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An update on the genetics of benign pituitary adenomas in children and adolescents

Fady Hannah-Shmouni, MD, FRCPC and **Constantine A. Stratakis, MD, D(Med)Sc***

Section on Endocrinology & Genetics (SEGEN), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), Bethesda, MD, 20892, USA

Abstract

Pituitary adenomas in children and adolescents are rare tumors that often result from a tumor predisposition syndrome. Several inherited causes for pituitary adenomas have been identified in the last few years, including multiple endocrine neoplasia type 1 and 4, Carney's complex, Tuberous sclerosis, DICER1 syndrome, neurofibromatosis type 1, McCune Albright syndrome, familial isolated pituitary adenoma, and pituitary adenoma association due to defects in succinate dehydrogenase genes. Recently, our group discovered X-linked acrogigantism (X-LAG), a new pediatric disorder that is caused by an Xq26.3 genomic duplication (involving the *GPR101* gene). Genes that predispose to pediatric Cushing disease, including *CABLES1* and *USP8*, were also recently identified. Genetic screening and counseling of affected or at risk individuals is a key component of their comprehensive care. In this review, we provide an up-to-date discussion on the latest pediatric genetic discoveries associated with pituitary adenomas with a focus on familial syndromes.

Keywords

Pituitary adenoma; Cushing disease; Gigantism; GH; Genetics; USP8

***Correspondence:** Constantine A. Stratakis MD D(Med)Sc, Senior Investigator and Scientific Director, NICHD, SEGEN, PDEGEN, NIH, Building 10, CRC, Room 1-3330, 10 Center Dr., MSC1103, Bethesda, Maryland. USA. 20892, Tel: 301-496-4686/496-6683, Fax: 301-402-0574/480-0378.
Submitting author: Fady Hannah-Shmouni, fady.hannah-shmouni@nih.gov

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Introduction

The adenohypophysis of the pituitary gland arises from epithelial cells of endodermal origins and consists of a heterogeneous population of well-differentiated hormone-secreting cells. These include somatotrophs, lactotrophs, mammosomatotrophs, corticotrophs, thyrotrophs and gonadotrophs [1], and comprise ~3.5–6% of all surgically treated pediatric pituitary tumors [2]. Pediatric pituitary adenomas are typically benign with the most frequently encountered tumors being prolactinomas (most are in adolescents), followed by corticotropinomas and somatotropinomas [3]. Pediatric nonfunctioning pituitary adenomas are encountered in 3–6% of all cases [4, 5].

Over the past three decades, our evolving understanding of molecular and genetic investigations have revealed a number of genetic defects predisposing to pituitary adenomas in childhood (Table 1) [6]. It is now well established that known germline gene abnormalities may cause up to approximately one-fifth of pituitary adenomas in children and adolescents. Multiple familial syndromes were identified, including multiple endocrine neoplasia type 1 and 4 (MEN1 and MEN4), Carney's complex (CNC), DICER1 syndrome, Tuberous sclerosis complex (TSC), neurofibromatosis type 1 (NF1), McCune Albright syndrome (MAS), familial isolated pituitary adenoma (FIPA), and pituitary adenoma association due to defects in familial succinate dehydrogenase genes (3PAs) [7, 8]. Recently, our group has discovered X-linked acrogigantism (X-LAG), a new pediatric disorder of gigantism that is caused by an Xq26.3 genomic duplication (*GPR101*) [9]. Additionally, genes that predispose to pediatric CD, including *CABLES1* and *USP8*, have also been uncovered [10, 11]. In this review, we provide an up-to-date discussion on the latest genetic discoveries in pediatric pituitary adenomas with a focus on familial syndromes that predispose to CD and gigantism and provide an algorithm for genetic counseling and testing of these conditions.

Genetics of Cushing disease

Cushing disease (CD) is a rare condition with an incidence of 1.2–1.7 cases per million per year [12]. CD arises from monoclonal proliferation of corticotrophs leading to endogenous ACTH-dependent hypercortisolemia. Pediatric CD is evenly distributed throughout childhood, and is the commonest cause of Cushing syndrome beyond infancy [3]. Genetic alterations in corticotropinomas rarely occur in the known proto-oncogenes or tumor suppressor genes (Table 1). In contrast with other pituitary tumor types, the genetic causes of corticotropinomas are largely unknown. Recent studies have shown that the most common genetic alteration found in over one third of pediatric corticotropinomas were recurrent activating somatic heterozygous driver mutations located in a hotspot region in exon 14 of the ubiquitin-specific protease 8 gene (*USP8*; chromosome 15q21.2) [10, 13]. Patients with CD harboring mutations in *USP8* were older at diagnosis with a higher likelihood of recurrence when compared with patients without mutations [10]. Moreover, *USP8* mutations lead to activation of epidermal growth factor receptor (EGFR) signaling, a potential target for CD treatment. There are no known germline *USP8* mutations in humans.

