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Genetics of Gigantism and Acromegaly

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Abstract

Gigantism and acromegaly are rare disorders that are caused by excessive GH secretion and/or high levels of its mediator, IGF-1. Gigantism occurs when excess GH or IGF-1 lead to increased linear growth, before the end of puberty and epiphyseal closure. The majority of cases arise from a benign GH-secreting pituitary adenoma, with an incidence of pituitary gigantism and acromegaly of approximately 8 and 11 per million person-years, respectively. Over the past two decades, our increasing understanding of the molecular and genetic etiologies of pituitary gigantism and acromegaly yielded several genetic causes, including multiple endocrine neoplasia type 1 and 4, McCune-Albright syndrome, Carney complex, familial isolated pituitary adenoma, pituitary adenoma association due to defects in familial succinate dehydrogenase genes, and the recently identified X-linked acrogigantism. The early diagnosis of these conditions helps guide early intervention, screening, and genetic counseling of patients and their family members. In this review, we provide a concise and up-to-date discussion on the genetics of gigantism and acromegaly.

Keywords

Acromegaly; Gigantism; IGF-1; GH; Genetics; X-LAG; Pituitary adenoma

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Introduction

Gigantism and acromegaly are distinguished by the status of the epiphyseal growth plates with respect to GH and/or IGF-1 excess; otherwise, the two disorders represent a continuum of clinical manifestations: it is not uncommon for acromegalics to be tall, and most giants have acromegalic features. Nevertheless, it is important to remember that gigantism occurs only when the epiphyseal growth plates are not fused, whereas acromegaly affects individuals with normal height. In both conditions, most of the time, the cause is a benign GH-secreting pituitary tumor (co-secretion of prolactin is called mammosomatotropic), and less likely from pituitary hyperplasia, ectopic GH or growth hormone releasing hormone (GHRH) secretion. The incidence of pituitary gigantism and acromegaly is likely under reported; approximately 8 and 11 cases per million person-years, respectively.[1-3] The term acromegaly was coined in 1886 using the Greek words “akron” and “mega” to describe the typical large features of this condition.[1,2] The childhood onset of gigantism and the fact that both giants and acromegalics were frequently known to have inherited a condition that run in their families, suggested early that at least pituitary-dependent GH excess could be a genetic disease. Indeed, over the past three decades, genetic investigations have revealed a number of genetic defects predisposing to gigantism or acromegaly (Tables 1 and 2, Fig. 1).[4] These syndromes have been widely studied and include multiple endocrine neoplasia (MEN) syndromes types 1 and 4 (MEN1 and MEN4), McCune-Albright syndrome (MAS), Carney complex (CNC), the 3Ps (paraganglioma, pheochromocytoma and pituitary adenoma) association (3PA) due to defects in genes coding for succinate dehydrogenase (*SDHx*), and familial isolated pituitary adenoma (FIPA).[5,6] Recently, we described a form of familial and sporadic acromegaly and gigantism that is caused by microduplications on chromosome Xq26.3, a disorder that we named X-LAG for X-linked acrogigantism.[7] X-LAG may be responsible for as many as 80% of the cases of pre-pubertal gigantism. Together, FIPA and X-LAG may explain a substantial number of patients with gigantism and acromegaly as shown by a recent study of 208 patients (78.4% males), mostly with macroadenomas (84%) causing GH excess: 29% of the patients had *AIP* mutations, whereas Xq26.3 microduplications were seen in two families previously diagnosed with FIPA and in 10 sporadic patients (10%).[8] In this report, we review the recent data on gigantism and acromegaly and provide recommendations for genetic screening of patients with GH excess.

1. Familial isolated pituitary adenoma (FIPA)

FIPA (OMIM #605555) represents the largest group of familial gigantism and acromegaly. Mutations in *AIP* are identified in approximately 15-20% of familial FIPA and predominantly cause a truncated or missing protein. The gene *AIP* is mapped to chromosome 11q13.3 and functions as a tumor suppressor gene.[9,10] Typically, mutations in *AIP* affect young patients, with or without a family history, with a low penetrance (approximately 15-30%). Gigantism is a relative manifestation of *AIP* mutations and occurs in about one-third of patients with a somatotropinoma.[6,8]

