Pituitary 1999;1:273–277

Familial Acromegaly: Case Report and Review of the Literature

Alain Verloes[1], Achille Stevenaert[2], Bin Tean Teh[3], Patrick Petrossians[4], and Albert Beckers[4]

[1]Wallonia Centre for human Genetics, Liège University, Departments of [2]Neurosurgery and [4]Endocrinology, Sart Tilman University Hospital, Liège, Belgium and [2]Department of Molecular Medecine, Karolinska hospital, Stockholm, Sweden

Abstract. **Familial acromegaly is an exceptional clinical entity when not associated with features of multiple endocrine neoplasia type 1 (MEN1). We report here 3 pedigrees in each of which 2 patients have been shown to develop acromegaly. In 4 patients, clinical follow-up, and biological screening allowed to confidently exclude MEN1. Absence of mutation in the MEN1 gene after direct DNA analysis in 2 pedigrees reinforces the conviction that the families do not have MEN1. In families 1 and 2, diagnosis was made at a very early age and voluminous adenomas with suprasellar expansion were already present at the time of diagnosis. We review the 20 previous reports of familial acromegaly, some of them questionable. Our 3 families, combined with some other published pedigrees, allow the delineation of a familial form of acromegaly, distinct from MEN1. Dominant inheritance with reduced, age-dependant penetrance is the most parsimonious model to explain the recurrences. Gs protein pathway could be the site of action of the gene responsible of familial acromegaly, but no data have been published to sustain or reject this hypothesis.**

Keywords. **acromegaly, familial acromegaly, chromophobe tumor, MEN1**

Introduction

Chronic growth hormone (GH) hypersecretion beyond puberty results in the apparition of acromegaly. Most cases are sporadic and are due to GH-secreting pituitary adenoma. Familial occurrence of acromegaly was reported as soon as 1901 by Fraenkel and thoroughly reviewed in the old literature [1], but, after delineation of multiple endocrine neoplasia type 1 (MEN1) by Wermer in 1954, most published cases turned out to be an expression of this dominantly inherited disorder. Since delineation of MEN1, only 20 pedigrees have been reported with non-MEN1-related familial acromegaly. We report here 3 families showing multiple occurrence of acromegaly, in order to further clinically delineate this rare entity.

Family Reports (Table 1)

Family 1

A pituitary adenoma invading the sinus cavernosus and secreting growth hormone (GH) and prolactin (PRL) was discovered in patient 1, a 26-year-old woman presenting with amenorrhea and galactorrhea. Biological work-up confirmed acromegaly with high basal levels of PRL, GH and somatomedin C. Trans-sphenoidal subtotal adenomectomy allowed the levels of GH and PRL to return to normality, despite a still abnormal GH secretion after TRH infusion test.

Acromegaly was diagnosed at age 31 in patient 2, a woman who was the first cousin of patient 1. Investigations revealed a pituitary adenoma of 2.5 cm of diameter expanding in the suprasellar area and to the sinus cavernosus, bilaterally. The tumor was partially removed by trans-sphenoidal surgery.

Histologically, both tumors were somatotroph adenomas. Calcium homeostasis, parathyroid function and dosages of insulin, glucagon, VIP, PP, and gastrin were normal and remained so for 10 years in both patients, making a diagnosis of MEN1 very unlikely.

The mothers of patient 1 and 2 were sisters. Patient 1 has 2 children and patient 2 has one girl. Clinical and biological investigation of the parents of patient 1 was negative. By anamnesis, parents of patient 2 and more distant relatives appeared unaffected.

Family 2

Patient 3, a 24-year-old woman, presented with acromegaly, galactorrhea and right amblyopia due to a large pituitary adenoma. High GH and PRL were found. Trans-sphenoidal adenomectomy allowed normalization of PRL, GH and somatomedin C. Histologically, the tumor was a lactosomatotroph adenoma.

Patient 4, the brother of patient 3, was first seen at

Address correspondence to: Pr Albert Beckers, Service d'Endocrinologie, C.H.U. Sart Tilman, B-4000 Liège, Belgium. Email: Albert.Beckers@chu.ulg.ac.be

Table 1. *Biological and histological data of the 6 patients*

Pedigree	Family 1		Family 2		Family 3	
Patient	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	F	F	F	M	M	F
Age at onset	25	30	22	27	51	?
Age at diagnosis	26	31	23	28	56	58
GH (μM/ml)	40	140	126	8	25	28
PRL (μU/ml)	2133	290	788	400	101	182
Sugery	1982	1992	1991	1994	1985	ND
Result	Relapsing	Not cured	Cured	Not cured	cured	
Grading	II A	III A	II A	II B	ND	ND

ND = not done.

the age of 28 with high GH and somatomedin C (Table 1). Neuroimaging revealed a large pituitary adenoma extending to the optic chiasma. The patient was initially treated with octreotide and later adenomectomized [2].

