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REVIEW

Acrodysostosis syndromes

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Acrodysostosis (ADO) refers to a heterogeneous group of rare skeletal dysplasia that share characteristic features including severe brachydactyly, facial dysostosis and nasal hypoplasia. The literature describing acrodysostosis cases has been confusing because some reported patients may have had other phenotypically related diseases presenting with Albright Hereditary Osteodystrophy (AHO) such as pseudohypoparathyroidism type 1a (PHP1a) or pseudopseudohypoparathyroidism (PPHP). A question has been whether patients display or not abnormal mineral metabolism associated with resistance to PTH and/or resistance to other hormones that bind G-protein coupled receptors (GPCR) linked to Gsα, as observed in PHP1a. The recent identification in patients affected with acrodysostosis of defects in two genes, *PRKAR1A* and *PDE4D*, both important players in the GPCR–Gsα–cAMP–PKA signaling, has helped clarify some issues regarding the heterogeneity of acrodysostosis, in particular the presence of hormonal resistance. Two different genetic and phenotypic syndromes are now identified, both with a similar bone dysplasia: ADOHR, due to PRKAR1A defects, and ADOP4 (our denomination), due to PDE4D defects. The existence of GPCR-hormone resistance is typical of the ADOHR syndrome. We review here the *PRKAR1A* and *PDE4D* gene defects and phenotypes identified in acrodysostosis syndromes, and discuss them in view of phenotypically related diseases caused by defects in the same signaling pathway.

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Introduction

Acrodysostosis refers to a heterogeneous group of rare skeletal dysplasia that share characteristic features, including severe brachydactyly, facial dysostosis and nasal hypoplasia[1–4] (**Figure 1**). Two sources of confusion had plagued the older literature describing patients with acrodysostosis. First, some reported patients may have had other phenotypically related diseases presenting with Albright hereditary osteodystrophy (AHO), such as pseudohypoparathyroidism type 1a (PHP1a, MIM103580) or pseudopseudohypoparathyroidism (PPHP, MIM 612463).[5–7] Second, it remained unclear whether patients displayed abnormal mineral metabolism associated with resistance to parathyroid hormone (PTH) and/or resistance to other hormones that bind G-protein-coupled receptors (GPCR) linked to Gsα, as is observed in PHP1a. Both of these issues have now been resolved in large measure by recent studies exploring the etiology of acrodysostosis.

Patients affected with acrodysostosis have been found to have genetic defects in one of two distinct genes, those coding for the type 1 regulatory subunit of cAMP-dependent protein kinase alpha (*PRKAR1A*)[8] or the cAMP-specific phosphodiesterase 4D (*PDE4D*).[9,10] As a consequence, genetic testing can now unambiguously establish the diagnosis in most patients.[8–13] Both of these proteins are important components in the GPCR-Gsα-cAMP-protein kinase A (PKA) signaling pathway.[14,15] Nevertheless, the impact of these mutations is different in different tissues, thereby explaining the phenotypic heterogeneity observed in acrodysostosis, and in particular the presence or absence of hormonal resistance. Two distinct genetic and phenotypic syndromes can now be identified that share common similar features of bone dysplasia: acrodysostosis with hormonal resistance (ADOHR), resulting from *PRKAR1A* defects, and acrodysostosis due to *PDE4D* defects (ADOP4) (our denomination).[11] As its name suggests, GPCR hormonal resistance is typical only of the ADOHR syndrome.

In this review, we discuss (i) the *PRKAR1A* and *PDE4D* gene defects, (ii) the phenotypic features that distinguish the two genotypes causing acrodysostosis and (iii), briefly, the pheno-

