patient with pseudohypoparathyroidism. J Bone Miner Res. 1996;11:8-14.

194. Murray T, Gomez Rao E, Wong MM, Waddell JP, McBroom R, Tam CS, et al. Pseudohypoparathyroidism with osteitis fibrosa cystica: direct demonstration of skeletal responsiveness to parathyroid hormone in cells cultured from bone. J Bone Miner Res. 1993;8:83-91.

195. Farfel Z. Pseudohypohyperparathyroidism-pseudohypoparathyroidism type Ib. J Bone Miner Res. 1999;14:1016.

196. Molinaro A, Tiosano D, Takatani R, Chrysis D, Russell W, Koscielniak N, et al. TSH elevations as the first laboratory evidence for pseudohypoparathyroidism type Ib (PHP-Ib). J Bone Miner Res. 2015;30(5):906-12.

197. 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.

198. Sano S, Iwata H, Matsubara K, Fukami M, Kagami M, and Ogata T. Growth hormone deficiency in monozygotic twins with autosomal dominant pseudohypoparathyroidism type Ib. Endocrine journal. 2015;62(6):523-9.

199. Laspa E, Bastepe M, Jüppner H, and Tsatsoulis A. Phenotypic and molecular genetic aspects of pseudohypoparathyroidism type ib in a Greek kindred: evidence for enhanced uric acid excretion due to parathyroid hormone resistance. J Clin Endocrinol Metab. 2004;89(12):5942-7.

200. Unluturk U, Harmanci A, Babaoglu M, Yasar U, Varli K, Bastepe M, et al. Molecular diagnosis and clinical characterization of pseudohypoparathyroidism type-Ib in a patient with mild Albright's hereditary osteodystrophy-like features, epileptic seizures, and defective renal handling of uric acid. Am J Med Sci. 2008;336(1):84-90.

201. Schipani E, Weinstein LS, Bergwitz C, Iida-Klein A, Kong XF, Stuhrmann M, et al. Pseudohypoparathyroidism type Ib is not caused by mutations in the coding exons of the human parathyroid hormone (PTH)/PTH-related peptide receptor gene. J Clin Endocrinol Metab. 1995;80:1611-21.

202. Fukumoto S, Suzawa M, Takeuchi Y, Nakayama K, Kodama Y, Ogata E, et al. Absence of mutations in parathyroid hormone (PTH)/PTH-related protein receptor complementary deoxyribonucleic acid in patients with pseudohypoparathyroidism type Ib. J Clin Endocrinol Metab. 1996;81:2554-8.

203. Bettoun JD, Minagawa M, Kwan MY, Lee HS, Yasuda T, Hendy GN, et al. Cloning and characterization of the promoter regions of the human parathyroid hormone (PTH)/PTH-related peptide receptor gene: analysis of deoxyribonucleic acid from normal subjects and patients with pseudohypoparathyroidism type Ib. J Clin Endocrinol Metab. 1997;82:1031-40.

204. Jüppner H, Schipani E, Bastepe M, Cole DEC, Lawson ML, Mannstadt M, et al. The gene responsible for pseudohypoparathyroidism type Ib is paternally imprinted and maps in four unrelated kindreds to chromosome 20q13.3. Proc Natl Acad Sci USA. 1998;95:11798-803.

205. Jan de Beur S, Ding C, LaBuda M, Usdin T, and Levine M. Pseudohypoparathyroidism 1b: exclusion of parathyroid hormone and its receptors as candidate disease genes. J Clin Endocrinol Metab. 2000;85:2239-46.

206. Bastepe M, Pincus JE, Sugimoto T, Tojo K, Kanatani M, Azuma Y, et al. Positional dissociation between the genetic mutation responsible for pseudohypoparathyroidism type Ib and the associated methylation defect at exon A/B: evidence for a long-range regulatory element within the imprinted GNAS1 locus. Hum Mol Genet. 2001;10:1231-41.

207. Bastepe M, Fröhlich LF, Hendy GN, Indridason OS, Josse RG, Koshiyama H, et al. Autosomal dominant pseudohypoparathyroidism type Ib is associated with a heterozygous microdeletion that likely disrupts a putative imprinting control element of GNAS. J Clin Invest. 2003;112(8):1255-63.

208. Linglart A, Gensure RC, Olney RC, Jüppner H, and Bastepe M. A Novel STX16 Deletion in Autosomal Dominant Pseudohypoparathyroidism Type Ib Redefines the Boundaries of a cis-Acting Imprinting Control Element of GNAS. Am J Hum Genet. 2005;76(5):804-14.

209. Elli FM, de Sanctis L, Peverelli E, Bordogna P, Pivetta B, Miolo G, et al. Autosomal dominant pseudohypoparathyroidism type Ib: a novel inherited deletion ablating STX16 causes loss of imprinting at the A/B DMR. J Clin Endocrinol Metab. 2014;99(4):E724-8.

210. Yang Y, Chu X, Nie M, Song A, Jiang Y, Li M, et al. A novel long-range deletion spanning STX16 and NPEPL1 causing imprinting defects of the GNAS locus discovered in a patient with autosomal-dominant pseudohypoparathyroidism type 1B. Endocrine. 2020;69(1):212-9.

211. Danzig J, Li D, Jan de Beur S, and Levine MA. High-throughput Molecular Analysis of Pseudohypoparathyroidism 1b Patients Reveals Novel Genetic and Epigenetic Defects. J Clin Endocrinol Metab. 2021;106(11):e4603-e20.