Systematic endocrinological screening for MEN1, similar to family 1, was negative in both patients, in their 2 healthy brothers and their parents, who were not consanguineous. By anamnesis, relatives that are more distant appeared unaffected.

Family 3

A diagnosis of acromegaly was proposed for patient 5 at the age of 56 years, although manifestations were already present 5 years before. CT showed intrasellar adenoma. After an unsuccessful therapeutic attempt with bromocryptin, he had trans-sphenoidal adenomectomy in 1985. GH and somatomedin C levels remained normal during more than 10 years, but he is currently relapsing his adenoma.

Patient 6, the sister of patient 5, was shown in 1983 to have acromegaly. At that time, CT scan and tomographies of the sella turcica were evocative of an intrasellar adenoma. The patient declined surgery. She was initially treated with bromocriptin. Despite frank clinical acromegaly, the patient declined any further investigations and escaped follow up.

The endocrinological screening for MEN1 (similar to family 1) was negative in patient 5 and his 2 unaffected sons. The parents of patients 5 and 6 were not consanguineous. By anamnesis, parents of patients 5 and 6, and more distant relatives appeared unaffected.

Genetic investigations

The recent discovery of the MEN1 gene allowed us to screen the gene in one affected person of families 1 and 2. No mutations were found in the 9 exons of MEN1 gene [3].

Discussion

We report here 3 pedigrees in which 2 patients have been shown to develop acromegaly. In 5/6 patients, clinical follow-up, and biological screening allowed to confidently exclude MEN1. Absence of mutation of MEN1 gene after direct DNA analysis in 2 of the 3 pedigrees reinforces our conviction that we are not dealing here with MEN1, although we have to recognize that mutation analysis is not positive in all cases of proven MEN1 cases [3,4]. In families 1 and 2, diagnosis was made at a very early age and voluminous adenomas with suprasellar expansion were already present at the time of diagnosis, resulting in incomplete surgical cure. In 2 instances, the adenoma was of a mixed, somatolactotroph type.

Acromegaly is a rare disorder; its incidence is estimated to be 1/300,000 and its prevalence 1/25,000 [5,6]. Mean age at diagnosis is 40 to 46 years, with a mean pre-diagnostic history of 10 years. It is commonly considered to be a non-genetic, sporadic disorder, an assumption sustained by several reports of discordant monozygotic twins (reviewed in [7]) Acromegaly re-

Table 2. *Etiologies of acromegaly*

Sporadic acromegaly
Non-syndromal hypophyseal adenoma (abnormal Gs protein in 40%)
isolated
  with PRL hypersecretion
  with TSH hypersecretion
  with hypersecretion of the α subunit of the glycoprotein hormones
Syndromal hypophyseal adenoma (abnormal Gs protein)
  McCune-Albright syndrome
Ectopic secretion of
  GHRH
  GH

Familial acromegaly
MEN1 (MEN1 gene)
  hypophyseal adenoma
  Ectopic secretion of GHRH
Familial acromegaly (gene unknown)
Carney syndrome (unknown gene mapped on chromosome 2)
Neurofibromatosis type 1 (gene NF1) and 2 (gene NF2)

sults from inappropriate GH secretion. Its major etiologies are summarized in Table 2. The most common forms are isolated somatotroph adenomas and mixed mammosomatotroph adenomas [8]. More than 95% are of pituitary origin and usually result of a monoclonal proliferation of pituitary tissue [9]. More rarely, diffuse pituitary hyperplasia is observed as the result of inappropriate hypothalamic secretion of GHRH (ganglioneurocytoma) or ectopic, paraneoplasic (e.a. with a pancreatic, thymic, pulmonary, intestinal or carcinoid tumor). Primary ectopic GH-secreting tumors. are exceptional.