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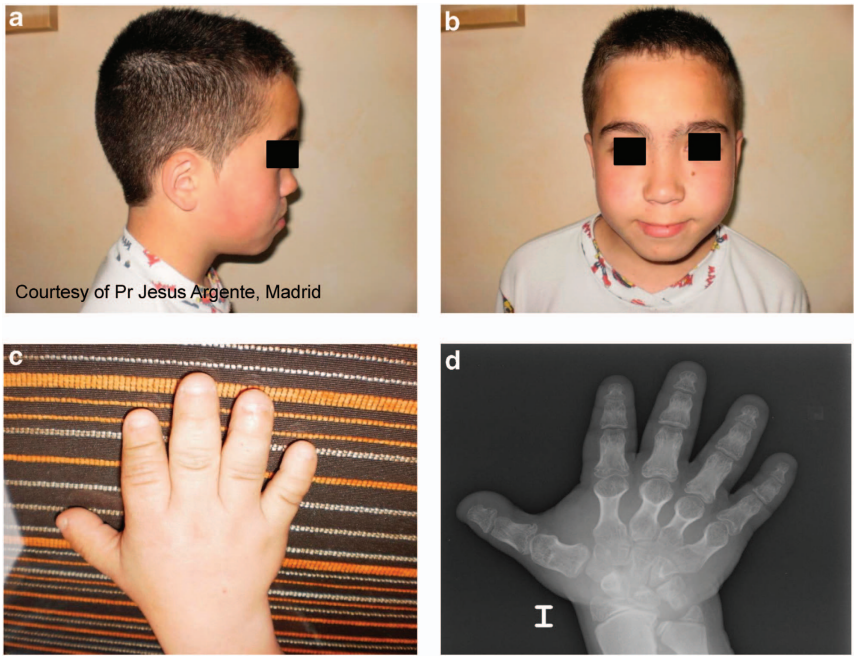

Figure 1 Photographs and X rays of the face and hand of a 12-year-old patient affected with ADOHR resulting from the R368X mutation in *PRKAR1A*. (**a**) Side and (**b**) front photographs of the face. Note the facial dysostosis and severe maxilla-nasal hypoplasia. Photograph (**c**) and radiograph (**d**) of the left hand. Note the shortening of all metacarpals and phalanges, and the bulky and stocky aspect of all the affected bones. Standard X-rays show the short and broad metacarpals and phalanges, the cone-shaped epiphyses and advanced carpal and tarsal maturation.

typic features that distinguish patients with ADOHR and other diseases resulting from defects in the PTH/PTH-related protein (PTHrP) receptor (PTH1R) signaling pathway, including PHP1a/PPHP. A review of the literature on acrodysostosis, including discussion of the features that distinguish ADOHR and these other diseases resulting from defects in the PTH1R signaling pathway, has been recently published.[16]

Genetic Defects

Defects in *PRKAR1A* and *PDE4D* were identified by candidate gene analysis in 2011[8] and exome sequencing in 2012.[9,10] To date, 39 patients with acrodysostosis have been screened for genetic defects.[8–13] All cases were sporadic, except for one family carrying a *PDE4D* mutation.[13] Mutations in *PRKAR1A* and *PDE4D* were identified in 22 and 17 patients, respectively. The disorder occurred in families of different ethnic background, and appears to affect male and female individuals with equal frequency (**Table 1**). *PRKAR1A* and *PDE4D* mutations identified in acrodysostosis were absent in all parents and siblings tested (except for the family reported[13]), and none has been observed in controls or database sequences. All mutations are heterozygous; all mutated residues are stringently conserved across mammalian species.

PRKAR1A. PKA is the most common effector of cAMP. In the absence of cAMP, PKA exists as a tetramer with two regulatory subunits locking the two catalytic subunits in an inactive state. A number of isoforms of both regulatory and catalytic subunits have been described;[14,15,17–19] PRKAR1A is the most abundantly expressed regulatory subunit. It is composed of a dimerization domain, an inhibitory site and two cAMP-binding domains (domains A and B), each containing a phosphate-binding cassette (**Figure 2**). Activation of the PKA enzyme requires the release of the catalytic subunits, which is triggered by the sequential binding of cAMP molecules first to domain B and then to domain A of each regulatory subunit.

Table 1 Male/female prevalence of ADOHR and ADOP4 in reported series

ADOHR		*ADOP4*		*Ref*
M	F	M	F	
7	7		2	8,11
1	4	4		10
2		2	1	9
	1			12
		5	3	13

Abbreviations: ADOHR, acrodysostosis with hormonal resistance; ADOP4, acrodysostosis due to *PDE4D* defects; F, female; M, male.