212. Richard N, Abeguile G, Coudray N, Mittre H, Gruchy N, Andrieux J, et al. A new deletion ablating NESP55 causes loss of maternal imprint of A/B GNAS and autosomal dominant pseudohypoparathyroidism type Ib. J Clin Endocrinol Metab. 2012;97(5):E863-7.

213. Bastepe M, Fröhlich LF, Linglart A, Abu-zahra HS, Tojo K, Ward LM, et al. Deletion of the NESP55 differentially methylated region causes loss of maternal GNAS imprints and pseudohypoparathyroidism type-Ib. Nat Genet. 2005;37(1):25-37.

214. Chillambhi S, Turan S, Hwang DY, Chen HC, Jüppner H, and Bastepe M. Deletion of the Noncoding GNAS Antisense Transcript Causes Pseudohypoparathyroidism Type Ib and Biparental Defects of GNAS Methylation in cis. J Clin Endocrinol Metab. 2010;95(8):3993-4002.

215. Rezwan FI, Poole RL, Prescott T, Walker JM, Karen Temple I, and Mackay DJ. Very small deletions within the NESP55 gene in pseudohypoparathyroidism type 1b. Eur J Hum Genet. 2015;23(4):494-9.

216. Perez-Nanclares G, Velayos T, Vela A, Munoz-Torres M, and Castano L. Pseudohypoparathyroidism type Ib associated with novel duplications in the GNAS locus. PLoS One. 2015;10(2):e0117691.

217. Nakamura A, Hamaguchi E, Horikawa R, Nishimura Y, Matsubara K, Sano S, et al. Complex Genomic Rearrangement Within the GNAS Region Associated With Familial Pseudohypoparathyroidism Type 1b. J Clin Endocrinol Metab. 2016;101(7):2623-7.

218. Grigelioniene G, Nevalainen PI, Reyes M, Thiele S, Tafaj O, Molinaro A, et al. A Large Inversion Involving GNAS Exon A/B and All Exons Encoding Gsalpha Is Associated With Autosomal Dominant Pseudohypoparathyroidism Type Ib (PHP1B). J Bone Miner Res. 2017;32(4):776-83.

219. Takatani R, Molinaro A, Grigelioniene G, Tafaj O, Watanabe T, Reyes M, et al. Analysis of Multiple Families With Single Individuals Affected by Pseudohypoparathyroidism Type Ib (PHP1B) Reveals Only One Novel Maternally Inherited GNAS Deletion. J Bone Miner Res. 2016;31(4):796-805.

220. Fröhlich LF, Bastepe M, Ozturk D, Abu-Zahra H, and Jüppner H. Lack of Gnas epigenetic changes and pseudohypoparathyroidism type Ib in mice with targeted disruption of syntaxin-16. Endocrinology. 2007;148(6):2925-35.

221. Yang H, Bai D, Li Y, Yu Z, Wang C, Sheng Y, et al. Allele-specific H3K9me3 and DNA methylation co-marked CpG-rich regions serve as potential imprinting control regions in pre-implantation embryo. Nature cell biology. 2022;24(5):783-92.

222. Yagi M, Kabata M, Ukai T, Ohta S, Tanaka A, Shimada Y, et al. De Novo DNA Methylation at Imprinted Loci during Reprogramming into Naive and Primed Pluripotency. Stem cell reports. 2019;12(5):1113-28.

223. Iwasaki Y, Aksu C, Reyes M, Ay B, He Q, and Bastepe M. The long-range interaction between two GNAS imprinting control regions delineates pseudohypoparathyroidism type 1B pathogenesis. J Clin Invest. 2023;133(8):e167953.

224. Chotalia M, Smallwood SA, Ruf N, Dawson C, Lucifero D, Frontera M, et al. Transcription is required for establishment of germline methylation marks at imprinted genes. Genes Dev. 2009;23(1):105-17.

225. Bastepe M, Lane AH, and Jüppner H. Paternal uniparental isodisomy of chromosome 20q (patUPD20q) - and the resulting changes in GNAS1 methylation - as a plausible cause of pseudohypoparathyroidism. Am J Hum Genet. 2001;68:1283-9.

226. Lecumberri B, Fernandez-Rebollo E, Sentchordi L, Saavedra P, Bernal-Chico A, Pallardo LF, et al. Coexistence of two different pseudohypoparathyroidism subtypes (Ia and Ib) in the same kindred with independent Gs{alpha} coding mutations and GNAS imprinting defects. J Med Genet. 2010;47(4):276-80.

227. Fernandez-Rebollo E, Lecumberri B, Garin I, Arroyo J, Bernal-Chico A, Goni F, et al. New mechanisms involved in paternal 20q disomy associated with pseudohypoparathyroidism. Eur J Endocrinol. 2010;163(6):953-62.

228. Dixit A, Chandler KE, Lever M, Poole RL, Bullman H, Mughal MZ, et al. Pseudohypoparathyroidism type 1b due to paternal uniparental disomy of chromosome 20q. J Clin Endocrinol Metab. 2013;98(1):E103-8.

229. Takatani R, Minagawa M, Molinaro A, Reyes M, Kinoshita K, Takatani T, et al. Similar frequency of paternal uniparental disomy involving chromosome 20q (patUPD20q) in Japanese and Caucasian patients affected by sporadic pseudohypoparathyroidism type Ib (sporPHP1B). Bone. 2015;79:15-20.

230. Maupetit-Mehouas S, Azzi S, Steunou V, Sakakini N, Silve C, Reynes C, et al. Simultaneous hyper- and hypomethylation at imprinted loci in a subset of patients with GNAS epimutations underlies a complex and different mechanism of multilocus methylation defect in pseudohypoparathyroidism type 1b. Hum Mutat. 2013;34(8):1172-80.