In a 2006 population-based series from Northern Finland, Vierimaa *et al.*[10] identified the first *AIP* mutations implicated in the pathogenesis of acromegaly. A founder Gln14-to-Ter (p.Q14*) substitution in exon 1 accounted for 16% of acromegalics.[10] In a subsequent study

of 73 FIPA families (156 patients with pituitary adenomas, including somatotropinomas, GH and prolactin co-secreting tumors, prolactinomas, and non-secreting tumors), 11 families were reported to harbor 10 different germline *AIP* mutations.[5] Tumors with mutation-positive *AIP* (FIPA representing 15%, familial somatotropinomas representing 50%) were significantly larger ($P = 0.0005$) and diagnosed at a younger age ($P = 0.0006$) than their mutation-negative counterparts.[5] Other studies confirmed the causative role for *AIP* point mutations and large deletions in pituitary tumorigenesis in the setting of FIPA and, more rarely, sporadic acromegaly.[9,11-14] The molecular pathway(s) affected by the defective AIP protein are being heavily investigated.[15-19] Interestingly, other mechanisms leading to reduced AIP protein expression in sporadic acromegaly in the absence of *AIP* mutations have been reported,[20,21] including the identification of potential modifier loci.[22]

Two recently published studies confirmed and extended the initial clinical and genetic spectrum for FIPA. Daly et *al.*[23] compared 96 patients with germline *AIP* mutations and pituitary adenomas to 232 *AIP* mutation-negative acromegalics in order to identify statistically significant features associated with *AIP* defects. They showed that *AIP* mutation-positive acromegalics were predominantly young males with approximately 50% of affected cases presenting during childhood or adolescence. Moreover, when compared to controls, their tumors secreted higher levels of GH and prolactin, were more likely to undergo surgical intervention, and were less responsive to somatostatin analogues.

The study by Hernandez-Ramirez *et al.*[6] also reported several important findings. The *AIP* variants were studied in 216 FIPA families and 404 sporadic acromegalics; pathogenic and likely pathogenic mutations were reported in 17.1% and 8.4% of patients, respectively. A positive genotype-phenotype correlation was found between truncating *AIP* mutations and younger age of onset. Screening of family members led to the diagnosis of a pituitary tumor in approximately 25% of the mutation carriers, highlighting the importance of prospective screening. The authors also examined the role of two putative disease modifying genes (*GNAS1* and *FGFR4)* in mediating the final phenotype of *AIP* mutation-positive patients and showed that neither of these genes were involved in tumorigenesis. In contrast to the study by Daly *et al.*[24], this large investigation showed no male predominance among *AIP* mutation-positive FIPA patients.

AIP defects that have been reported in association with GH excess include promoter, splice-site, and missense mutations; given the fact that *AIP* is highly polymorphic in the population it is essential that functional studies are performed with each newly identified sequence variant. Beyond protein truncation, missense and even silent sequence changes have been linked to abnormal splicing, reduced AIP expression, and loss of crucial protein interactions.[9,11,17,25]

The prevalence of *AIP* mutations in patients with sporadic pituitary adenomas is approximately 4%[26], and there are no known somatic mutations of *AIP* reported to date.

2. X-linked acrogigantism (X-LAG)

X-LAG (OMIM #300942) is a rare cause of early childhood-onset gigantism resulting from GH oversecretion due to a pituitary adenoma or hyperplasia. The median age of onset is 12 months. Nearly all of the patients identified so far also had hyperprolactinemia at the time of presentation.[7,27] Unlike most *AIP* mutations, germline microduplications on chromosome Xq26.3 causing X-LAG mainly arise *de novo*. Since most index cases are females with a *de novo* defect, it is likely that most affected male hemizygous embryos are not viable (although not all), as it is true in other X-linked dominant disorders. Only two instances of X-LAG inheritance have been reported so far, and in both kindreds the affected mother transmitted the microduplication to their affected sons. While females present with germline mutations, male patients harbor the mutation in a mosaic state, which could be missed from a peripheral leukocyte-, saliva-, and buccal cell-derived DNA for microduplication in Xq26.3 or *GPR101*.[28, 29] In such circumstances, DNA isolated from the pituitary tissue and forearm skin proved essential to show a duplicated dosage of *GPR101*[29].

