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 PHP⁷ 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 kilobases¹¹ 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.

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 detail¹³⁻¹⁶ and those in which there was doubt about the diagnosis of pseudopseudohypoparathyroidism in the presence of familial multiple exostoses¹⁷ 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, $p=2.3 \times 10^{-7}$). 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-

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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 $p = 2.2 \times 10^{-8}$.

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 Hall⁵⁵ 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.

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- Albright F, Burnett CH, Smith PH, Parson W. Pseudohypoparathyroidism - an example of 'Seabright Bantam syndrome'. *Endocrinology* 1942;30:922-32.
- Albright F, Forbes AP, Henneman PH. Pseudo-pseudohypoparathyroidism. *Trans Assoc Am Physicians* 1952;65:337-50.
- Mann JB, Alterman MD, Hills AG. Albright's hereditary osteodystrophy comprising pseudohypoparathyroidism and pseudo-pseudohypoparathyroidism. *Ann Intern Med* 1962;56:315-42.
- Fitch N. Albright's hereditary osteodystrophy: a review. *Am J Med Genet* 1982;11:11-29.
- Chase LR, Melson GL, Aurbach GD. Pseudohypoparathyroidism: defective secretion of 3',5'-AMP in response to parathyroid hormone. *J Clin Invest* 1969;48:1832-44.
- Levine MA, Downs RW Jr, Singer M, Marx SJ, Aurbach GD, Spiegel AM. Deficient activity of guanine nucleotide regulatory protein in erythrocytes from patients with pseudohypoparathyroidism. *Biochem Biophys Res Commun* 1980;94:1319-24.
- Levine MA, Jap T, Mauseth RS, Downs RW, Spiegel AM. Activity of the stimulatory guanine nucleotide-binding protein is reduced in erythrocytes from patients with pseudohypoparathyroidism and pseudopseudohypoparathyroidism: biochemical, endocrine and genetic analysis of Albright's hereditary osteodystrophy in six kindreds. *J Clin Endocrinol Metab* 1986;62:497-502.
- Levine MA, Downs RW, Moses AM, et al. Resistance to multiple hormones in patients with pseudohypoparathyroidism. *Am J Med* 1983;74:545-56.
- Patten JL, Johns DR, Valle D, et al. Mutation in the gene encoding the stimulatory G protein of adenylate cyclase in Albright's hereditary osteodystrophy. *N Engl J Med* 1990;322:1412-9.
- Van Dop C, Bourne HR, Neer RM. Father to son transmission of decreased Ns activity in pseudohypoparathyroidism type 1a. *J Clin Endocrinol Metab* 1990;59:825-8.
- Kozasa T, Itoh H, Tsukamoto T, Kaziro I. Isolation and characterization of the human Gs alpha gene. *Proc Natl Acad Sci USA* 1988;84:2081-5.
- Weinstein LS, Gejman PV, Friedman E, et al. Mutations of the Gs alpha-subunit gene in Albright hereditary osteodystrophy detected by denaturing gradient gel electrophoresis. *Proc Natl Acad Sci USA* 1990;87:8287-90.
- Spranger JW. Skeletal dysplasias and the eye: Albright's hereditary osteodystrophy. *Birth Defects* 1969;V:122-8.
- Temtamy S. Albright's hereditary osteodystrophy. *Birth Defects* 1971;VII:269.
- Minozzi M, Faggiano M, Bianco A, Coligianni A. Su un caso di osteodistrofia ereditaria di Albright, varieta normocalcemia, con documentata trasmissione da maschio a maschio. *Folia Endocrinol* 1963;16:168-88.
- Geominne L. Albright's hereditary poly-osteochondrodystrophy. *Acta Genet Med Gemellol* 1965;14:226-79.
- Uhr N, Bezahler HB. Pseudo-pseudohypoparathyroidism: report of three cases in one family. *Ann Intern Med* 1961;54:443-51.
- Stirling HF, Barr DGD, Kelnar CJH. Familial growth hormone releasing factor deficiency in pseudopseudohypoparathyroidism. *Arch Dis Child* 1991;66:533-5.
- Dickson LG, Morita Y, Cowser EJ, Graves J, Meyer JS. Neurological, electroencephalographic, and heredo-familial aspects of pseudohypoparathyroidism and pseudopseudohypoparathyroidism. *J Neurol Neurosurg Psychiatry* 1960;23:33-9.
- Lee JB, Tashjian AH, Streeto JM, Frantz AG. Familial pseudohypoparathyroidism. Role of parathyroid hormone and thyrocalcitonin. *N Engl J Med* 1968;279:1179-84.
- Henkin RI. Impairment of olfaction and of the tastes of sour and bitter in pseudohypoparathyroidism. *J Clin Endocrinol Metab* 1968;28:624-8.
- Weinberg AG, Stone RT. Autosomal dominant inheritance in Albright's hereditary osteodystrophy. *J Pediatr* 1971;79:996-9.
- Stogmann W, Fischer JA. Pseudohypoparathyroidism: disappearance of the resistance to parathyroid extract during treatment with vitamin D. *Am J Med* 1975;59:140-4.
- Werder EA, Kind HP, Egert F, Fischer JA, Prader A.