231. Bliek J, Verde G, Callaway J, Maas SM, De Crescenzo A, Sparago A, et al. Hypomethylation at multiple maternally methylated imprinted regions including PLAGL1 and GNAS loci in Beckwith-Wiedemann syndrome. Eur J Hum Genet. 2009;17(5):611-9.

232. Mackay DJ, Callaway JL, Marks SM, White HE, Acerini CL, Boonen SE, et al. Hypomethylation of multiple imprinted loci in individuals with transient neonatal diabetes is associated with mutations in ZFP57. Nat Genet. 2008;40(8):949-51.

233. Bakker B, Sonneveld LJ, Woltering MC, Bikker H, and Kant SG. A Girl With Beckwith-Wiedemann Syndrome and Pseudohypoparathyroidism Type 1B Due to Multiple Imprinting Defects. J Clin Endocrinol Metab. 2015;100(11):3963-6.

234. Rochtus A, Martin-Trujillo A, Izzi B, Elli F, Garin I, Linglart A, et al. Genome-wide DNA methylation analysis of pseudohypoparathyroidism patients with GNAS imprinting defects. Clin Epigenetics. 2016;8:10.

235. Hanna P, Francou B, Delemer B, Juppner H, and Linglart A. A Novel Familial PHP1B Variant With Incomplete Loss of Methylation at GNAS-A/B and Enhanced Methylation at GNAS-AS2. J Clin Endocrinol Metab. 2021;106(9):2779-87.

236. Kawashima S, Yuno A, Sano S, Nakamura A, Ishiwata K, Kawasaki T, et al. Familial Pseudohypoparathyroidism Type IB Associated with an SVA Retrotransposon Insertion in the GNAS Locus. J Bone Miner Res. 2022;37(10):1850-9.

237. Miller DE, Hanna P, Galey M, Reyes M, Linglart A, Eichler EE, et al. Targeted Long-Read Sequencing Identifies a Retrotransposon Insertion as a Cause of Altered GNAS Exon A/B Methylation in a Family With Autosomal Dominant Pseudohypoparathyroidism Type 1b (PHP1B). J Bone Miner Res. 2022;37(9):1711-9.

238. Linglart A, Bastepe M, and Jüppner H. Similar clinical and laboratory findings in patients with symptomatic autosomal dominant and sporadic pseudohypoparathyroidism type Ib despite different epigenetic changes at the GNAS locus. Clinical endocrinology. 2007;67(6):822-31.

239. Brehin AC, Colson C, Maupetit-Mehouas S, Grybek V, Richard N, Linglart A, et al. Loss of methylation at GNAS exon A/B is associated with increased intrauterine growth. J Clin Endocrinol Metab. 2015;100(4):E623-31.

240. de Nanclares GP, Fernandez-Rebollo E, Santin I, Garcia-Cuartero B, Gaztambide S, Menendez E, et al. Epigenetic defects of GNAS in patients with pseudohypoparathyroidism and mild features of Albright's hereditary osteodystrophy. J Clin Endocrinol Metab. 2007;92(6):2370-3.

241. Mariot V, Maupetit-Mehouas S, Sinding C, Kottler ML, and Linglart A. A maternal epimutation of GNAS leads to Albright osteodystrophy and parathyroid hormone resistance. J Clin Endocrinol Metab. 2008;93(3):661-5.

242. Mantovani G, de Sanctis L, Barbieri AM, Elli FM, Bollati V, Vaira V, et al. Pseudohypoparathyroidism and GNAS epigenetic defects: clinical evaluation of albright hereditary osteodystrophy and molecular analysis in 40 patients. J Clin Endocrinol Metab. 2010;95(2):651-8.

243. Wu WI, Schwindinger WF, Aparicio LF, and Levine MA. Selective resistance to parathyroid hormone caused by a novel uncoupling mutation in the carboxyl terminus of Gas: A cause of pseudohypoparathyroidism type Ib. J Biol Chem. 2001;276(1):165-71.

244. Linglart A, Carel JC, Garabedian M, Le T, Mallet E, and Kottler ML. GNAS1 Lesions in Pseudohypoparathyroidism Ia and Ic: Genotype Phenotype Relationship and Evidence of the Maternal Transmission of the Hormonal Resistance. J Clin Endocrinol Metab. 2002;87(1):189-97.

245. Linglart A, Mahon MJ, Kerachian MA, Berlach DM, Hendy GN, Jüppner H, et al. Coding GNAS mutations leading to hormone resistance impair in vitro agonist- and cholera toxin-induced adenosine cyclic 3',5'-monophosphate formation mediated by human XLas. Endocrinology. 2006;147(5):2253-62.

246. Thiele S, de Sanctis L, Werner R, Grotzinger J, Aydin C, Jüppner H, et al. Functional characterization of GNAS mutations found in patients with pseudohypoparathyroidism type Ic defines a new subgroup of pseudohypoparathyroidism affecting selectively Gsalpha-receptor interaction. Hum Mutat. 2011;32(6):653-60.

247. Drezner M, Neelon FA, and Lebovitz HE. Pseudohypoparathyroidism type II: a possible defect in the reception of the cyclic AMP signal. N Engl J Med. 1973;289(20):1056-60.

248. Van Dop C. Pseudohypoparathyroidism: clinical and molecular aspects. Seminars in nephrology. 1989;9(2):168-78.

249. Kruse K, and Kustermann W. Evidence for transient peripheral resistance to parathyroid hormone in premature infants. Acta Paediatr Scand. 1987;76(1):115-8.

250. Lee CT, Tsai WY, Tung YC, and Tsau YK. Transient pseudohypoparathyroidism as a cause of late-onset hypocalcemia in neonates and infants. J Formos Med Assoc. 2008;107(10):806-10.