PRKAR1A mutations identified in acrodysostosis. To date, nine missense *PRKAR1A* (reference NM_002734, NP_002725) mutations associated with acrodysostosis have been identified in 22 patients[8–12] (**Figure 2**). The first-described mutation, R368X, initially identified in three patients,[8] has subsequently been found in 10 additional patients, confirming that it is recurrent. Each of the other eight mutations was identified in a single patient. Eight mutations are localized in domain B and one in domain A (T239A) (**Figure 2**).

PRKAR1A: *functional defect*. Western blot analysis of mutant proteins performed either in cells from patients or following transfection demonstrated that all mutant proteins are expressed[8,12] (unpublished results). Functional analysis has

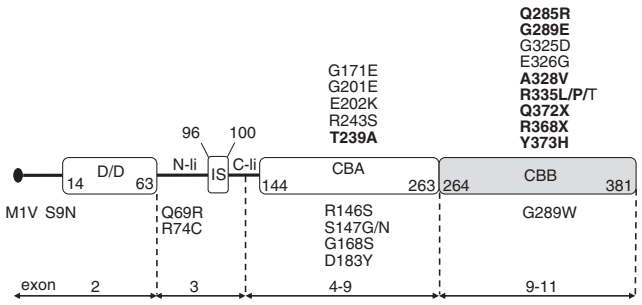

Figure 2 Schematic representation of PRKAR1A indicating the functionally important domains. The numbers indicate the amino-acid residues at the domain boundaries (NP_002725). The exons coding for the domains are also indicated. The activatory mutations identified in ADOHR patients (bold) and in cell lines are indicated above the diagram. Inhibitory point mutations identified in patients with the Carney complex are indicated below the diagram. DD, dimerization domain; N-li, N-linker; IS, inhibitory site; C-li, C linker; CBA and CBB, cAMP-binding domain A and B.

been performed using either Cre-luciferase reporter assays after expressing mutant proteins in either COS cells (R368X and Y373A) or HEK 293 cells (T239A), BRET (bioluminescence resonance energy transfer) technology (R368X and Y373A mutants) and Western blot analysis of P-CREB (phospho-cAMP response element-binding protein) expression in patient-derived lymphoblastoid cell lines[8,12] (unpublished results). Taken together, results of these studies demonstrate that the mutations cause a defect in PKA activation by cAMP, associated with a decreased responsiveness of PKA to cAMP. In agreement, creb phosphorylation was reduced in cells from patients compared with cells from controls. Thus, the mutants act as a dominant negative for PKA function and partially inactivate the catalytic subunit.

Other PRKAR1A *gain-of-function mutations in cell lines*. Spontaneously occurring point mutations in PRKAR1A proteins leading to a decreased affinity of domain A or B for cAMP have been identified in clones of cAMP-resistant mouse S49 lymphoma and Y1 adrenocortical tumor cells (**Figure 2**).[20–22] These mutations act also in a dominant manner to repress PKA activity. One residue (R335) has been found affected by different substitutions, both in patients and in cell lines, indicating that the codon for this residue may be a hot spot for mutation. A mouse model expressing one such dominant-negative mutation (G325D) in a cell-specific manner has been recently described.[23]

Dominant-negative effect of PRKAR1A *mutations for PKA function*. The dominant-negative effect of the mutations is mostly attributable to the preferential binding of catalytic subunits to mutant regulatory subunits in cells heterozygous for the mutation, forming either tetrameric kinases with mutant regulatory subunit homodimers or trimeric kinases with regulatory subunit wild-type–mutant heterodimers.[14,24] This results in preferential stabilization of mutant regulatory subunits, but preferential release and accelerated degradation of wild-type PRKAR1A subunits, ultimately leading to the suppression of kinase activation. Indeed, we found that mutated PRKAR1A was present at higher levels than the wild-type protein in cells from patients, a finding that is consistent with a faster rate of degradation of wild-type PRKAR1A subunits compared with that of abnormal PRKAR1A subunits.[8] It is important to emphasize, however, that the mutations identified in patients and in cells lead to an impairment, not a total absence, of PKA activity.

