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Pituitary gigantism

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Current Opinion in Endocrinology, Diabetes, and Obesity "Pituitary gigantism: Update on Molecular Biology and Management"

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Abstract

Purpose of review—To provide an update on the mechanisms leading to pituitary gigantism, as well as to familiarize the practitioner with the implication of these genetic findings on treatment decisions.

Recent findings—Prior studies have identified gigantism as a feature of a number of monogenic disorders, including mutations in the aryl hydrocarbon receptor interacting protein (*AIP*) gene, multiple endocrine neoplasia types 1 and 4, McCune Albright Syndrome, Carney Complex, and the paraganglioma, pheochromocytoma and pituitary adenoma association (3PA) due to succinate dehydrogenase defects. We recently described a previously uncharacterized form of early-onset pediatric gigantism caused by microduplications on chromosome Xq26.3 and we termed it X-LAG (X-linked acrogigantism). The age of onset of increased growth in X-LAG is significantly younger than other pituitary gigantism cases, and control of growth hormone excess is particularly challenging.

Summary—Knowledge of the molecular defects that underlie pituitary tumorigenesis is crucial for patient care as they guide early intervention, screening for associated conditions, genetic counseling, surgical approach (partial or total hypophysectomy), and choice of medical management. Recently described microduplications of Xq26.3 account for more than 80% of the cases of early-onset pediatric gigantism. Early recognition of X-LAG may improve outcomes, as successful control of growth hormone excess requires extensive anterior pituitary resection and are difficult to manage with medical therapy alone.

Keywords

gigantism; X chromosome; pituitary adenoma; X-LAG syndrome; GPR101

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Introduction

Pituitary gigantism is caused by an excess of growth hormone (GH), either from a GH-secreting pituitary tumor or from pituitary hyperplasia. Excess GH leads to gigantism only in childhood, when the skeleton maintains open epiphyseal growth plates. Pituitary gigantism is extremely rare: the incidence of pituitary tumors in children is approximately 0.1 in one million, and only between 1 and 10% of childhood pituitary tumors secrete GH (1, 2). Tumors that secrete both GH and prolactin (PRL), termed mammosomatotrophic, may occur as these cells have a shared embryonic origin. When pituitary gigantism is suspected, the clinician should consider the presence of disorders known to be associated with GH-secreting pituitary tumors, including McCune Albright syndrome (MAS) (3), Carney complex (CNC), multiple endocrine neoplasia types 1 and 4 (MEN 1, MEN 4) (4), familial isolated pituitary adenoma (FIPA), the paraganglioma, pheochromocytoma and pituitary adenoma association (3PA) due to succinate dehydrogenase defects, and X-linked acrogigantism (X-LAG). The molecular genetics of *AIP*-associated FIPA, MAS, CNC, and MEN 1 have been extensively studied and reviewed, especially in children and young adults (5–12). In this review we thus mainly focus on the recently identified X-LAG syndrome (13).

Pathophysiology and presentation

The characteristic clinical presentation of pituitary gigantism consists of unusually tall stature with abnormally rapid growth velocity. Associated constitutional findings may be present, including pubertal delay, visual defects, headache, excessive appetite, hyperhidrosis, and menstrual irregularity. Of note, tall stature is often not viewed negatively - due to this impression, there may be an associated delay in patients coming to medical attention. Physical features characteristic of acromegaly are variably present in adolescents, including prognathism, coarse facial features, large hands and feet.

Evaluation

The preferred screening test for pituitary gigantism is an IGF-1 level. If IGF-1 levels are elevated when compared to puberty and gender- and age-matched standards, the level of suspicion for a GH-secreting pituitary tumor is high, as IGF-1 correlates well with the degree of GH hypersecretion (14). Prolactin should be measured because these tumors may be co-secreting in about half of the cases. Serial overnight GH sampling may show loss of pulsatility. Additionally, oral glucose tolerance test shows failure to suppress GH levels (15). After biochemical evidence of GH excess has been established, dedicated pituitary MRI must be performed to delineate the lesion, and a bone age should be performed, in addition to formal visual field testing. A careful family history should be obtained to rule out tumors consistent with MEN 1, including parathyroid and pancreatic tumors. If characteristic spotty skin pigmentation of CNC is suspected, screening for associated conditions should rule out cardiac tumors and primary pigmented nodular adrenocortical disease. If the family history is consistent with familial isolated pituitary adenoma, the *AIP* gene should be sequenced. If the child has other characteristics associated with MAS, including café-au-lait spots, precocious puberty, and fibrous dysplasia, evaluation and

appropriate follow up is indicated. An overview of clinical characteristics reviewing known causes of pituitary gigantism is outlined in Table 1.