251. Manzar S. Transient pseudohypoparathyroidism and neonatal seizure. J Trop Pediatr. 2001;47(2):113-4.

252. Linglart A, Menguy C, Couvineau A, Auzan C, Gunes Y, Cancel M, et al. Recurrent PRKAR1A mutation in acrodysostosis with hormone resistance. N Engl J Med. 2011;364(23):2218-26.

253. Robinow M, Pfeiffer RA, Gorlin RJ, McKusick VA, Renuart AW, Johnson GF, et al. Acrodysostosis. A syndrome of peripheral dysostosis, nasal hypoplasia, and mental retardation. Am J Dis Child. 1971;121(3):195-203.

254. Maroteaux P, and Malamut G. [Acrodysostosis]. La Presse medicale. 1968;76(46):2189-92.

255. 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.

256. Nagasaki K, Iida T, Sato H, Ogawa Y, Kikuchi T, Saitoh A, et al. PRKAR1A mutation affecting cAMP-mediated G protein-coupled receptor signaling in a patient with acrodysostosis and hormone resistance. J Clin Endocrinol Metab. 2012;97(9):E1808-13.

257. Silve C. Acrodysostosis: A new form of pseudohypoparathyroidism? Ann Endocrinol (Paris). 2015;76(2):110-2.

258. Michot C, Le Goff C, Goldenberg A, Abhyankar A, Klein C, Kinning E, et al. Exome sequencing identifies PDE4D mutations as another cause of acrodysostosis. Am J Hum Genet. 2012;90(4):740-5.

259. Bruystens JG, Wu J, Fortezzo A, Del Rio J, Nielsen C, Blumenthal DK, et al. Structure of a PKA RIalpha Recurrent Acrodysostosis Mutant Explains Defective cAMP-Dependent Activation. Journal of molecular biology. 2016;428(24 Pt B):4890-904.

260. Le Stunff C, Tilotta F, Sadoine J, Le Denmat D, Briet C, Motte E, et al. Knock-In of the Recurrent R368X Mutation of PRKAR1A that Represses cAMP-Dependent Protein Kinase A Activation: A Model of Type 1 Acrodysostosis. J Bone Miner Res. 2017;32(2):333-46.

261. Rhayem Y, Le Stunff C, Abdel Khalek W, Auzan C, Bertherat J, Linglart A, et al. Functional Characterization of PRKAR1A Mutations Reveals a Unique Molecular Mechanism Causing Acrodysostosis but Multiple Mechanisms Causing Carney Complex. J Biol Chem. 2015;290(46):27816-28.

262. 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.

263. Lynch DC, Dyment DA, Huang L, Nikkel SM, Lacombe D, Campeau PM, et al. Identification of novel mutations confirms PDE4D as a major gene causing acrodysostosis. Hum Mutat. 2013;34(1):97-102.

264. Conti M, and Beavo J. Biochemistry and physiology of cyclic nucleotide phosphodiesterases: essential components in cyclic nucleotide signaling. Annu Rev Biochem. 2007;76:481-511.

265. Boda H, Uchida H, Takaiso N, Ouchi Y, Fujita N, Kuno A, et al. A PDE3A mutation in familial hypertension and brachydactyly syndrome. J Hum Genet. 2016;61(8):701-3.

266. Weinstein LS. The Genetics of Osteoporosis and Metabolic Bone Disease. Humana Press; 2000:163-77.

267. Weinstein LS, and Collins MT. Principles of Bone Biology. Elsevier; 2008:1453-77.

268. Cole DE, Fraser FC, Glorieux FH, Jequier S, Marie PJ, Reade TM, et al. Panostotic fibrous dysplasia: a congenital disorder of bone with unusual facial appearance, bone fragility, hyperphosphatasemia, and hypophosphatemia. American journal of medical genetics. 1983;14(4):725-35.

269. Landis CA, Masters SB, Spada A, Pace AM, Bourne HR, and Vallar L. GTPase inhibiting mutations activate the alpha chain of Gs and stimulate adenylyl cyclase in human pituitary tumours. Nature. 1989;340(6236):692-6.

270. Iiri T, Herzmark P, Nakamoto JM, Dop Cv, and Bourne HR. Rapid GDP release from Gs in patients with gain and loss of function. Nature. 1994;371(6493):164-8.

271. Nakamoto JM, Zimmerman D, Jones EA, Loke KY, Siddiq K, Donlan MA, et al. Concurrent hormone resistance (pseudohypoparathyroidism type Ia) and hormone independence (testotoxicosis) caused by a unique mutation in the G alpha s gene. Biochemical and molecular medicine. 1996;58(1):18-24.

272. Makita N, Sato J, Rondard P, Fukamachi H, Yuasa Y, Aldred MA, et al. Human G(salpha) mutant causes pseudohypoparathyroidism type Ia/neonatal diarrhea, a potential cell-specific role of the palmitoylation cycle. Proc Natl Acad Sci U S A. 2007;104(44):17424-9.

273. Wentworth K, Hsing A, Urrutia A, Zhu Y, Horvai AE, Bastepe M, et al. A Novel T55A Variant of Gs alpha Associated with Impaired cAMP Production, Bone Fragility, and Osteolysis. Case Rep Endocrinol. 2016;2016:2691385.

274. Biebermann H, Kleinau G, Schnabel D, Bockenhauer D, Wilson LC, Tully I, et al. A New Multisystem Disorder Caused by the Galphas Mutation p.F376V. J Clin Endocrinol Metab. 2019;104(4):1079-89.