Table 3 Expression in affected offspring of transmitting parents.

Offspring		
AHO+	60	0
AHO-	0	6

- Effective longterm treatment of pseudohypoparathyroidism with oral 1 alpha-hydroxy and 1,25-dihydroxy cholecalciferol. *J Pediatr* 1976;89:266-8.
- 25 Werder EA, Fischer JA, Illig R, et al. Pseudohypoparathyroidism and idiopathic hypoparathyroidism: relationship between serum calcium and parathyroid hormone levels and urinary cyclic adenosine-3',5'-monophosphate response to parathyroid extract. *J Clin Endocrinol Metab* 1978;46:872-9.
 - 26 Williams AJ, Wilkinson JL, Taylor WH. Pseudohypoparathyroidism. *Arch Dis Child* 1977;52:798-800.
 - 27 Farfel Z, Brickman AS, Kaslow HR, Brothers VM, Bourne HR. Defect of receptor-cyclase coupling protein in pseudohypoparathyroidism. *N Engl J Med* 1980;303:237-42.
 - 28 Farfel Z, Brothers VM, Brickman AS, Bourne HR. Pseudohypoparathyroidism: inheritance of a deficient receptor-cyclase coupling activity. *Proc Natl Acad Sci USA* 1981;78:3098-102.
 - 29 Fischer JA, Burne HR, Dambacher MA, et al. Pseudohypoparathyroidism: inheritance an expression of deficient receptor-cyclase coupling protein activity. *Clin Endocrinol* 1983;19:747-54.
 - 30 Faull CM, Welbury RR, Paul N, Kendall Taylor P. Pseudohypoparathyroidism: its phenotypic variability and associated disorders in a large family. *Q J Med* 1991;78:251-64.
 - 31 Izraeli S, Metzker A, Horev G, Karmi D, Merlob P, Farfel Z. Albright hereditary osteodystrophy with hypothyroidism, normocalcaemia and normal Gs protein activity: a family presenting with congenital osteoma cutis. *Am J Med Genet* 1992;43:764-7.
 - 32 Selye H. *Textbook of endocrinology*. 2nd ed. Montreal: Acta Endocrinologica Inc, 1949:569.
 - 33 Bakwin H, Gorman WF, Ziegler SR. Pseudohypoparathyroid tetany. *J Pediatr* 1950;36:567-76.
 - 34 Frame B, Carter S. Pseudohypoparathyroidism. Clinical picture and relation to convulsive seizures. *Neurology* 1955;5:297-310.
 - 35 Cusmano JV, Baker DH, Finby N. Pseudohypoparathyroidism. *Radiology* 1956;67:845-53.
 - 36 Ray EW, Gardner LI. Pseudo-pseudo-hypoparathyroidism in a child. Report of the youngest case. *Pediatrics* 1959;23:520-9.
 - 37 Cohen ML, Donnell GN. Pseudohypoparathyroidism with hypothyroidism. *J Pediatr* 1960;56:369-82.
 - 38 Tanz SS. Pseudo-pseudohypoparathyroidism. Three cases in one family. *Am J Med Sci* 1960;239:453-61.
 - 39 Pappiannou AC, Matsas BE. Albright's hereditary osteodystrophy (without hypocalcaemia). Brachymetacarpal dwarfism without tetany, or pseudopseudohypoparathyroidism. Report of a case and review of the literature. *Pediatrics* 1963;31:599-607.