PRKAR1A loss-of-function mutations. *PRKAR1A* 'loss-of-function' mutations leading to unrestrained PKA activity have been identified in patients with the Carney complex (OMIM #160980).[25–28] Most of the mutations result in the degradation of mRNA by nonsense-mediated decay and therefore haploinsufficiency at the level of the protein expression. Several missense mutations or in-frame deletions/insertions resulting in the expression of modified proteins have also been identified[27,28] (**Figure 2**). These mutations have been shown to increase cAMP-specific PKA activation, but may do so through a variety of different mechanisms, including accelerated degradation of the mutant proteins due to structural abnormalities, alteration of the interaction with the catalytic subunit and facilitation of cAMP binding to the regulatory subunits, thereby accelerating their dissociation from the catalytic subunits in response to cAMP.

A G289E substitution located in the cAMP-binding site B, identified in a patient with acrodysosotosis, modifies a glycine residue previously found to be mutated (G289W) in the Carney complex.[27,28] On the basis of the ADOHR patient phenotype, we speculate that the G289E mutation alters the binding of cAMP, as demonstrated for the R368X, Y373A[8] and T239A mutations,[29] whereas the G289W mutation, which replaces the smallest amino acid with the biggest one, may alter the protein structure, resulting in accelerated degradation and haploinsufficiency typically observed in the Carney complex. Previous examples of different substitutions affecting the same amino acid but causing different effects on protein function have been described in the literature.

PDE4D. *PDE4D* (Reference NP_001098101, NM_001104631) encodes PDE4D, a class IV cAMP-specific PDE that hydrolyzes cAMP, and this enzyme is thought to make important contributions to control the specificity and temporal/spatial compartmentalization of cAMP-induced PKA signaling.[30] In humans, the members of the PDE4D family are derived from a single gene, but consist of at least nine isoforms that arise through differential splicing events that modify the N-terminal region of the protein. Six of the isoforms are classified as 'long' (PDE4D 3, 4, 5, 7, 8 and 9), two as 'short' (PDE4D 1 and 2) and one as 'super-short' (PDE4D 6).[31,32] All isoforms express the same C-terminal catalytic domain. All long isoforms express the upstream conserved region 1 (ucr1), and all isoforms except the super-short isoform express the upstream conserved region 2 (ucr2). Little is known about the specific expression, function and regulation of these isoforms in human tissues.

PDE4D *mutations identified in acrodysostosis*. To date, 12 missense *PDE4D* mutations associated with acrodysostosis have been identified in 17 patients (**Figure 3**).[9–11,13] One mutation (E590A) was found in two patients. Six mutations involve amino acids located in ucr1 shared by all the long isoforms. One of these mutations affects a PKA consensus phosphorylation site, and four affect contiguous amino acids. Three mutations are in ucr2. Three mutations cause missense mutations in the catalytic region. Notably, the mutations identified in *PDE4D* are located on the three main functional domains, indicating that

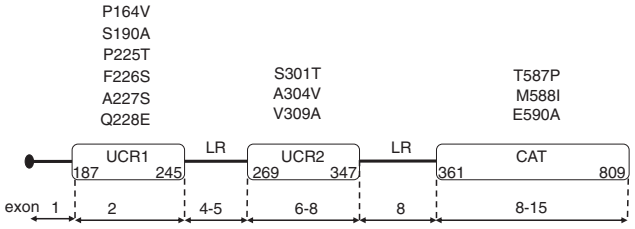

Figure 3 Schematic representation of long isoforms of PDE4D indicating the functionally important domains. The numbers indicate the amino-acid residues at the domain boundaries (NP_001098101). The exons coding for the domains are also indicated. The catalytic domain is shared by all isoforms, the upstream conserved region 1 (ucr1) is shared by all long isoforms, and the upstream conserved region 2 (ucr2) is shared by all isoforms except for the super-short isoform. The missense mutations identified in patients with ADOP4 are shown above the diagram. UCR, upstream conserved region; LR, linker region; Cat, catalytic domain.

defects in all isoforms (long, short and super-short) can cause ADOP4 (**Figure 3**).