The common duplicated genomic region shared by the first reported patients covered approximately 500 kb, including *CD40LG, ARHGEF6, RBMX*, and *GPR101*. To date, no pathogenic point mutations were identified to cause X-LAG in any of the duplicated genes. Among the coding sequences from this region, only *GPR101,* which codes for an orphan G-protein coupled receptor (GPCR), was highly over-expressed in the pituitary lesions of the affected patients. This finding, along with the fact that *GPR101* strongly activates cyclic (c) AMP generation through *GNAS1*, a pathway known to be involved in GH-producing tumors, suggested that it might be the causative gene for X-LAG.[7,27] A rare *GPR101* missense variant (p.E308D) was identified in approximately 4% of patients with sporadic acromegaly; it was also seen at least once to occur *de novo* at the somatic level. In a GH-secreting cell line model, over-expression of this variant led to an increase in GH secretion.[7] Screening for *GPR101* point variants was recently carried out in two other cohorts of patients with pituitary adenomas, reporting conflicting results with regards to the p.E308D variant.[30,31] In one study, patients with sporadic familial acromegaly did not show an increased prevalence of the c.924G > C (p.E308D) *GPR101* variant when compared to public databases.[28] Although the specific role of *GPR101* in stimulating GH secretion remains elusive, recent evidence supports an effect on GHRH secretion.[7,32] Whether this is the main mechanism leading to pituitary tumorigenesis in XLAG, or that there are additional roles of *GPR101* in the pituitary somatomammotroph cells remains to be seen.

3. Carney complex (CNC)

CNC (OMIM #160980) is an autosomal dominant (AD) disorder that consists of skin pigmentation, cardiac myxomas, GH and prolactin-secreting pituitary tumors or hyperplasia, and Cushing syndrome from primary pigmented nodular adrenocortical disease (PPNAD).[33,34] CNC is mainly caused by mutations of *PRKAR1A*, a tumor suppressor gene on chromosome 17q22-24 (the CNC1 locus); a second locus (CNC2) on chromosome 2p16 has not led to the identification of a specific genetic defect, whereas a single case of CNC has been described in association with *PRKACB* amplification.[34-36] The most common *PRKAR1A* mutations causing CNC are protein-truncating; in approximately 32% of the

cases, these defects are *de novo*.[34,36] Acromegaly is seen in approximately 79% of patients with CNC and is usually due to somatotroph cell hyperplasia, and less likely from microadenomas, which can be multiple.[34] Somatic alterations in *PRKAR1A* or *PRKACB* are infrequently found in sporadic GH-secreting pituitary adenomas.[37]

4. Multiple endocrine neoplasia 1 (MEN1)

MEN1 (OMIM #131100) describes the association of pituitary, parathyroid, and pancreatic neuroendocrine tumors caused by germline (and rarely somatic) mutations in *MEN1*.[38] *MEN1* is located on chromosome 11q13 and consists of 10 exons that encode for the tumor suppressor nuclear protein *menin*.[39] Over 1300 germline mutations have been discovered to date, and are scattered throughout its entire 1,830 bp coding region; many are at splice sites of the gene.[40] The majority of these inactivating mutations are frameshift deletions or insertions.[39] The incidence of GH-secreting pituitary adenomas in MEN1 is approximately 10% by age 40.[38]

5. Multiple endocrine neoplasia 4 (MEN4)

MEN4 (MIM #610755) describes the association of pituitary and parathyroid neoplasms with pheochromocytomas, thyroid and other tumors. MEN4 is caused by heterozygous loss-of-function germline mutations in *CDKN1B*, which is located on chromosome 12p13.[41,42,43] Mutations in the non-coding regions of *CDKN1B* have also been reported.[44] In *MEN1* mutation-negative cases, which are seen in less than 10% of suspected MEN-1,[40] the possibility of MEN4 should be sought. Although gigantism or acromegaly is rare in MEN4, one study found a novel heterozygous mutation in the *CDKN1B* 5'-UTR region (c.-29_-26delAGAG) causing gigantism.[45] This mutation was associated with a reduction in *CDKN1B* mRNA levels and reduced transcriptional activity *in vitro*.[45] *CDKN1B* mutations in sporadic gigantism or acromegaly appear to be rare.[46]

6. McCune-Albright Syndrome (MAS)

MAS (OMIM #174800) is characterized by poly or monostotic fibrous dysplasia, caféau-lait spots, peripheral precocious puberty and hyperfunctioning endocrinopathies as a result of gain-of-function mutations in *GNAS1* in the mosaic state.[47] The mutation renders the gene functionally constitutive, which affects the stimulatory subunit (Gs alpha) of the heterotrimeric G protein complex responsible for intracellular signaling of GPCRs. Acromegaly is seen in 20–30% of MAS patients, with a mean age at diagnosis of 24.4 years (range 3-64 years), and accompanying hyperprolactinemia in the majority of cases.[48] Somatotroph hyperplasia involves the entire pituitary gland, with or without development of somatotroph adenoma.[49]