Treatment

Available treatment modalities for pituitary gigantism include surgery, medical therapy, and radiation. The ideal treatment is surgical excision of the tumor by an experienced neurosurgeon. In children, GH-secreting pituitary adenomas tend to be larger and more invasive than in adults (15). Recurrent or persistent GH excess is frequently found, requiring pharmacologic intervention. Permanent panhypopituitarism after transsphenoidal surgery is an inevitable result of radical tumor resection, with partial or transient hypopituitarism occurring in a subset of children who undergo partial resection of the gland. Medical treatment to inhibit GH secretion consists of octreotide (a somatostatin analogue) (16), bromocriptine or cabergoline (dopamine agonists), or pegvisomant (a GH receptor antagonist) (17).

There is limited experience of somatostatin analogues specifically in children. Side effects include glucose intolerance, diarrhea, and gallstones. Long-term safety data on the use of pegvisomant for acromegaly management in adults was recently published (18). Importantly, although the numbers of treated patients are small, different genetic etiologies of pituitary gigantism show distinct responsiveness to categories of medical therapies. This raises potential treatment implications that tailor to the specific genetic defect. Radiation therapy is another treatment modality that is indicated as an adjuvant to medical or surgical therapy in patients with residual hypersecretion of GH. However, efficacy is limited and hypopituitarism as well as potential effects on cognition are both of concern.

Overview of known genetic causes of pituitary gigantism

Table 2 provides an overview of the genetics and molecular biology underlying the disorders known to cause pituitary gigantism; each disorder is discussed separately below.

Mc Cune Albright Syndrome

MAS is a heterogeneous disorder classically recognized as the triad of precocious puberty, café-au-lait skin pigmentation, and fibrous dysplasia. Activating mutations of Gsα, the stimulatory subunit of the heterotrimeric G protein complex responsible for intracellular signaling of G protein-coupled receptors (GPCRs), are the source of the clinical manifestations found in MAS. Dysregulated signal transduction leads to downstream gene activation. Acromegaly affects 20–30% of MAS patients (19). A recent review of 112 patients with acromegaly associated with MAS found a mean diagnosis of 24.4 years, most patients had accelerated growth and hyperprolactinemia, and acromegaly was almost always associated with skull base fibrous dysplasia. Pituitary surgery very rarely cured the GH/IGF-1 excess. Somatostatin analogs improved GH/IGF-1 levels in most patients but failed to achieve control of acromegaly in the majority of patients, while pegvisomant achieved normal IGF-1 levels in more than 75% of the cases (19). In MAS, early diagnosis and treatment of growth hormone excess is specifically critical to prevent craniofacial expansion and optic neuropathy (20).

Multiple Endocrine Neoplasia-type 1 (MEN 1)

MEN 1 is a multiple tumor syndrome inherited in an autosomal dominant manner and characterized by pituitary, parathyroid, and pancreatic tumors. Mutations in the gene encoding for the tumor suppressor nuclear protein menin lead to the development of neoplasia. Individuals with MEN 1 have a 10% incidence of developing GH-secreting pituitary adenomas by age 40. A 5-year old boy reported to present with growth acceleration in the context of MEN 1 and a GH- and prolactin-secreting pituitary adenoma is the youngest reported case (4). If a patient is identified to have MEN 1, specific guidelines that recommend surveillance for associated tumors should be followed, as well as mutational testing in first-degree relatives (21). The most recent Endocrine Society guidelines recommend screening beginning at age 5 with annual biochemistry for prolactin and IGF-1 and MRI of the pituitary every 3 years. In patients with pituitary gigantism with other features of MEN 1 but without a detectable MEN 1 mutation, screening for MEN 4 via sequencing of cyclin-dependent kinase (CDKN) 1B *(CDKN1B)* should be considered (22–25). Recently, a patient with pituitary gigantism was found to have a deletion in the 5′UTR of *CDKN1B* leading to reduced transcriptional activity of the gene (24, 26).