PDE4D: functional defect. Functional studies of the mutant PDE4D proteins have not been performed, and the evidence supporting the pathogenicity of the putative causative *PDE4D* mutations is not as established as in the case of *PRKAR1A*. On the basis of the bone phenotype, the mutations are expected to cause a defect in PKA activation, at least in endochondral bone (see below). As PDEs catabolize cAMP, and the mutations are heterozygous, we speculate that the mutations lead to a dominant gain of function. Interestingly, and supporting our hypothesis, heterozygous loss-of-function mutations in two other PDE family members, PDE11A and PDE8B, have been associated with adrenal hyperplasia, a major clinical feature of the Carney complex.[33–35] A murine model of *PDE4D* deficiency has been developed.[36] Mice with homozygous *PDE4D* deficiency exhibited delayed growth at birth, but growth rate returned to normal after 2 weeks. This phenotype appears to be different from that seen in acrodysostosis. In addition, the PDE4D$^{+/-}$ mice had a phenotype similar to the PDE4D$^{+/+}$ mice, an observation that also differs from the acrodysostosis patients. Clearly, additional functional studies exploring the PDE4D mutants *in vivo* and *in vitro* will be of great interest.

Inheritance. Genetic inheritance of acrodysostosis has not yet been reported in ADOHR.[16] Observations of familial ADOHR with apparent autosomal dominant inheritance have been reported on the basis of phenotypic criteria. Autosomal dominant inheritance has been reported for one family carrying a *PDE4D* mutation.[13]

Phenotypic Similarities and Differences Associated with PRKAR1a and PDE4D Mutations causing Acrodysostosis

Acrodysostosis. *Features*. The dysostosis characterizing acrodysostosis is similar in patients affected by ADOHR and ADOP4. Typical clinical features comprise a facial dysostosis (broad face, widely spaced eyes, maxillonasal hypoplasia) associated with a peripheral dysostosis characterized by small broad hands and feet with stubby digits, except for the big toe, which is enlarged[1–4] (**Figure 1**). Adults usually have a severe short stature (-3 to -5 SD).

A number of radiological abnormalities have been identified. Typically, patients have hypoplasia of the skull and thickened calvaria. All tubular bones of the hands and feet are symmetrically affected by a severe brachydactyly type E (BDE) and present cone-shaped epiphyses with early epiphyseal fusion.[1–4,11] Most patients have a loss of the widening of the lumbar interpediculate distance that typically occurs in the cephalocaudal direction. In the majority of patients evaluated during childhood or adolescence, bone age is advanced.[11,16]

Abnormalities restricted to a subgroup of patients have also been observed. Two of 22 individuals with ADOHR had brachymetacarpy and/or brachymetatarsy that were more severe in certain digits. In one patient, a brachymetacarpy affecting mostly the fourth and fifth digits and a brachymetatarsy affecting mostly the third to fifth digits was observed, and the other patient had a brachymetatarsy affecting predominantly the third and fourth digits. In these cases, as in other patients with acrodysostosis, however, all digits were affected to some extent.[11] Each of these patients carried a different, previously undescribed *PRKAR1A* mutation (not R368X).

Although generally similar, some differences in the dysostosis seen in ADOHR and ADOP4 have been noted. The maxillo-nasal hypoplasia with flattening of nasal ridge appears to be more severe in ADOP4 patients.[10,11] One patient with ADOP4 was originally diagnosed as having acroskyphodysplasia.[11] The majority of patients with ADOHR are born small for gestational age, and this does not appear to be the case for patients with ADOP4.[10,11] Some patients with ADOP4 do not present a short stature.[13]

Pathogenesis. As indicated above, the skeletal phenotype defining acrodysostosis is quite similar in ADOHR and ADOP4. A major characteristic is the severity of the BDE, with severe and symmetrical growth defects seen in all tubular bones of the hands and feet (metacarpals and metatarsals and/or phalanges, except the big toes). Affected bones, in particular the tubular bones of the hands and feet, develop through endochondral ossification, a process highly regulated by ligand–receptor interactions between PTHrP and PTH1R.[37,38] PTH1R belongs to the group B of the GPCR family, and signals mainly through the Gsα-cAMP-PKA pathway.[39] Inhibition of this pathway accelerates the normal differentiation process of growth plate chondrocytes, and leads to advanced skeletal maturation. We speculate that most of the skeletal abnormalities in acrodysostosis result from the impairment in PKA activation by PTHrP due to *PRKAR1A* or *PDE4D* mutations. Accordingly, some features of the dysostosis, and in particular the BDE, are reminiscent of defects to that observed in AHO caused by Gsα haploinsufficiency,[40] and in Blomstrand lethal chondrodysplasia, caused by homozygous or compound heterozygous inactivating mutations in the PTH1R.[41] The BDE in AHO is variable and affects most frequently the fourth and fifth metacarpals. In Blomstrand lethal chondrodysplasia, it is extremely severe and associated with a major advance in skeletal maturation. Thus, the severity of the abnormalities seen in acrodysostosis are intermediate between those seen in these two entities.