275. Eddy MC, De Beur SM, Yandow SM, McAlister WH, Shore EM, Kaplan FS, et al. Deficiency of the alpha-subunit of the stimulatory G protein and severe extraskeletal ossification. J Bone Miner Res. 2000;15(11):2074-83.

276. Kaplan FS, and Shore EM. Progressive osseous heteroplasia. J Bone Miner Res. 2000;15(11):2084-94.

277. Shore EM, and Kaplan FS. Inherited human diseases of heterotopic bone formation. Nat Rev Rheumatol. 2010;6(9):518-27.

278. Yeh GL, Mathur S, Wivel A, Li M, Gannon FH, Ulied A, et al. GNAS1 mutation and Cbfa1 misexpression in a child with severe congenital platelike osteoma cutis. J Bone Miner Res. 2000;15(11):2063-73.

279. Adegbite NS, Xu M, Kaplan FS, Shore EM, and Pignolo RJ. Diagnostic and mutational spectrum of progressive osseous heteroplasia (POH) and other forms of GNAS-based heterotopic ossification. Am J Med Genet A. 2008;146A(14):1788-96.

280. Shore EM, Ahn J, Jan de Beur S, Li M, Xu M, Gardner RJ, et al. Paternally inherited inactivating mutations of the GNAS1 gene in progressive osseous heteroplasia. N Engl J Med. 2002;346(2):99-106.

281. Ahmed SF, Barr DG, and Bonthron DT. GNAS1 mutations and progressive osseous heteroplasia. N Engl J Med. 2002;346(21):1669-71.

282. Cairns DM, Pignolo RJ, Uchimura T, Brennan TA, Lindborg CM, Xu M, et al. Somitic disruption of GNAS in chick embryos mimics progressive osseous heteroplasia. J Clin Invest. 2013;123(8):3624-33.

283. Gardella TJ, and Vilardaga JP. International Union of Basic and Clinical Pharmacology. XCIII. The parathyroid hormone receptors--family B G protein-coupled receptors. Pharmacol Rev. 2015;67(2):310-37.

284. Scillitani A, Jang C, Wong BY, Hendy GN, and Cole DE. A functional polymorphism in the PTHR1 promoter region is associated with adult height and BMD measured at the femoral neck in a large cohort of young caucasian women. Hum Genet. 2006;119(4):416-21.

285. Jüppner H, Schipani E, and Silve C. Principles of Bone Biology. Elsevier; 2008:1431-52.

286. Blomstrand S, Claësson I, and Säve-Söderbergh J. A case of lethal congenital dwarfism with accelerated skeletal maturation. Pediatr Radiol. 1985;15:141-3.

287. Karaplis AC, Bin He MT, Nguyen A, Young ID, Semeraro D, Ozawa H, et al. Inactivating Mutation in the Human Parathyroid Hormone Receptor Type 1 Gene in Blomstrand Chondrodysplasia. Endocrinology. 1998;139:5255-8.

288. Karperien M, van der Harten HJ, van Schooten R, Farih-Sips H, den Hollander NS, Kneppers SLJ, et al. A Frame-Shift Mutation in the Type I Parathyroid Hormone (PTH)/PTH-Related Peptide Receptor Causing Blomstrand Lethal Osteochondrodysplasia. The Journal of Clinical Endocrinology &amp; Metabolism. 1999;84(10):3713-20.

289. Loshkajian A, Roume J, Stanescu V, Delezoide AL, Stampf F, and Maroteaux P. Familial Blomstrand Chondrodysplasia with advanced skeletal maturation: further delineation. Am J Med Genet. 1997;71:283-8.

290. Zhang P, Jobert AS, Couvineau A, and Silve C. A homozygous inactivating mutation in the parathyroid hormone/parathyroid hormone-related peptide receptor causing Blomstrand chondrodysplasia. J Clin Endocrinol Metab. 1998;83:3365-8.

291. Hoogendam J, Farih-Sips H, Wynaendts LC, Lowik CW, Wit JM, and Karperien M. Novel mutations in the parathyroid hormone (PTH)/PTH-related peptide receptor type 1 causing Blomstrand osteochondrodysplasia types I and II. J Clin Endocrinol Metab. 2007;92(3):1088-95.

292. Oostra R, van der Harten J, Rijnders W, Scott R, Young M, and Trump D. Blomstrand osteochondrodysplasia: three novel cases and histological evidence for heterogeneity. Virchows Arch. 2000;436:28-35.

293. Duchatelet S, Ostergaard E, Cortes D, Lemainque A, and Julier C. Recessive mutations in PTHR1 cause contrasting skeletal dysplasias in Eiken and Blomstrand syndromes. Hum Mol Genet. 2005;14(1):1-5.

294. Couvineau A, Wouters V, Bertrand G, Rouyer C, Gerard B, Boon LM, et al. PTHR1 mutations associated with Ollier disease result in receptor loss of function. Hum Mol Genet. 2008;17(18):2766-75.

295. Hopyan S, Gokgoz N, Poon R, Gensure RC, Yu C, Cole WG, et al. A mutant PTH/PTHrP type I receptor in enchondromatosis. Nat Genet. 2002;30(3):306-10.

296. Rozeman LB, Sangiorgi L, Briaire-de Bruijn IH, Mainil-Varlet P, Bertoni F, Cleton-Jansen AM, et al. Enchondromatosis (Ollier disease, Maffucci syndrome) is not caused by the PTHR1 mutation p.R150C. Hum Mutat. 2004;24(6):466-73.