Recently, our group has identified 4 potentially pathogenic missense germline variants in CDK5 and ABL1 enzyme substrate 1 (*CABLES1*; chromosome 18q11.2), a tumor suppressor gene that regulates cell cycle progression. Genetic alterations in *CABLES1* were found in 4 female patients (2 young adults and 2 children) with large corticotropinomas that were difficult to manage [11]. Other somatic events reported in CD with aggressive behavior include genetic alterations in *p53* (chromosome 17p13.1) tumor suppressor gene [14].

Several familial syndromes predispose to CD. MEN's are a diverse group of autosomal dominant (AD) syndromes that predispose to tumor formation in multiple organs. MEN-1 (OMIM #131100) is characterized by tumor formation in over 30 tissues, including pituitary, parathyroid, and pancreas. MEN-1 is caused by germline (and rarely somatic) mutations in *MEN1* (chromosome 11q13) [15], with over 1300 germline mutations reported [16]. Pediatric corticotropinomas are rare in MEN-1 but have been reported as its first manifestation [17]. In one study of 74 patients with sporadic CD and 4 patients with syndromic CD, MEN-1 mutations were only identified in 2 syndromic patients with genetically confirmed MEN-1 relatives [18].

MEN-2 is divided into MEN-2A (OMIM # 171400) and MEN-2B (OMIM #162300) and caused by activating mutations of the proto-oncogene *RET* (chromosome 10q11.21) [19]. Pituitary involvement in MEN-2 is exceedingly rare; our group has recently reported the a case of pediatric CD due to a microcorticotropinoma in MEN-2B [20], providing evidence for the role of this gene in corticotroph tumorigenesis.

MEN-4 (OMIM #610755) is MEN-1 like, and caused by germline inactivating mutations in *CDKN1B* (chromosome 12p13.1), a putative tumor suppressor gene coding for p27 that regulates cell cycle progression [21]. Pituitary adenomas are the second most common phenotypic feature of MEN-4, affecting ~ 37% of the reported cases with an age of diagnosis of 30–79 years [21]. CD has been reported in only one adult with MEN-4 due to a heterozygous 19-bp duplication (c.59_77dup19) in *CDKN1B*, leading to a truncated protein [22], and none in pediatric cohorts with CD [18, 23]. In one study, the common *CDKN1B* rs2066827 polymorphism was shown to play a role in corticotropinoma susceptibility and tumorigenesis likely through epigenetic mechanisms [24].

CNC (OMIM #160980) is an AD syndrome that is primarily caused by mutations in the tumor suppressor gene *PRKAR1A* (chromosome 17q22-24; CNC1 locus). A specific genetic alteration on chromosome 2p16 (CNC2 locus) has not yet been identified, whereas a single case of CNC has been described in association with *PRKACB* amplification (CNC3 locus) [25–27]. CNC manifests with skin pigmentation, cardiac myxomas, GH and prolactin-secreting pituitary tumors or hyperplasia, and adrenal Cushing syndrome primarily from primary pigmented nodular adrenocortical disease (PPNAD) [27, 28]. Previous investigations did not reveal somatic or germline *PRKAR1A* mutations in pediatric CD [18]. Recently, our group reported a pediatric case of CD that was subsequently followed by PPNAD in a patient carrying an inactivating *PRKAR1A* germline mutation [29], providing evidence for the role of *PRKAR1A* in corticotroph tumorigenesis.

FIPA (OMIM #605555) is characterized by the occurrence of pituitary adenomas in multiple family members. The tumor suppressor gene aryl hydrocarbon receptor-interacting protein (*AIP*, chromosome 11q13.3) is identified in approximately 15–20% of familial FIPA [30, 31]. These mutations typically affect young patients, with or without a family history, with a low penetrance of ~ 15–30%.

Other syndromes that predispose to pediatric CD include MAS (OMIM #174800) due to gain-of-function mutations in *GNAS1* in the mosaic state [32, 33], TSC (OMIM #191100 and #613254) as a result of germline mutations in 2 tumor suppressor genes (*TSC1*; chromosome 9q34.13, and *TSC2*; chromosome 12q15) [34], and DICER1 syndrome as a result of loss-of-function mutations in the *DICER1* gene (chromosome 14q32.13) [35]. The recently discovered syndrome, X-LAG (see below) due to Xq26.3 genomic duplication (*GPR101*) has not been implicated in pediatric CD. Screening a cohort of pediatric CD did not reveal germline or somatic *GPR101* mutations [36].