Hormonal resistance. *Features*. Resistance to hormones acting through GPCR-Gsα-cAMP-PKA signaling pathway, and

in particular PTH and thyroid-stimulating hormone (TSH), has been analyzed in 20/22 patients with ADOHR and in 14/17 patients with ADOP4.[8,10–13] All patients with ADOHR were resistant to PTH, as indicated by increased circulating PTH levels in the presence of low or normal serum calcium, and normal or increased serum phosphate, and in the absence of vitamin D deficiency or renal insufficiency. ADOHR patients had increased basal urinary cAMP levels and showed a sharp rise in urinary cAMP after infusion of recombinant PTH, consistent with a defect in the PTH-GPCR-Gsα-cAMP pathway downstream of adenylyl cyclase.[8] In ADOHR, resistance to TSH was documented by increased TSH with normal or low thyroxine levels in 16/20 patients. Current evidence indicates that responses to LH, FSH, calcitonin, GHRH and epinephrine are also altered in some patients with PRKAR1A mutations and ADOHR, but to a variable extent, as has also been described for PHP1a. One patient with the R368X *PRKAR1A* mutation gave birth to a normal child after a spontaneous pregnancy, indicating the absence of infertility.[11]

By contrast, neither PTH nor TSH resistance has been consistently observed in ADOP4 patients.[8,10,11,13] One ADOP4 patient (the only studied for this parameter) had basal urinary cAMP levels that were within the normal range, and no obvious alterations in renal cAMP production were present.[11] One ADOP4 patient, for whom the possibility of PTH resistance was raised, may have had vitamin D deficiency, which would explain his normal serum phosphate, low 25-OH cholecalciferol and high serum PTH.[10] Congenital hypothyroidism was reported in two ADOP4 patients.[9,13]

Pathogenesis. Thus, it appears that PRKAR1A but not PDE4D patients express a general resistance to hormones acting through GPCR-Gsα-cAMP-PKA signaling, shared by numerous agonists.[39]

The observation that *PRKAR1A* mutations result in a broad phenotype of GPCR-Gsα-cAMP-PKA resistance, causing skeletal dysostosis and hormonal resistance, is likely due to the fact that PRKAR1A is the most abundantly expressed and ubiquitous regulatory subunit of PKA, the most common downstream effector of cAMP. The phenotype is broadly reminiscent of PHP1a,[40,42] where maternally inherited loss of function in *GNAS*, the post-receptor regulator of the GPCR-Gsα-cAMP pathway, results in resistance to PTH and TSH and in a somewhat comparable skeletal dysplasia (see below).

In contrast to patients with ADOHR, patients with ADOP4 do not demonstrate obvious abnormalities in mineral metabolism or renal cAMP production, as would be expected if renal PTH hormonal resistance were present. However, the presence of the dysostosis indicates that there is a defect in the cAMP signaling pathway in skeletal tissues. A possible explanation for these differences is that the affected PDE4D isoforms are not similarly active in different tissues, which could explain the absence of PTH resistance in the kidney but the presence of PTHrP resistance in the growth plate, thereby accounting for the bone phenotype. Alternatively, PDE4D may be expressed in both renal proximal tubule and bone cells, but not involved in the renal response to PTH. It is also possible that there is some phenotypic variability in the biochemical and endocrine consequences of the PDE4D mutations. Clearly, evaluation of additional patients affected with ADOP4 will be required to confirm these findings. These findings highlight the specific contributions of PRKAR1A and PDE4D in cAMP signaling in different tissues.