 - 40 Hermans PE, Gorman CA, Martin WJ, Kelly PJ. Pseudopseudohypoparathyroidism (Albright's hereditary osteodystrophy): a family study. *Mayo Clin Proc* 1964;39:81-91.
 - 41 Ritchie GM. Dental manifestations of pseudohypoparathyroidism. *Arch Dis Child* 1965;40:565-72.
 - 42 Gwinn JL, Lee FA. Radiological case of the month. *Am J Dis Child* 1969;119:447-8.
 - 43 Zisman E, Lotz M, Jenkin ME, Bartter FC. Studies in pseudohypoparathyroidism: two new cases with probable selective deficiency of thyrotropin. *Am J Med* 1969;46:464-71.
 - 44 Bell NH, Avery S, Sinha T, Clark CM Jr, Allen DO, Johnston C Jr. Effects of dibutyryl cyclic adenosine 3',5'-monophosphate and parathyroid extract on calcium and phosphorus metabolism in hypoparathyroidism and pseudohypoparathyroidism. *J Clin Invest* 1972;51:816-23.
 - 45 Greenberg SR, Karabel S, Saade GA. Pseudohypoparathyroidism: a disease of the second messenger (3'-5'-cyclic AMP). *Arch Intern Med* 1972;129:633-7.
 - 46 Brito Suarez M, Hernandez C, de la Rosa J. Pseudohypoparathyroidismo. A proposito de 3 casos familiares de osteo-distrofia hereditaria de Albright. *Rev Esp Reum Enfem Osteoart* 1975;18:199-216.
 - 47 Farriaux JP. Pseudohypoparathyroidism. *Am J Dis Child* 1976;130:780.
 - 48 Wolfsdorf JL, Rosenfield RL, Fang VS, Kobayashi R, Razdan AK, Kim MH. Partial gonadotrophin-resistance in pseudohypoparathyroidism. *Acta Endocrinol (Copenh)* 1978;88:321-8.
 - 49 Gaudal N, Milman N, Nielsen LS, Niebuhr E, Bonde J. Coexistent pseudohypoparathyroidism and D brachydactyly in a family. *Clin Genet* 1986;30:449-55.
 - 50 Kinard RE, Walton JE, Buckwater JA. Pseudohypoparathyroidism. Report on a family with four affected sisters. *Arch Intern Med* 1979;139:204-7.
 - 51 Drezner MK, Haussler MR. Normocalcaemic pseudohypoparathyroidism. Association with normal Vitamin D3 metabolism. *Am J Med* 1979;66:503-8.
 - 52 Johnson WG. Metabolic interference and the + - heterozygote. A hypothetical form of simple inheritance which is neither dominant nor recessive. *Am J Hum Genet* 1980;32:374-86.
 - 53 Heutink P, van der Mey AGL, Sandkuijl LA, et al. A gene subject to genomic imprinting and responsible for hereditary paragangliomas maps to chromosome 11q23-qter. *Hum Med Genet* 1992;1:7-10.
 - 54 Myers RH, Madden JJ, Teague JL, Falek A. Factors related to onset age of Huntington disease. *Am J Hum Genet* 1982;34:481-8.
 - 55 Hall JG. Genomic imprinting: review and relevance to human diseases. *Am J Hum Genet* 1990;46:857-73.
 - 56 DeChiara TM, Robertson EJ, Efstratiadis A. Parental imprinting of the mouse insulin-like growth factor II gene. *Cell* 1991;64:849-59.