As a rule, acromegaly is a sporadic event with these etiologies. Somatroph cell proliferation and GH secretion are regulated by the Gs protein, a heterotrimeric GTP binding protein with stimulatory function [10]. In 4% in one series [11], and 30–40% in other series of human somatotroph adenomas [12,13], GH hypersecretion have been shown to be linked to the presence of somatic activating mutations of alpha subunit of the Gs protein (Gsα). Those mutations (*gsp* mutations) cause a constitutive activation of the membrane adenylyl cyclase that results in uncontrolled cyclic adenosine monophosphate (cAMP) elevation and, simultaneously, in an increase of the phosphodiesterase activity [14] Those mutations are similar to those described in tissues of patients with McCune-Albright syndrome [15].

Acromegaly is a well-known component of MEN1 (Wermer syndrome) and Carney syndrome. Classically, adult patients with MEN1 have hyperparathyroidism (in >95%), about 2/3 of them have pituitary adenoma (which, in about 10–20% of cases lead to acromegaly), in 60 to 80% of cases, a pancreatic tumor (gastrinoma, insulinoma, PP-secreting or VIP-secreting tumors) is observed [16,19]. Pheochromocytoma is rarely observed in MEN1. There has been some reports of the association pheochromocytoma-acromegaly of uncertain signification (incomplete expression of MEN1? [20]). Over 80% of the carriers are symptomatic by the fifth decade. Patients who would present isolated acromegaly are thus extremely unlikely among MEN1 families. The gene for MEN1 has recently been cloned and numerous mutations have been reported, without obvious genotype/phenotype correlation [4,21,24]. *Gsp* mutation has been described in a mixed (GH/PRL) pituitary adenoma from a MEN1 patient [25] and a compound phenotype of McCune-Albright and MEN1 has been observed in one pedigree [26]. Those reports illustrate the complex relationships between Gs protein and the product of the MEN1 gene.

Carney complex is a rare autosomal dominant disease associating cardiac, cutaneous and mammary myxoid tumors, spotty cutaneous pigmentation (lentiginosis, blue naevi), primary nodular adrenocortical disease, testicular tumor and acromegaly [27] was an other, easily excluded possibility.

By contrast, familial isolated acromegaly (or hypophyseal gigantism) is an exceptional entity in the literature posterior to the delineation of MEN1, and most cases have been reported by Japanese authors. Levin [28] described 2 brothers with acromegaly and acanthosis nigricans. Unfortunately, abnormal pancreatic or parathyroid hormonal secretions were not investigated. Jones [29] described a boy and his uncle with acromegaly without evidence of MEN1. Familial data were not available. Other older reports include those of Himuro (two sisters with acromegaly and non-functioning adenoma [30]), Kurisaka (monozygotic male twins with acromegaly [31]), Abbassioun (3 brothers with acromegalo-gigantism [32]) Two other pair of sibs (brother and sister) were reported in Japanese, one with acromegaly, the other with non functioning adenomas [33]. Pestell [34] described a pedigree in which 5 patients in 3 generations showed GH-secreting pituitary adenoma. MEN1 was excluded by appropriate parathyroid and pancreatic testings. Penetrance was incomplete, as at least 7 asymptomatic carriers linked the 5 affected relatives. Unfortunately, linkage analysis with the MEN1 gene was not possible at the time of publication and the data have not been updated. McCarthy [7] described 3 families with recurrent acromegaly. Two of them seem convincing cases of hereditary isolated acromegaly transmitted by a mother to her son. The first pedigree is less convincing (as noted by the authors): several family members have multiple lipomas and high PTH in the two acromegalic patients let suspect this family to be a clinical variant of MEN1 or possibly Cowden disease. Tamburrano [35] described 2 males and one female sibs with seemingly isolated acromegaly. The pedigree was compatible with dominant inheritance as the mother and grandmother had acromegaloid features, and another female sib (and her girl) had increased GH levels. Links described a father with acromegaly and pituitary adenoma and his 32 year-old son with GH-,TSH- and alpha-subunit–cosecreting pituitary adenoma, without evidence of MEN1 in the son [36]. Matsuno described two sisters with early onset gigantism, operated of large adenomas at the age 10 and 14, respectively [37]. There was no biological evidence of MEN1 and mutation screening for the 2 Gsα mutations was negative. Benlian reported a mother and a son with acromegaly (and possible acromegalo-gigantism in a great-grandmother) and excluded linkage to the MEN1 locus [38]. Interestingly, hypothyroid goiter and lipoma was present in a non-acromegalic obligate carrier. A most intriguing family was recently reported by Stock [39]: a 84-year-old woman was found to have mild primary hyperparathyroidism; one of her sons and one of her daughters developed acromegaly (at age 60 and 58 respectively); and one of her grand-daughters (whose parents were unaffected) developed PRL adenoma at the age 22. The three latter patients had no parathyroid dysfunction. Asymptomatic hyperparathyroidy was further noted in 1 relative, and acromegaly in 2 relatives among 26 screened. Several others had increased levels of IGF-1 without other signs of endocrinopathy. Segregation analysis excluded MEN1 locus.