7. Paraganglioma, pheochromocytoma, and pituitary adenoma association (3PA)

Germline and sporadic defects in *SDHx* have been implicated in 3PA, a recently identified form of familial paragangliomas and pheochromocytomas (PPGL) and other tumors.[50] The

first description of an acromegalic with paraganglioma due to a pathogenic mutation in *SDHD* was reported by Xekouki *et al.*[51] Dénes *et al.*[52] sequenced the known genes of PPGL and pituitary adenomas in 39 patients with sporadic or familial 3PA and found 11 germline mutations (5 *SDHB*, 1 *SDHC*, 1 *SDHD*, 2 *VHL*, and 2 *MEN1*) and 4 variants of unknown significance (2 *SDHA*, 1 *SDHB*, and 1 *SDHAF2*).[52] Further genetic studies are required to better elucidate the molecular and genetic underpinning of this recently described syndrome which points to the involvement of the mitochondrial oxidation pathway in the pathogenesis of GH-producing tumors.

Other genetic conditions and molecular pathways associated with GH excess

Neurofibromatosis type-1 (NF1, OMIM #162200) is a multiple tumor syndrome characterized by café-au-lait spots, neurofibromas, freckling in the inguinal and axillary regions and ocular Lisch nodules with an extremely variable clinical presentation.[53] NF1 commonly arises from point mutations in the *neurofibromin* (*NF1*) gene, including splicing, nonsense, frameshift, and missense variants, while whole-gene deletions are present in approximately 5% of patients.[53,54] GH excess has been reported in children and adults with NF1. Rarely, patients with NF1 and GH excess may have a co-existing pituitary adenoma; in a patient we recently saw, one such tumor stained negative for GH, GHRH, and somatostatin expression suggesting an unlikely association (unpublished data). Loss of somatostatinergic inhibition from infiltrating optic tract gliomas (OTG) leading to a dysregulated GH secretion has been suggested as a possible mechanism of GH excess in patients with NF1.[55,56] A recent study described a series of five children with OTG (3 due to NF1) and GH excess without a clear etiology for gigantism.[57]

A signaling pathway previously not suspected to be involved in gigantism or acromegaly is that of the suppressors of cytokine signaling (SOCS) family of proteins. The JAKSTAT pathway mediates the intracellular signaling of GH, and is regulated by SOCS, including SOCS2. Polymorphisms in *SOCS2* have been implicated in GH sensitivity throughout the body.[58] Although there appears to be a genetic association between *SOCS2* and longitudinal height growth from birth to adulthood,[59] further studies to help determine the association between *SOCS2* and gigantism or acromegaly may be of interest.

Recently, a possibly pathogenic germline variant (p.N604T) in *IGSF1,* a plasma membrane protein of the immunoglobulin superfamily (OMIM #300137), was identified in patients with somatomammotroph lesions from the same family.[60] This variant was associated with increased IGSF1 staining in pituitary tissue when compared with a GH-secreting adenoma from a patient that was negative for the *IGSF1* variant, and with a normal control pituitary tissue. Since the affected family was later reported to be affected by the X-LAG syndrome,[7] the findings may imply that *IGSF1*, while not playing a direct causative role in GH excess, could act synergistically in pituitary tumorigenesis.

Summary and genetic counseling

Over the last three decades, advances in genetics have led to the characterization of several molecular defects leading to gigantism or acromegaly. Although more than half of sporadic GH-producing tumors do not have an identifiable germline or somatic genetic defect, most cases of gigantism and acromegaly in young adults are in the context of the conditions described in this review (*AIP* mutations and/or FIPA, X-LAG, CNC, MAS, MEN1, MEN4, 3PA). Thus, dealing with a young patient with gigantism or acromegaly should always involve genetic counseling regardless of family history, as many of these conditions (FIPA, MEN1, and MEN4, in particular) have decreased penetrance and first-degree relatives that are carriers may not be affected. These patients should also be carefully screened for the defects described in the review. An older patient with sporadic acromegaly (over the age of 30 years) and no family history of any condition may not necessarily need to be screened for any of these genetic defects. However, the clinician should bear in mind that the occasional patient with sporadic acromegaly could also have a genetic mutation and have a low threshold for exploring genetic testing if the clinical phenotype warrants it.