297. Collinson M, Leonard SJ, Charlton J, Crolla JA, Silve C, Hall CM, et al. Symmetrical enchondromatosis is associated with duplication of 12p11.23 to 12p11.22 including PTHLH. Am J Med Genet A. 2010;152A(12):3124-8.

298. Decker E, Stellzig-Eisenhauer A, Fiebig BS, Rau C, Kress W, Saar K, et al. PTHR1 loss-of-function mutations in familial, nonsyndromic primary failure of tooth eruption. Am J Hum Genet. 2008;83(6):781-6.

299. Frazier-Bowers SA, Hendricks HM, Wright JT, Lee J, Long K, Dibble CF, et al. Novel mutations in PTH1R associated with primary failure of eruption and osteoarthritis. Journal of dental research. 2014;93(2):134-9.

300. Frazier-Bowers SA, Simmons D, Wright JT, Proffit WR, and Ackerman JL. Primary failure of eruption and PTH1R: the importance of a genetic diagnosis for orthodontic treatment planning. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics. 2010;137(2):160 e1-7; discussion -1.

301. Risom L, Christoffersen L, Daugaard-Jensen J, Hove HD, Andersen HS, Andresen BS, et al. Identification of six novel PTH1R mutations in families with a history of primary failure of tooth eruption. PLoS One. 2013;8(9):e74601.

302. Yamaguchi T, Hosomichi K, Narita A, Shirota T, Tomoyasu Y, Maki K, et al. Exome resequencing combined with linkage analysis identifies novel PTH1R variants in primary failure of tooth eruption in Japanese. J Bone Miner Res. 2011;26(7):1655-61.

303. Konrad M, Schlingmann KP, and Gudermann T. Insights into the molecular nature of magnesium homeostasis. Am J Physiol Renal Physiol. 2004;286(4):F599-605.

304. Astor MC, Lovas K, Wolff AS, Nedrebo B, Bratland E, Steen-Johnsen J, et al. Hypomagnesemia and functional hypoparathyroidism due to novel mutations in the Mg-channel TRPM6. Endocr Connect. 2015;4(4):215-22.

305. Janett S, Camozzi P, Peeters GG, Lava SA, Simonetti GD, Goeggel Simonetti B, et al. Hypomagnesemia Induced by Long-Term Treatment with Proton-Pump Inhibitors. Gastroenterol Res Pract. 2015;2015:951768.

306. Fatuzzo P, Portale G, Scollo V, Zanoli L, and Granata A. Proton pump inhibitors and symptomatic hypomagnesemic hypoparathyroidism. J Nephrol. 2017;30(2):297-301.

307. Bilezikian JP, Brandi ML, Cusano NE, Mannstadt M, Rejnmark L, Rizzoli R, et al. Management of Hypoparathyroidism: Present and Future. J Clin Endocrinol Metab. 2016;101(6):2313-24.

308. Brandi ML, Bilezikian JP, Shoback D, Bouillon R, Clarke BL, Thakker RV, et al. Management of Hypoparathyroidism: Summary Statement and Guidelines. J Clin Endocrinol Metab. 2016;101(6):2273-83.

309. Mittendorf EA, Merlino JI, and McHenry CR. Post-parathyroidectomy hypocalcemia: incidence, risk factors, and management. Am Surg. 2004;70(2):114-9; discussion 9-20.

310. Khan MI, Waguespack SG, and Hu MI. Medical management of postsurgical hypoparathyroidism. Endocr Pract. 2011;17 Suppl 1:18-25.

311. Arlt W, Fremerey C, Callies F, Reincke M, Schneider P, Timmermann W, et al. Well-being, mood and calcium homeostasis in patients with hypoparathyroidism receiving standard treatment with calcium and vitamin D. Eur J Endocrinol. 2002;146(2):215-22.

312. Okano K, Furukawa Y, Morii H, and Fujita T. Comparative Efficacy of Various Vitamin D Metabolites in the Treatment of Various Types of Hypoparathyroidism. The Journal of Clinical Endocrinology &amp; Metabolism. 1982;55(2):238-43.

313. Astor MC, Løvås K, Debowska A, Eriksen EF, Evang JA, Fossum C, et al. Epidemiology and Health-Related Quality of Life in Hypoparathyroidism in Norway. The Journal of Clinical Endocrinology &amp; Metabolism. 2016;101(8):3045-53.

314. Mantovani G, Bastepe M, Monk D, de Sanctis L, Thiele S, Ahmed SF, et al. Recommendations for Diagnosis and Treatment of Pseudohypoparathyroidism and Related Disorders: An Updated Practical Tool for Physicians and Patients. Hormone research in paediatrics. 2020;93(3):182-96.

315. Mantovani G, Bastepe M, Monk D, de Sanctis L, Thiele S, Usardi A, et al. Diagnosis and management of pseudohypoparathyroidism and related disorders: first international Consensus Statement. Nat Rev Endocrinol. 2018;14(8):476-500.

316. (FDA) USFaDA. Natpara - Drug Approval Package. <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125511Orig1s000TOC.cfm>.

317. Jolette J, Wilker CE, Smith SY, Doyle N, Hardisty JF, Metcalfe AJ, et al. Defining a Noncarcinogenic Dose of Recombinant Human Parathyroid Hormone 1–84 in a 2-Year Study in Fischer 344 Rats. Toxicologic Pathology. 2006;34(7):929-40.

318. Capriani C, Irani D, and Bilezikian JP. Safety of osteoanabolic therapy: A decade of experience. Journal of Bone and Mineral Research. 2012;27(12):2419-28.

319. Krege JH, Gilsenan AW, Komacko JL, and Kellier-Steele N. Teriparatide and Osteosarcoma Risk: History, Science, Elimination of Boxed Warning, and Other Label Updates. JBMR Plus. 2022;6(9):e10665.