Incidentally, we regret that the authors kept a diagnosis of MEN1 in this family: MEN1 should be limited to those families that segregates a mutation of the MEN1 locus in 11q13.

Most familial examples of acromegaly concern small pedigrees, with 2 affected relatives. Based on the prevalence of the disorder, chance occurrence of acromegaly in 3 different families from the French part of Belgium is extremely small. With an multifactorial/polygenic model of inheritance (where recurrence risk in first degree relative is close to the square root of the general incidence of the trait), an empirical recurrence risk of 1/500 is expected for a disorder with an incidence of 1/250,000, thus not unlikely is pedigrees where clinical data are perfectly similar to the profile of sporadic acromegaly (as in our family 3).

Nevertheless, in most familial cases (including families 1 and 2 of the present report), the age of diagnosis extend between puberty and age 30, and some cases were diagnosed in the pediatric age [30,34,37]. Earlier onset is a common characteristic for the genetic forms of usually sporadic tumors (retinoblastoma, Wilms tumor, breast or colon cancer, etc.). This anticipated apparition of symptoms in familial cases is usually explained by Knudson's two hits hypothesis.

The histologic type of the adenoma vary from somatotroph (most cases) to mammosomatotroph [7,34], even in a single family [38]. GH/TSH/alpha-subunit adenoma has been reported once [36] Another characteristic of familial cases is the preponderance of invasive macroadenomas at the time of diagnosis. Not unexpectedly, asymptomatic carriers have been shown to have elevated GH in several families. More disturbing is the observation of mild or latent hyperparathyroidism in at least 2 families [7,39], MEN1 locus having been excluded in the latter.

Atypical symptoms have been observed in some relatives: thyroid nodules [28,29], hyperthyroidism [7,35] or hypothyroidism [38]. Lipomas were mentioned twice [7,38]

As a whole, 20 pedigrees of familial, non-MEN1 acromegaly have been reported with 45 affected persons. (including ours). In 10/20 instances, the disorder only affected sibs. In the other pedigrees, the familial distribution involves vertical transmission or other familial relationships. Multiple familial reports and earlier onset of symptoms in familial cases are strong arguments for the existence of a specific, genetically determined form of acromegaly. Mode of inheritance and possible genetic heterogeneity are unresolved issues. Early reports discussed autosomal recessive inheritance [32]. Pestell's Tamburrano's, Benlian's and Stock's families clearly point to a dominant mode of inheritance. In Pestell's and Links reports, there is male-to-male transmission, incompatible with an X linked inheritance. With this hypothesis, pseudorecessive pattern of inheritance observed in single-generational cases could be explained either by incomplete penetrance or by gonadic mosaicism, but, of course, genetic heterogeneity cannot be ruled out. It should be pointed, nevertheless, that consanguinity was never observed. Tamburrano suggested a relationship between acromegaly and HLA, as 2 affected sibs were haplo-identical. Benlian [38] speculated over possible genomic imprinting effects to explain an excess of acromegaly in the maternal branch of published pedigrees.

Our 3 families, combined with some other published pedigrees (Pestell) allow the delineation of a familial form of acromegaly, distinct from MEN1. Dominant inheritance with reduced, age-dependant penetrance is the most parsimonious model to explain the recurrences. Although Gs protein pathway is a possible site of action of the gene(s) responsible of familial acromegaly, no data has been published to sustain or reject this hypothesis. No animal model of familial acromegaly is known, but an inherited form of early onset lactotroph adenoma is known in the rat [40]. Inheritance is autosomal dominant, with partial sex-influenced expression. Gene defect is not known.