Mental retardation. Mental retardation was reported in 8/9 ADOP4 patients.[9–11] Patients with ADOHR do not present with mental retardation, although behavioral disorders were observed in 7/19 patients for whom information was available, and mild developmental disabilities were noted in four.[8–12] Mild-to-moderate mental retardation is common in patients with PHP1a and Gsα deficiency.[40] In some of these cases, retardation may be, at least in part, a consequence of hypocalcemia and hypothyroidism. Controlling these abnormalities, however, has not always prevented cognitive dysfunction, raising the possibility that other mechanisms, such as an abnormality in neurotransmitter signaling, may be involved. Taken together, these results illustrate the important role played by the Gsα-cAMP-PKA signaling pathway in the central nervous system and its influence on the development of specific cognitive and psychic brain functions. Careful evaluation of intellectual abilities and neuronal activity of patients should provide insights into the role of the different components of this pathway in cerebral functions such as learning and memory.

Subcutaneous ossification. Subcutaneous ectopic ossifications are not reported in ADOHR and ADOP4. One patient with the recurrent R368X *PRKAR1A* mutation presented calcifications of the central nervous system.[8]

Skin spots. The presence of pigmented skin spots was evaluated in 16 patients with acrodysostosis for whom genetic analysis was also performed. Pigmented skin spots were observed in 7/14 and 1/2 patients, respectively, with ADOHR and ADOP4.[11] These lesions are reminiscent of the café-au-lait spots observed in the McCune Albright syndrome[43] and the Carney complex,[44] two diseases associated with constitutive activation of the PKA-mediated pathway downstream of the melanocortin 1 receptor.

Acrodysostosis and Other Diseases Resulting from LOF Defects in the PTH1R/Gsα/cAMP/PKA Pathway

For recent reviews, refer to.[16,41]

PTHLH. Heterozygous loss-of-function mutations in *PTHLH*, the gene coding PTHrP, an agonist equipotent with PTH for stimulation of PTH1R, cause autosomal-dominant BDE associated with short stature.[45–47] The BDE is fairly mild with variable expressivity. No hormonal resistance is present, as expected.

PTH1R. As indicated above, compound heterozygous or homozygous inactivating mutations in *PTH1R* lead to Blomstrand's lethal chondrodysplasia (OMIM #215045), an autosomal recessive disorder characterized by strikingly accelerated chondrocyte differentiation and multiple additional abnormalities.

Gsα/GNAS locus. The *GNAS* locus encodes four alternative transcripts in addition to Gsα, and is imprinted in a tissue-specific manner.[42] Genetic and epigenetic defects in the *GNAS* locus cause, according to their allelic origin, the heterogeneous syndromic diseases, pseudohypoparathyroidism (PHP), PPHP and progressive osseous heteroplasia. The distinction between

Table 2 Major distinct features associated with *PRKAR1A* and *PDE4D* heterozygous mutations and maternally inherited Gsα mutation

Gene defect	*PRKAR1A*	*PDE4D*	*Gsα*
Functional defect	Gain of function	Gain of function (putative)	Loss of function
Disease	Acrodysostosis/ADOHR	Acrodysostosis/ADOP4	PHP1a
Transmission	Sporadic/AD	Sporadic/AD	AD/maternally inherited
Peripheral dysostosis			
Short stature	++	+/−	+
Onset	Prenatal	?	Post natal
Face	Nasal/maxillary hypoplasia	Nasal/maxillary hypoplasia	Rounded
Brachydactyly	Severe[a]	Severe	Variable
Cone-shaped epiphyses	Constant	Constant	Discussed
Resistance to hormones signaling through cAMP			
PTH/TSH	+/+	−/−	++/++
PTHrP	++	++	+
Others	+	?	+
Intellectual ability	Behavorial disorder/no mental retardation	Mental retardation	Moderate mental retardation
Subcutaneous ossifications	Not reported	Not reported	+
Pigmentary skin spots	+	+	No