320. Winer KK, Yanovski JA, and Cutler GB, Jr. Synthetic human parathyroid hormone 1-34 vs calcitriol and calcium in the treatment of hypoparathyroidism. Jama. 1996;276(8):631-6.

321. Winer KK, Ko CW, Reynolds JC, Dowdy K, Keil M, Peterson D, et al. Long-Term Treatment of Hypoparathyroidism: A Randomized Controlled Study Comparing Parathyroid Hormone-(1–34)<i>Versus</i>Calcitriol and Calcium. The Journal of Clinical Endocrinology &amp; Metabolism. 2003;88(9):4214-20.

322. Winer KK, Sinaii N, Peterson D, Sainz B, Jr., and Cutler GB, Jr. Effects of once versus twice-daily parathyroid hormone 1-34 therapy in children with hypoparathyroidism. The Journal of clinical endocrinology and metabolism. 2008;93(9):3389-95.

323. Winer KK, Sinaii N, Reynolds J, Peterson D, Dowdy K, and Cutler GB, Jr. Long-term treatment of 12 children with chronic hypoparathyroidism: a randomized trial comparing synthetic human parathyroid hormone 1-34 versus calcitriol and calcium. The Journal of clinical endocrinology and metabolism. 2010;95(6):2680-8.

324. Winer KK, Yanovski JA, Sarani B, and Cutler Jr GB. A Randomized, Cross-Over Trial of Once-Daily Versus Twice-Daily Parathyroid Hormone 1–34 in Treatment of Hypoparathyroidism. The Journal of Clinical Endocrinology &amp; Metabolism. 1998;83(10):3480-6.

325. Winer KK, Fulton KA, Albert PS, and Cutler GB, Jr. Effects of pump versus twice-daily injection delivery of synthetic parathyroid hormone 1-34 in children with severe congenital hypoparathyroidism. The Journal of pediatrics. 2014;165(3):556-63.e1.

326. Winer KK, Zhang B, Shrader JA, Peterson D, Smith M, Albert PS, et al. Synthetic human parathyroid hormone 1-34 replacement therapy: a randomized crossover trial comparing pump versus injections in the treatment of chronic hypoparathyroidism. J Clin Endocrinol Metab. 2012;97(2):391-9.

327. Santonati A, Palermo A, Maddaloni E, Bosco D, Spada A, Grimaldi F, et al. PTH(1–34) for Surgical Hypoparathyroidism: A Prospective, Open-Label Investigation of Efficacy and Quality of Life. The Journal of Clinical Endocrinology &amp; Metabolism. 2015;100(9):3590-7.

328. Mittelman SD, Hendy GN, Fefferman RA, Canaff L, Mosesova I, Cole DEC, et al. A Hypocalcemic Child with a Novel Activating Mutation of the Calcium-Sensing Receptor Gene: Successful Treatment with Recombinant Human Parathyroid Hormone. The Journal of Clinical Endocrinology &amp; Metabolism. 2006;91(7):2474-9.

329. Theman TA, Collins MT, Dempster DW, Zhou H, Reynolds JC, Brahim JS, et al. PTH(1-34) replacement therapy in a child with hypoparathyroidism caused by a sporadic calcium receptor mutation. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2009;24(5):964-73.

330. Clarke BL, Kay Berg J, Fox J, Cyran JA, and Lagast H. Pharmacokinetics and Pharmacodynamics of Subcutaneous Recombinant Parathyroid Hormone (1–84) in Patients With Hypoparathyroidism: An Open-Label, Single-Dose, Phase I Study. Clinical Therapeutics. 2014;36(5):722-36.

331. Rubin MR, Sliney J, McMahon DJ, Silverberg SJ, and Bilezikian JP. Therapy of hypoparathyroidism with intact parathyroid hormone. Osteoporosis International. 2010;21(11):1927-34.

332. Sikjaer T, Amstrup AK, Rolighed L, Kjaer SG, Mosekilde L, and Rejnmark L. PTH(1-84) replacement therapy in hypoparathyroidism: A randomized controlled trial on pharmacokinetic and dynamic effects after 6 months of treatment. Journal of Bone and Mineral Research. 2013;28(10):2232-43.

333. Cusano NE, Rubin MR, McMahon DJ, Irani D, Anderson L, Levy E, et al. PTH(1-84) is associated with improved quality of life in hypoparathyroidism through 5 years of therapy. The Journal of clinical endocrinology and metabolism. 2014;99(10):3694-9.

334. Cusano NE, Rubin MR, McMahon DJ, Zhang C, Ives R, Tulley A, et al. Therapy of Hypoparathyroidism with PTH(1–84): A Prospective Four-Year Investigation of Efficacy and Safety. The Journal of Clinical Endocrinology &amp; Metabolism. 2013;98(1):137-44.

335. Sikjaer T, Rejnmark L, Rolighed L, Heickendorff L, and Mosekilde L. The effect of adding PTH(1-84) to conventional treatment of hypoparathyroidism: A randomized, placebo-controlled study. Journal of Bone and Mineral Research. 2011;26(10):2358-70.

336. Rubin MR, Dempster DW, Sliney J, Jr., Zhou H, Nickolas TL, Stein EM, et al. PTH(1-84) administration reverses abnormal bone-remodeling dynamics and structure in hypoparathyroidism. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2011;26(11):2727-36.

337. Cusano NE, Rubin MR, McMahon DJ, Irani D, Tulley A, Sliney J, Jr., et al. The effect of PTH(1-84) on quality of life in hypoparathyroidism. The Journal of clinical endocrinology and metabolism. 2013;98(6):2356-61.