References

1. Koch G, Tiwisina T. Contribution to the hereditary of acromegaly and hyperostosis generalisata with pachyderma (chromophobe hypophysis adenoma in father and son). *Arznemittel Furschung* 1959;13:489–504.
2. Stevenaert A, Beckers A. Presurgical octreotide: treatment in acromegaly. *Metab Clin Exp* 1996;45(suppl. 1):72–74.
3. Teh BT, Kytölä S, Farnebo L, Bergman FK, Wong K, et al. Mutation analysis of the MEN1 gene in multiple endocrine neoplasia type I, familial acromegaly and familial isolated hyperparathyroidism. *J Clin Endocrinol Metab* 1998;83: 2621–2628.
4. Poncin J, Abs B, Velkeniers M, Bonduelle M, Abramovicz M, et al. Mutation analysis of the MEN1 gene in Belgian patients with multiple endocrine neoplasia type 1 and related diseases. *Human Mutation* 1998;(in press)
5. Alexander L, Appleton D, Hall R, Ross WM, Wilkinson R. Epidemiology of acromegaly in the Newcastle region. *Clin Endocrinol (Oxf)* 1980;12:71–79.
6. Bengtsson BA, Eden S, Ernest I, Oden A, Sjoegren B. Epidemiology and long-term survival in acromegaly. *Acta Medica Scand* 1988;223:327–335.
7. McCarthy MI, Noonan K, Wass JAH, Munson JP. Familial acromegaly: Studies in 3 families *Clin Endocrinol (Oxf)* 1990;32:719–728.
8. Beckers A, Courtoy R, Stevenaert A, Bonniver J, Closset J, et al. Mammosomatotropes in human pituitary adenomas as revealed by electron microscopic double gold immunostaining method. *Acta Endocrinol (Copenh)* 1988;118:503–512.
9. Herman V, Fagin J, Govsky R, Kovacs K, Melmed S. Clonal origin of pituitary adenomas. *J Clin Endocrinol Metab* 1990; 71:1427–1433.
10. Vallar L, Spada A, Giancannattasio G. Altered Gs and adenylate cyclase activity in human GH-secreting pituitary adenomas. *Nature* 1987;330:566–568.
11. Hosoi E, Yokogoshi Y, Horie H, Yamada S, Saito S. Analysis of the GS alpha gene in growth hormone-secreting pituitary adenomas by the polymerase chain reaction-direct sequenc-

