Imprinting in Albright's hereditary osteodystrophy

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Abstract

Review of published reports of Albright's hereditary osteodystrophy (AHO) involving two or more generations shows a marked excess of maternal transmission. Full expression of the gene (AHO + hormone resistance, pseudohypoparathyroidism) occurs in maternally transmitted cases and partial expression (AHO alone) when the gene is inherited from the father, suggesting the involvement of genomic imprinting in the expression of this disorder.

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Albright *et al*[1] first described a syndrome with characteristic features of short stature, round face, obesity, brachydactyly, and subcutaneous calcification in the presence of hypocalcaemia and parathormone resistance (pseudohypoparathyroidism, PHP). They further used the term pseudopseudohypoparathyroidism (PPHP) for those patients with the somatic features but normal biochemistry.[2] Mann *et al*[3] described a mother and son with complete expression (PHP) in successive generations and considered PPHP to be incomplete expression of the same genetic condition. Sex linked dominant inheritance was invoked to explain the initially described 2:1 ratio of affected females to males, but autosomal dominant transmission with probable sex modification of expression has now been suggested.[4]

A markedly reduced urinary cyclic AMP response to exogenous parathormone was found in some patients with PHP (type 1 PHP).[5] The guanine nucleotide regulatory (Gs) protein activity, which activates adenyl cyclase and increases cAMP, was reduced in the erythrocytes of patients with type 1 PHP.[6] These patients with reduced Gs protein activity have been designated type 1a PHP. Most patients with AHO have type 1a PHP[7] and multiple resistance to hormones which act by increasing cAMP.[8] Reduced Gs protein activity to 50% of normal control values has been described in families with AHO, both in hypocalcaemic and normocalcaemic members,[9] and dominant inheritance has been confirmed by male to male transmission.[10] The alpha unit of the Gs protein is encoded by a single 13 exon gene spanning 20 kilobases[11] and mutations have been described in this gene in families with AHO.[12]

The conundrum of AHO is why some family members have the somatic features with resistance to parathormone and other hormones which act via cAMP, while others have the somatic features alone. A review of published reports presented here indicates that expression in the offspring depends on the sex of the transmitting parent and is likely to result from genomic imprinting.

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Methods

Published reports concerning AHO and pseudohypoparathyroidism were reviewed and 57 pedigrees with suggested transmission through two or more generations were ascertained. Care was taken to exclude duplicated reports of the same family. Because of the difficulty in differentiating between AHO without hormone deficiency (PPHP) and other conditions with short stature and brachydactyly, we excluded pedigrees of AHO without biochemical detail[13-16] and those in which there was doubt about the diagnosis of pseudopseudohypoparathyroidism in the presence of familial multiple exostoses[17] and growth hormone releasing factor deficiency.[18] Fifty-one remaining pedigrees were scrutinised for adequate clinical, biochemical, and, when available, molecular data to confirm which parent was affected and to determine the severity of expression in parent and offspring. In total, 31 such definite families were ascertained.[3 7 9 10 12 19-31] In the remaining 20 reports there was insufficient detail to verify the affected parent.[21 32-49] The family originally reported by Kinard *et al*[50] in 1979 of four affected daughters whose father was deemed to be affected on the basis of a short fifth metacarpal was reported again in 1990 by Weinstein *et al*,[12] indicating that the father had an old injury of his metacarpal while the mother had clinical and molecular evidence of carrying the allele, and therefore is included in the study as a family with maternal transmission.

Results

In the 31 reports of AHO in two or more generations, 36 parent to child transmissions were noted. Of these, 33 were maternal transmissions and three were paternal, that is, 33 out of 36 transmitting parents (92%) were female (95% confidence interval of 78–98, $p = 2{\cdot}3 \times 10^{-7}$). The transmitting parents included those in whom the syndrome was fully (AHO + hormone resistance) and partially (AHO alone) expressed (table 1).

There were 66 affected offspring, 36 females and 30 males, which is not significantly different from the 1:1 ratio expected in dominant inheritance (table 2). The 60 offspring who had inherited the gene from their mother had full expression of the syndrome; the six offspring with paternal transmission all had par-

Table 1 Transmitting parents.

Pedigrees	31
Transmitting parents	36
Maternal	33
AHO+	9
AHO−	24
Paternal	3
AHO+	2
AHO−	1

Table 2 Affected offspring.

Affected offspring	66
Female	36
AHO+	33
AHO−	3
Male	30
AHO+	27
AHO−	3

tial expression (table 3). A two tailed Fisher 'exact' test for the hypothesis of a difference between the observed proportions of 60/60 and 0/6 yields $p = 2{\cdot}2 \times 10^{-8}$.

Discussion

Inheritance of AHO with hormone resistance (type 1a PHP) has been difficult to explain because of the apparent excess of affected females and the presence within known families of members with the same somatic features (AHO) but no evidence of hormone resistance (PPHP). The significant excess of maternal transmission has been previously attributed to reduced fertility in affected males.[4] Recent molecular investigation of Gs protein in these families has shown the same reduction in Gs protein activity and the same mutation in both AHO+ and AHO− family members.[9] Theories suggested to explain this variable expression have included an added effect of vitamin D levels,[51] interaction of alleles giving metabolic interference,[52] and anticipation.[31]

Our study suggests that full expression in AHO is associated with inheritance of the maternally transmitted allele, while inheritance of the paternally transmitted allele results in partial expression irrespective of the expression in the parent. The excess of AHO females could be explained by increased ascertainment of transmitting mothers through their classically affected children. The differential effect of the gene depending on whether it is maternally or paternally transmitted suggests a role for genetic imprinting in AHO as has been suggested in other dominantly inherited conditions.[53 54]

The gene for Gs protein has been mapped to chromosome 20q13.11 which is homologous to mouse chromosome area 2H(T1Sn–T28H) involved in both maternal and paternal imprinting and AHO already has been suggested by Hall[55] as a candidate disease for imprinting by virtue of location to this area. To explain the presence of the molecular defect and somatic features in all AHO patients, but with hormone resistance only in those who have inherited the allele from their mother, requires tissue specific parental imprinting, a phenomenon which has been described in the IGF-11 gene in the mouse.[56] Further study will elucidate whether tissue specific imprinting of maternally and paternally inherited alleles accounts for unusual inheritance and variable expression found in other dominantly inherited conditions.

Table 3 Expression in affected offspring of transmitting parents.

Offspring		
AHO+	60	0
AHO−	0	6

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