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Highlights

- Over the past two decades, our increasing understanding of the molecular and genetic etiologies of pituitary gigantism and acromegaly yielded several genetic causes, including multiple endocrine neoplasia type 1 and 4, McCune-Albright syndrome, Carney complex, familial isolated pituitary adenoma, pituitary adenoma association due to defects in familial succinate dehydrogenase genes, and X-linked acrogigantism.
- Recently, we described a form of familial and sporadic acromegaly and gigantism that is caused by microduplications on chromosome Xq26.3, a disorder that we named X-LAG for X-linked acrogigantism. X-LAG may be responsible for as many as 80% of the cases of pre-pubertal gigantism.
- Dealing with a young patient with gigantism or acromegaly should always involve genetic counseling regardless of family history, as many of these conditions (FIPA, MEN1, and MEN4, in particular) have decreased penetrance and first-degree relatives that are carriers may not be affected.
- The early diagnosis of these conditions helps guide early intervention, screening, and genetic counseling of patients and their family members.

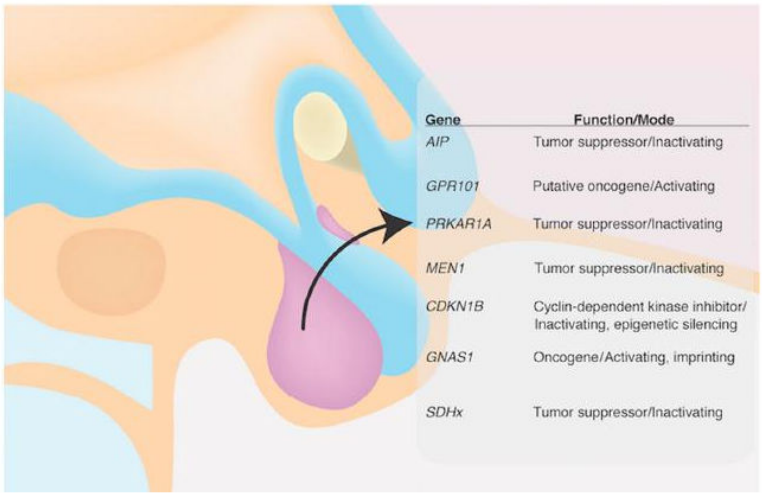

Figure 1.
Genetic mutations associated with gigantism and acromegaly.

Table 1

Nonstandard abbreviations, acronyms and definitions

3PA: pituitary adenoma association
AC: adenyl cyclase
(c) AMP: cyclic adenosine monophosphate
CNC: Carney complex
FIPA: familial isolated pituitary adenoma
GPCRs: G protein-coupled receptors
MAS: McCune-Albright syndrome
MEN: Multiple endocrine neoplasia
NF1: neurofibromatosis 1
PKA: protein kinase A
PPNAD: primary pigmented nodular adrenocortical disease
PRKAR1A: protein kinase A regulatory subunit type 1
SOCS: suppressors of cytokine signaling
X-LAG: X-linked acrogigantism

Table 2

Genetic syndromes associated with gigantism and acromegaly.

Syndrome	Gene	Chromosome	Function	Inheritance
Familial isolated pituitary adenoma (FIPA)	*AIP*	11q13.3	Tumor suppressor	Autosomal dominant or sporadic
X-linked acrogigantism (X-LAG)	*GPR101*	Xq26.3	Putative oncogene	X-linked dominant or sporadic
Carney complex (CNC)	*PRKAR1A*	17q24.2	Tumor suppressor	Autosomal dominant
Multiple endocrine neoplasia type 1 (MEN1)	*MEN1*	11q13.1	Tumor suppressor	Autosomal dominant or sporadic
Multiple endocrine neoplasia type 4 (MEN4)	*CDKN1B*	12p13.1	Tumor suppressor	Autosomal dominant
McCune-Albright Syndrome (MAS)	*GNAS1*	20q13.32	Oncogene	Sporadic
Paraganglioma, pheochromocytoma, and pituitary adenoma association (3PA)	*SDHA* *SDHB* *SDHC* *SDHD**	5p15.33 1p36.13 1q23.3 11q23.1	Tumor suppressor	Autosomal dominant or sporadic **SDHD* with genomic imprinting