Abbreviations: AD, autosomal dominant; ADOHR, acrodysostosis with hormonal resistance; ADOP4, acrodysostosis due to *PDE4D* defects; PDE4D, phosphodiesterase 4D; PHP1a, pseudohypoparathyroidism type 1a; PRKAR1A, type 1 regulatory subunit of cAMP-dependent protein kinase alpha; PTH, parathyroid hormone; PTHrP, PTH-related protein; TSH, thyroid-stimulating hormone.
[a]2/22 patients with acrodysostosis each with a novel *PRKAR1A* mutation presented some variability in the brachydactyly reminiscent of that observed in PHP1a.[11]

these pathologies relies essentially on the presence or absence of the AHO and of hormonal resistance, in particular, to PTH. AHO is a constellation of variable developmental and skeletal defects, including BDE, caused by Gsα haploinsufficiency.[40] Paternally inherited heterozygous inactivating germ-line mutations in *GNAS* cause PPHP (typically characterized by the presence of AHO and the absence of hormonal resistance) and progressive osseous heteroplasia (OMIM #166350). Maternally inherited heterozygous inactivating germ-line mutations in *GNAS* cause PHP1a, characterized by the presence of AHO and hormonal resistance. Maternally inherited epigenetic defects in the *GNAS* locus cause PHP1b, typically characterized by resistance to PTH and no AHO.

Since the first reports, some clinical and radiological findings in acrodysostosis were noted to be similar to those observed in PHP1a/PPHP syndromes.[5–7] However, distinct differences exist[16] (**Table 2**). In particular, although both conditions present with stocky appearance and BDE, the brachydactyly in the PHP1a/PPHP syndromes is of variable severity. By contrast, the skeletal phenotype in both ADOHR and ADOP4 is severe and quite stereotypic. In contrast to the skeletal dysplasia, resistance to PTH and other hormones signaling through GPCR, such as TSH, are less pronounced in ADOHR than in PHP1a and absent in ADOP4.

An overlap may exist, however, between the features of brachydactyly in patients with acrodysostosis and PHP. As indicated above, occasional patients with ADOHR present brachydactyly affecting more severely the fourth and fifth metacarpals. Conversely, some patients with PHP1a and maternally inherited Gsα mutations can present with a severe metacarpy and metatarsy, resembling that typically seen in ADOP4 and ADOHR, although phalanges are usually spared in PHP1a. Although patients with PHP1b usually lack evidence of AHO, mild AHO and brachydactyly have been reported in a few patients with PHP1b and *GNAS* methylation defects.[48,49] Thus, patients with BDE with or without hormone resistance should be evaluated for a panel of genetic alterations, including *GNAS*, *PRKAR1A*, *PDE4D* and *PTHLH*, as well as epigenetic alterations within the *GNAS* locus.

HDAC4. Heterozygous deletions or mutations of *HDAC4* coding for histone deacetylase 4 have been identified in patients with Brachydactyly Mental Retardation Syndrome. This syndrome presents with a range of features, including intellectual disabilities, developmental delays, behavioral abnormalities, autism spectrum disorder and craniofacial and skeletal abnormalities comprising BDE.[50] Interestingly, a link between PTHrP–PKA signaling and HDAC4 regulation of chondrocyte differentiation has been demonstrated.[51]

Acrodysostosis and Other Gene Defects

Michot *et al.*[10] reported one patient with acrodysostosis without maxillonasal hypoplasia and no evidence of hormonal resistance, in whom they could not identify point mutations in the coding sequence of *PRKAR1A* or *PDE4D*.

Conclusion

In conclusion, a recent series of studies evaluating patients with acrodysostosis syndrome has allowed the subdivision of this entity into two different genetic and phenotypic diseases referred here as ADOHR, resulting from mutations in *PRKAR1A*, and ADOP4, resulting from mutations in *PDE4D*. GPCR hormone resistance is typical only of the ADOHR syndrome. In addition to clarifying the etiology of these diseases, these results highlight the specific contributions of PRKAR1A and PDE4D in cAMP signaling in different tissues, and the key role played by the GPCR-Gsα-cAMP-PKA signaling pathway and its

specific effectors for the development of cognitive functions. Additional *in vivo* and *in vitro* work exploring the function of PDE4D mutants will be of great interest, as will be the study of the molecular mechanisms leading to similar pigmented skin lesions in genetic disorders resulting from both constitutive inhibition and activation of the PKA-mediated pathway. Finally, current evidence does not exclude the possibility that defects in other genes can cause acrodysostosis with or without hormonal resistance.

Conflict of Interest

The authors declare no conflict of interest.

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