Carney Complex (CNC)

CNC is a rare autosomal dominant disorder that includes spotty skin pigmentation, cardiac tumors (myxomas), GH- and prolactin-secreting pituitary tumors and hyperplasia, and autonomous cortisol secretion by bilateral adrenal primary pigmented nodular adrenocortical disease (PPNAD). Mutations in the gene encoding the regulatory subunit 1α of protein kinase A (*PRKAR1A*) are responsible for the majority of cases of CNC (27). Abnormal GH secretion is found in up to 50% of patients with CNC, while acromegaly manifests in approximately 10–15% of patients with CNC and usually occurs after puberty (27).

Familial Isolated Pituitary Adenoma

Inactivating mutations in the gene encoding the aryl hydrocarbon receptor interacting protein (AIP) have been identified in about 20% of families with FIPA (8). Germline mutations in *AIP* are associated with large pituitary adenomas in children/adolescents and young adults, and usually are associated with somatotropinomas in 35% of the cases (28). A recent study compared 96 patients with germline *AIP* mutations and pituitary adenomas to 232 matched *AIP*-negative acromegaly controls (28). The population with *AIP* mutations was predominantly young and male with presentation during childhood. 93% of tumors were macroadenomas with frequent extension and invasion into the cavernous sinus. Somatotropinomas comprised 78.1% of the cohort; there were also prolactinomas, nonsecreting adenomas, and one TSH-secreting adenoma. GH-secreting tumors associated with *AIP* mutations were more likely to cosecrete prolactin (28) Another recent study examined AIP mutational status of FIPA and young pituitary adenoma patients, and found 37 FIPA families and 34 sporadic patients had AIP mutations. One-quarter of the AIP mutation carriers screened were diagnosed with pituitary disease, justifying this screening and suggesting a variable clinical course for patients carrying AIP mutations (29)Patients with *AIP* mutations underwent more surgical interventions and had a poor response to

somatostatin analogues with lower decreases in GH and IGF-I and less tumor shrinkage (28). Because we now know that *AIP* is a predisposing factor for aggressive GH secreting pituitary macroadenomas, screening family members in order to have an earlier diagnosis of pituitary adenomas may lead to improved outcomes.

The paraganglioma, pheochromocytoma and pituitary adenoma association (3PA)

Germline mutations in genes coding for the succinate dehydrogenase (SDH) subunits A, B, C, and D have been identified in familial paragangliomas/pheochromocytomas and other tumors. The first GH-secreting pituitary adenoma caused by a *SDHD* mutation in a patient with familial paragangliomas was described in 2012 (30). A patient with an *SDHB* mutation, a somatotropinoma and paragangliomas was subsequently identified in addition to other patients with pituitary tumors and SDH defects (31). Most recently, 39 cases of sporadic or familial pheochromocytoma and paraganglioma and pituitary adenomas were investigated and 7 additional SDHB, C, and D germline mutations were identified (32). Recent recommendations therefore advocate for genetic testing for SDHx genes in patients with pheochromocytoma/paragangliomas in addition to pituitary adenomas (32).

X-linked Acrogigantism

Microduplication of Xq26.3 was initially identified in 14 individuals with gigantism (13). Within this chromosomal region, one gene, *GPR101*, which encodes a G protein-coupled receptor, was overexpressed in patients' pituitary lesions. X-linked acrogigantism, termed X-LAG, is characterized by early-onset gigantism resulting from an excess of GH, with a median age of onset of 12 months.

All 18 X-LAG patients analyzed to date harbor germline microduplications on chromosome Xq26.3 (13, 33). These microduplications were also identified in their pituitary tissues and did not harbor pathogenic point mutations. No other genomic rearrangements were shared by all affected cases. The Xq26.3 microduplications were initially identified by whole-genome array comparative genomic hybridization (aCGH) and subsequently confirmed by fluorescent *in situ* hybridization (FISH) and TaqMan copy number variant (CNV) assays. The use of high-resolution aCGH, long-range PCR, and sequencing of the breakpoints, facilitated exact determination of the boundaries of each rearrangement and revealed underlying genomic complexities. In particular, various microhomology sequences were observed in several patients suggesting that a replicative-based mitotic mechanism named FoSTeS/MMBIR (Fork Stalling and Template Switching/Microhomology-Mediated Break-Induced Replication) is responsible for CNV formation (13, 34, 35). Consistent with the nature of this mechanism, all the identified rearrangements are nonrecurrent, with breakpoint junctions occurring at different loci in each patient, thus generating duplicated DNA segments of different size. From a molecular point of view X-LAG syndrome represents a classical example of genomic disorder (36).