338. Mannstadt M, Clarke BL, Vokes T, Brandi ML, Ranganath L, Fraser WD, et al. Efficacy and safety of recombinant human parathyroid hormone (1‚Äì84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study. The Lancet Diabetes &amp; Endocrinology. 2013;1(4):275-83.

339. Clarke BL, Vokes TJ, Bilezikian JP, Shoback DM, Lagast H, and Mannstadt M. Effects of parathyroid hormone rhPTH(1-84) on phosphate homeostasis and vitamin D metabolism in hypoparathyroidism: REPLACE phase 3 study. Endocrine. 2017;55(1):273-82.

340. Khan AA, Rubin MR, Schwarz P, Vokes T, Shoback DM, Gagnon C, et al. Efficacy and Safety of Parathyroid Hormone Replacement With TransCon PTH in Hypoparathyroidism: 26-Week Results From the Phase 3 PaTHway Trial. J Bone Miner Res. 2023;38(1):14-25.

341. Nemeth EF, and Goodman WG. Calcimimetic and Calcilytic Drugs: Feats, Flops, and Futures. Calcified tissue international. 2015;98(4):341-58.

342. Dong B, Endo I, Ohnishi Y, Kondo T, Hasegawa T, Amizuka N, et al. Calcilytic Ameliorates Abnormalities of Mutant Calcium-Sensing Receptor (CaSR) Knock-In Mice Mimicking Autosomal Dominant Hypocalcemia (ADH). Journal of Bone and Mineral Research. 2015;30(11):1980-93.

343. Hannan FM, Walls GV, Babinsky VN, Nesbit MA, Kallay E, Hough TA, et al. The Calcilytic Agent NPS 2143 Rectifies Hypocalcemia in a Mouse Model With an Activating Calcium-Sensing Receptor (CaSR) Mutation: Relevance to Autosomal Dominant Hypocalcemia Type 1 (ADH1). Endocrinology. 2015;156(9):3114-21.

344. Roberts MS, Gafni RI, Brillante B, Guthrie LC, Streit J, Gash D, et al. Treatment of Autosomal Dominant Hypocalcemia Type 1 With the Calcilytic NPSP795 (SHP635). Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2019;34(9):1609-18.

345. Hu J, and Spiegel AM. Structure and function of the human calcium-sensing receptor: insights from natural and engineered mutations and allosteric modulators. J Cell Mol Med. 2007;11(5):908-22.

346. Letz S, Haag C, Schulze E, Frank-Raue K, Raue F, Hofner B, et al. Amino alcohol- (NPS-2143) and quinazolinone-derived calcilytics (ATF936 and AXT914) differentially mitigate excessive signalling of calcium-sensing receptor mutants causing Bartter syndrome Type 5 and autosomal dominant hypocalcemia. PLoS One. 2014;9(12):e115178.

347. Letz S, Rus R, Haag C, D√∂rr H-Gn, Schnabel D, M√∂hlig M, et al. Novel Activating Mutations of the Calcium-Sensing Receptor: The Calcilytic NPS-2143 Mitigates Excessive Signal Transduction of Mutant Receptors. The Journal of Clinical Endocrinology &amp; Metabolism. 2010;95(10):E229-E33.

348. Roszko KL, Bi RD, and Mannstadt M. Autosomal Dominant Hypocalcemia (Hypoparathyroidism) Types 1 and 2. Front Physiol. 2016;7:458.

349. Hannan FM, Babinsky VN, and Thakker RV. Disorders of the calcium-sensing receptor and partner proteins: insights into the molecular basis of calcium homeostasis. Journal of molecular endocrinology. 2016;57(3):R127-R42.

350. Babinsky VN, Hannan FM, Gorvin CM, Howles SA, Nesbit MA, Rust N, et al. Allosteric Modulation of the Calcium-sensing Receptor Rectifies Signaling Abnormalities Associated with G-protein Œ±-11 Mutations Causing Hypercalcemic and Hypocalcemic Disorders. The Journal of biological chemistry. 2016;291(20):10876-85.

351. Roszko KL, Bi R, Gorvin CM, Brauner-Osborne H, Xiong XF, Inoue A, et al. Knockin mouse with mutant Galpha(11) mimics human inherited hypocalcemia and is rescued by pharmacologic inhibitors. JCI Insight. 2017;2(3):e91079.

352. Xiong X-F, Zhang H, Underwood CR, Harps√∏e K, Gardella TJ, W√∂ldike MF, et al. Total synthesis and structure-activity relationship studies of a series of selective G protein inhibitors. Nat Chem. 2016;8(11):1035-41.

353. Sato K, Hasegawa Y, Nakae J, Nanao K, Takahashi I, Tajima T, et al. Hydrochlorothiazide Effectively Reduces Urinary Calcium Excretion in Two Japanese Patients with Gain-of-Function Mutations of the Calcium-Sensing Receptor Gene. The Journal of Clinical Endocrinology &amp; Metabolism. 2002;87(7):3068-73.

354. Mantovani G, Ferrante E, Giavoli C, Linglart A, Cappa M, Cisternino M, et al. Recombinant human GH replacement therapy in children with pseudohypoparathyroidism type Ia: first study on the effect on growth. J Clin Endocrinol Metab. 2010;95(11):5011-7.

355. Ertl DA, de Nanclares GP, Juppner H, Hanna P, Pagnano A, Pereda A, et al. Recombinant growth hormone improves growth and adult height in patients with maternal inactivating GNAS mutations. Eur J Endocrinol. 2023;189(1):123-31.

 **-- In memory of Dr. Geoffrey N. Hendy --**