ing method using paraffin-embedded tissues. *Acta Endocrinol (Copenh)* 1993;129:301–306.
12. Landis CA, Masters SB, Spada A, Pace AM, Bourne HR, et al. GTPase inhibiting mutations activate the alpha chain of of Gs and stimulate adenylate cyclase in human pituitary tumors. *Nature* 1989;340:692–696.
13. Faglia G, Arosio M, Spada A. GS protein mutations and pituitary tumors: Functional correlates and possible therapeutic implications. *Metabolism* 1996;45 (suppl.1):117–119.
14. Lania A, Persani L, Ballare E, Mantovani S, Losa M, et al. Constitutively active Gs alpha is associated with an increased phosphodiesterase activity in human growth hormone-secreting adenomas. *J Clin Endocrinol Metab* 1998; 85:1624–1628.
15. Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, et al. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. *New Engl J Med* 1991;325:1738–1740.
16. Croizier JC, Azerad E, Lubetski J. L'adénomatose polyendocrinienne (syndrome de Wermer): a propos d'une observation personnelle. Revue de la littérature. *Sem Hôp Paris* 1971;47:494–525.
17. Eberle F, Grün R. Multiple endocrine neoplasia, type 1. *Ergebn Inn Med Kinderheilk (Berlin)* 1981;46:75–142.
18. Benson L, Ljunghall S, Akerström G, Öberg K. Hyperparathyroidism presenting as the first lesion in multiple endocrine neoplasia type 1. *Am J Med* 1987;82:731–737.
19. Samaan NA, Ouais S, Ordonez NG, Choksi UA, Sellin RV, et al. Multiple endocrine syndrome type 1. Clinical, laboratory findings and management in five families. *Cancer* 1989;84: 741–752.
20. Tateishi A, Wada A, Ishiguro S, Ehara M, Sakamoto H, et al. Coexistence of bilateral pheochromocytoma and pancreatic islet cell tumor: report of a case and review of the literature. *Cancer* 1978;42:2928–2934.
21. Lemmens I, Van de Ven WJ, Kas K, Zhang CX, Giraud S, et al. Identification of the multiple endocrine neoplasia type 1 (MEN1) gene. The European Consortium on MEN1. *Hum Mol Genet* 1997;6:1177–1183.
22. Agarwal SK, Kester MB, Debelenko LV, Heppner C, Emmert-Buck MR, et al. Germline mutations of the MEN1 gene in familial multiple endocrine neoplasia type 1 and related states. *Hum Mol Genet* 1997;6:1169–1175.
23. Bassett JH, Forbes SA, Pannett AA, Lloyd SE, Christie PT, et al. Characterization of mutations in patients with multiple endocrine neoplasia type 1. *Am J Hum Genet* 1998;62:232–244.
24. Giraud S, Zhang CX, Serova-Sinilnikova O, Wautot V, Salandre J, et al. Germ-Line Mutation Analysis in Patients with Multiple Endocrine Neoplasia Type 1 and Related Disorders. *Am J Hum Genet* 1998;63:455–467.
25. Hosoi E, Yokogoshi Y, Yokoi K, Sano T, Saito S. A pituitary-specific point mutation of codon 201 of the GSalpha genein a pituitary adenoma of a patient with multiple endocrine neoplasia (MEN) type 1. *Endocrinol Jpn* 1992;39:319–324.
26. O'Halloran DJ, Shalet SM. A family pedigree exhibiting features of both multiple endocrine neoplasia type 1 and McCune-Albright syndromes. *J Clin Endocrinol Metab* 1994;78:523–525.
27. Carney JA, Gordon H, Carpenter PCSBV, Go VLW. The complex of myxomas, spotty pigmentation and endocrine overactivity. *Medicine* 1985;64:270–283.
28. Levin SR, Hofeldt PD, Becker N, Wilson CB, Seymour R, et al. Hypersomatotropism and acanthosis nigricans in 2 brothers. *Arch Intern Med* 1974;1974:355–357.
29. Jones MK, Evans PJ, Jones IR, Thomas TS. Familial acromegaly. *Clin Endocrinol (Oxf)* 1984;20:355–358.
30. Himuro H, Kobayashi EKH, Jimbo M, Kitazawa M. Pituitary adenomas in two members of a family. *Neurol Surg* 1976;4:371–377.
31. Kurisaka M, Takei Y, Tsubokawa T, Moriyasu N. Growth hormone-secreting pituitary adenoma in uniovular twin brothers. Case report. *Neurosurgery* 1981;8:226–230.
32. Abbassioun K, Fatourehchi V, Amirjamshidi A, Meibodi NA. Familial acromegaly with pituitary adenoma: report of 3 affected siblings. *J Neurosurg* 1986;64:510–512.
33. Yuasa H, Tokito S, Nakagaki H, Kitazawa M. Familial pituitary adenoma, report of four cases from two unrelated families (in Japanese, with English abstract). *Neurol Med Chir (Tokyo)* 1990;30:1016–1019.
34. Pestell RG, Alford FP, Best JD. Familial acromegaly. *Acta Endocrinol (Copenh)* 1989;121:286–289.
35. Tamburrano G, Jaffrain-Rea ML, Grossi A, Lise A, Bulletta C. L'acromégalie familiale: a propos d'une observation. Revue de la litterature. *Ann Endocrinol (Paris)* 1992;53:201–207.
36. Links TP, Monkelban JF, Dullaart RPF, van Haeften TW. Growth hormone-, alpha-subunit and thyrotrophin-cosecreting pituitary adenoma in familial setting of pituitary tumor. *Acta Endocrinol (Copenh)* 1993;129:516–518.
37. Matsuno A, Teramoto A, Yamada S, Kitanaka T, et al. Gigantism in siblings unrelated to multiple endocrine neoplasia: case report. *Neurosurgery* 1994;35:952–955.
38. Benlian P, Giraud S, Lahlou N, Roger M, Blin C, et al. Familial acromegaly: A specific clinical entity— Further evidence from the genetic study of a three-generation family. *Eur J Endocrinol* 1995;133:451–456.
39 Stock JL, Warth MR, Teh BT, Coderre JA, Overdorf JH, et al. A kindred with a variant of multiple endocrine neoplasia type 1 demonstrating frequent expression of pituitary tumors but not linked to the multiple endocrine neoplasia type 1 locus at chromosome region 11q13. *J Clin Endocrinol Metab* 1997;82:486–492.
40 Chedid A, Hoversi, Chefiec, McCune SA, Jurin RR, et al. Hereditary pituitary proclamation: A new rat mode. *Acta Endocrinol (Copenh)* 1988;119:535–542.