The majority of identified X-LAG patients are sporadic females, suggesting that the origin of the CNV is postzygotic, which is consistent with the identified FoSTeS/MMBIR

mutational mechanism, and that hemizygous male embryos are probably not viable. However, two instances of X-LAG transmission have also been identified. The inheritance was dominant and involved in both cases transmission from affected mother to affected son(s) (13, 33).

The common duplicated genomic segment shared by all patients is about 500 kb in length, ranging from chromosomal position 135,627,637 to 136,118,269 (GRCh37/hg19 assembly), and consists of two smallest regions of overlap (SRO). SRO1 (135,627,637–135,986,830) encompasses three protein-coding genes: *CD40LG* (MIM#300386), *ARHGEF6* (MIM# 300267), and *RBMX* (MIM# 300199); while SRO2 (136,045,310–136,118,269) contains the sole *GPR101* gene (MIM# 300393). *GPR101* consists of a single 1.5 kb long exon that encodes for an orphan GPCR; it is the only duplicated gene found to be highly over-expressed in the pituitary tumors of the patients (13). Interestingly, very low levels of GPR101 mRNA were seen in patients' leucocytes, suggesting that *GPR101* is a dosage sensitive gene whose pituitary-specific over-expression might be caused by perturbed chromatin regulation or by an unknown promoter sequence created by the chromosomal rearrangement (13, 37). Moreover, GPR101 over-expression in a GH-secreting cell line was shown to strongly activate the cAMP pathway, whose mitogenic effects in pituitary somatotroph cells are very well known (38). These findings thus strongly implicate *GPR101* as the causative gene. However, the neurophysiological mechanisms through which GPR101 activation might lead to increased GH secretion remain unclear at present. Several studies in rodents showed that *GPR101* is expressed at high levels in the hypothalamus (13, 39–43). Moreover, some X-LAG patients, as well as previously reported patients with disease phenotypes that closely resemble X-LAG, showed elevated GHRH levels (33, 44–46). These findings suggest that hypothalamic GHRH dysregulation may also play a role in the etiology of the syndrome (33). We can speculate that GPR101 might have two potential physiopathological functions: one as a regulator of GHRH secretion and the other via increased pituitary expression. The generation of transgenic animal models will greatly help to elucidate that.

As X-LAG syndrome, although very rare, will be increasingly recognized by physicians all over the world, more giants with unknown genetic defects will be screened for Xq26.3 microduplications. The identification of new X-LAG cases might help to narrow down the SRO, thus providing a strong indication if *GPR101* is the only disease driver or if the other duplicated genes also contribute to the phenotype. In any case, the identification of the molecular defects underlying X-LAG already offers an opportunity to study a new pathway involved in the central regulation of human growth. For example, the identification of compounds that bind to and block GPR101 activity might be very beneficial for the treatment of X-LAG patients, given the fact their tumors are very aggressive, do not respond well to commonly used drugs such as somatostatin analogs, and thus generally require radical surgical resection with consequent hypopituitarism (33).

FUTURE DIRECTIONS

Pituitary gigantism is a very rare condition and only a few hundred cases have been reported in the medical literature to date (5). The search for potential variants to explain pituitary

tumor formation continue; a recently identified variation in immunoglobulin superfamily member 1 (*IGSF1*) has been described in the germline DNA of three patients with gigantism in the same family (47). This family was also found to harbor an Xq26.3 duplication, but this potentially functional *IGSF1* variant might act as a disease-modifier (13, 47, 48).

In the largest retrospective study of gigantism conducted so far, 143 patients were genetically tested and known genetic defects were identified in about half of them: 29% had *AIP* mutations/deletions associated with sporadic or familial (FIPA) cases of gigantism, 10% X-LAG syndrome, 5% MAS, 1.5% familial CNC, and one was a MEN 1-mutated case. In the remaining 54% of investigated cases no genetic cause was identified; interestingly, these patients exhibit very aggressive disease features (49). Given what we now know about recently identified causes of pituitary gigantism, an updated decision tree for suggested genetic testing and screening is presented in Figure 1.

While not characterized as pituitary gigantism because not directly related specifically to a pituitary tumor, some children with neurofibromatosis type 1 (NF1) and an optic glioma or hypothalamic tumor have also been reported to present with GH excess and early-childhood onset gigantism. While mutations in the *NF1* gene would most likely explain these cases, it is still unclear the origin of the GH excess, being the tumors that have been analyzed negative for GH, growth hormone releasing hormone (GHRH), and somatostatin expression. It has been hypothesized that GH over-secretion is the consequence of loss of somatostatinergic inhibition due to tumor infiltration (5, 50). A lot and exiting work still awaits endocrinologists and geneticists studying gigantism: how loss of *AIP* predisposes to pituitary tumor formation, despite being studied for almost a decade now, is still unknown; the origin of GH excess in some NF1 cases is still a mystery; X-LAG characterization is still in its infancy; and, very importantly, the genetic defects in about 50% of gigantism cases have not been discovered yet. The recent advent and continuously increased use of very sensitive whole genome assays (which were instrumental in the discovery of X-LAG), and the study of sequences not routinely screened in genes known to cause gigantism like their promoter and untranslated regions (and the regulatory factors binding to those sequences) (51), might be the key to identify the genetic defects in the remaining 50% of genetically unexplained patients.

Conclusion

Pituitary gigantism is a condition characterized by excessive growth that results from an over-secretion of GH and occurs before the closure of growth plates. This implies that gigantism affects pediatric patients and occurs during the infancy, childhood or adolescence stage of human growth. Gigantism can present either sporadically or be inherited and can occur as the only feature or as part of an endocrine tumor syndrome. Syndromes characterized by GH excess include NF1, MAS, MEN 1, CNC, FIPA, 3PA, and most recently, X-LAG.

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Key points

- Investigation of a patient with pituitary gigantism should include assessment of the family history and possibility of related diagnostic features; early-onset gigantism should prompt screening for the recently described entity X-LAG.
- A number of genetic conditions are associated with an increased predisposition to the development of GH secreting pituitary tumors; every gene identified to be involved in pituitary gigantism is a potent oncogene or tumor suppressor with important roles in signaling.
- Identification of the genetic etiology of pituitary gigantism has critical implications for treatment decisions, genetic counseling, and screening for associated abnormalities outside of the pituitary gland.

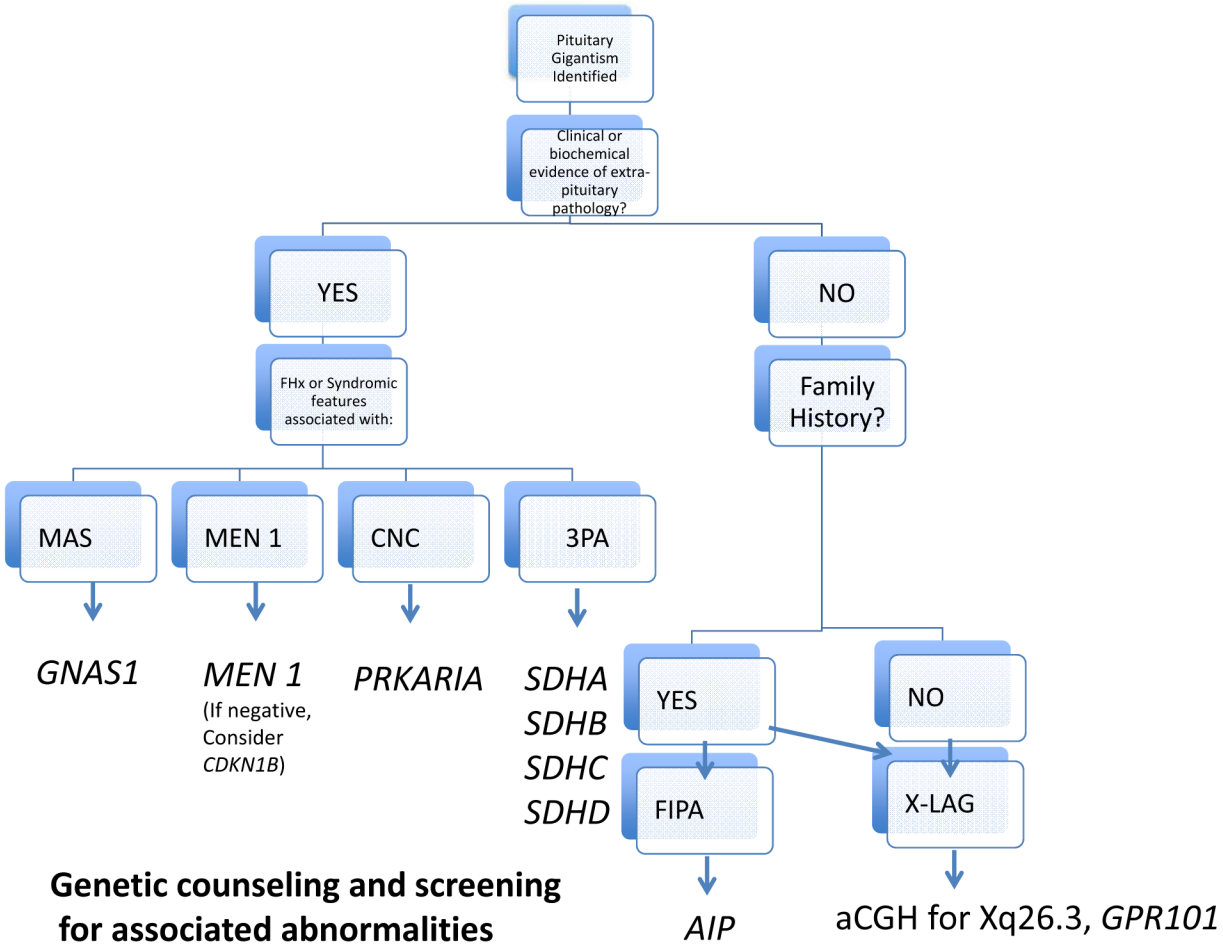

Figure 1.
Genetic Counseling and screening for associated abnormalities

Table 1

Disorder	Clinical Features	Mode of Inheritance	Age of Onset of acromegaly/gigantism	Frequency of Acromegaly/Gigantism	Screening recommendations
X-linked acrogigantism	Isolated GH excess	Sporadic or X-linked	Early childhood with onset in late infancy or onset during adolescence	Unknown	As clinically indicated in unaffected family members
McCune-Albright syndrome	Precocious Puberty Café au lait skin pigmentation Fibrous bone dysplasia Multiple endocrinopathies	Sporadic	Early childhood on	20–30%	Annually
Carney complex	Multiple endocrine tumors Skin lentigines Cardiac myxomas Neural sheath tumors	Autosomal Dominant or Sporadic	Usually 3rd& 4th decade	10–15%	Annually beginning after puberty
Multiple endocrine neoplasia type 1	Pituitary, pancreatic and parathyroid adenomas	Autosomal Dominant or Sporadic	10% by age 40 but has occurred as early as age 5	10%	Annually beginning at age 5
Familial isolated pituitary adenoma	Isolated GH-secreting pituitary adenomas	Autosomal Dominant or Sporadic	Childhood and adolescence	GH secreting adenomas are the most frequent tumors among FIPA patients	As clinically indicated in unaffected family members
Multiple endocrine neoplasia type 4	Acromegaly Pituitary adenoma Parathyroid adenoma Carcinoid tumors	Autosomal Dominant or Sporadic	Unknown	Unknown	Unknown
3PAs	Pituitary adenomas Pheochromocytomas paragangliomas	Autosomal dominant or Sporadic	Unknown	Unknown	Unknown

Curr Opin Endocrinol Diabetes Obes. Author manuscript; available in PMC 2017 February 01.

Table 2

Disorder	Gene name	Mendelian Inheritance in Man (MIM) number	Location (Chromosome)	Function	Tumor suppressor gene or oncogene	Defect
X-linked acrogigantism	*GPR101*	300942	Xq26.3	Contiguous gene duplication syndrome	Oncogene	Overexpression of GPR101
McCune-Albright syndrome	*GNAS (GNAS1)*	139320	20q13.32	Alpha subunit of the stimulatory G protein that activates adenylate cyclase	Oncogene	Gain-of-function somatic mutations
Carney complex	*PRKAR1A*	188830	17q24.2	Loss of inhibition of protein kinase A	Tumor suppressor gene	Loss-of function mutations
Multiple endocrine neoplasia type 1	*MEN1*	613733	11q13.1	Transcriptional regulator	Tumor suppressor gene	Loss-of function mutations and deletions
Familial isolated pituitary adenoma	*AIP*	605555	11q13.2	Co-chaperone protein	Tumor suppressor gene	Decreased expression in somatotrophinomas
Multiple endocrine neoplasia type 4	*CDKN1B*	610755	12p13.1	Cell cycle regulator of p27 in neuroendocrine cells	Tumor suppressor gene	Loss of function mutations and deletions
3PAs	*SDHA* *SDHB* *SDHC* *SDHD*	600857 185470 602413 602690	5p15.33 1p36.13 1q23.3 11q23.1	Mitochondrial oxidation defects	Tumor suppressor gene	Loss of function mutations and deletions

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