Newer genetic approaches, such as whole exome sequencing and transcriptomic analysis, have helped uncover new genes in the predisposition of sporadic and familial pediatric CD. These include cadherin-related 23 (*CDH23*; chromosome 10q22.1), cyclin D2 (*CCND2*; 12p13.32), Zinc-finger 676 protein (*ZNF676*; chromosome 19p12), death-associated protein kinase 1 (*DAPK1*; chromosome 9q21.33) and metalloproteinase inhibitor 2 (*TIMP2*; chromosome 17q25.3) [37, 38]. Their role in the pathogenesis of pediatric CD should be further ascertained in well-designed studies.

Genetics of Gigantism

Disorders of GH-excess can be grossly divided into two major categories; gigantism and acromegaly. The two disorders represent a continuum of clinical manifestations and depend on whether the epiphyseal growth plates are not fused (gigantism), or fused (acromegaly). The most common pituitary pathology is a benign GH-secreting pituitary tumor, called somatotropinoma. The incidence of pituitary gigantism and acromegaly are approximately 8 and 11 cases per million person-years, respectively [39]. The cyclic AMP pathway is frequently dysregulated in sporadic somatotropinomas; somatic activating mutations in *GNAS*, which encodes for Gsα, are found in the heterozygous state [40], and on the maternal allele [41], representing the first and largest somatic genetic alteration in somatotropinomas [42].

Most cases of pediatric gigantism are familial. X-LAG (OMIM #300942) is the most common cause of early childhood-onset gigantism in ~80% of pre-pubertal gigantism. X-LAG is caused by GH (and prolactin) over secretion due to a pituitary macroadenoma or hyperplasia [9], with a median age of onset of 12 months. Germline microduplications on chromosome Xq26.3 causing X-LAG mainly to arise *de novo*. The culprit gene in this duplicated region is *GPR101,* which codes for an orphan G-protein coupled receptor (GPCR) [9, 43]. In sporadic acromegaly, a rare missense variant in *GPR101* (p.E308D) was identified in approximately 4% of cases [44].

Gigantism can occur in association with *AIP* mutations (FIPA) and seen in ~30% of patients with a somatotropinoma [8, 45]. In one study, Daly et *al.* [46] showed that *AIP* mutation-positive acromegalics were predominantly young males with the majority presenting during childhood or adolescence. These cases were associated with higher levels of GH and prolactin, were more likely to undergo transphenoidal surgery, and were less responsive to somatostatin analogues. The prevalence of *AIP* mutations in patients with sporadic pituitary adenomas is ~4% [47]. However, there are no reports to date of somatic mutations of *AIP.*

In MAS, GH-excess is seen in ~20–30%, with a mean age at diagnosis of 24.4 years [48]. Somatotroph hyperplasia involves the entire pituitary gland, with or without somatotroph adenoma [49]. The incidence of GH-secreting pituitary adenomas in MEN-1 is ~10% by age 40 and rarely occurs in childhood [15]. GH-excess is rare in MEN-4; only one case of gigantism due to a heterozygous mutation in the 5'-UTR region (c.-29_-26delAGAG) of *CDKN1B* [21, 50]. Mutations in *CDNK1B* rarely occur in association with sporadic gigantism or acromegaly [51]. In CNC, GH-excess is seen in ~79% of patients and usually due to somatotroph cell hyperplasia [27]. Somatic alterations in *PRKAR1A* or *PRKACB* have never been found in sporadic GH-secreting pituitary adenomas.

Recently, our group has identified a new syndrome, that we termed 3PAs, which refers to the co-existence of familial paragangliomas and pheochromocytomas (PPGL) and pituitary adenomas. 3PAs is caused by germline *SDHx* mutations [52]. The first case was in an acromegalic with paraganglioma due to a pathogenic mutation in *SDHD* [53].

Other rare genetic defects that have been implicated in the pathogenesis of gigantism include NF1 (OMIM #162200) [54, 55] and pathogenic germline variant (p.N604T) in *IGSF1* (OMIM #300137), a membrane of the immunoglobulin superfamily, identified in a family with somatomammotroph lesions [56].

Genetic counseling and testing

The identification of the genes responsible for syndromic CD and gigantism has enabled the genetic diagnosis and early identification of patients and their at-risk family members. Genetic testing in clinical practice for familial syndrome has become routine. When faced with a rare endocrinopathy, such as CD, clinicians are encouraged to obtain a detailed family history and pedigree to deduce dominance and distinguish autosomal from X-linked inheritance.

Most pediatric CD cases are sporadic but can rarely arise from familial syndromes. Conversely, most pediatric gigantism is caused by familial syndromes such as FIPA, X-LAG, CNC, and MEN and rarely occur sporadically. Thus, when a clinician encounters a pediatric patient with gigantism, genetic testing and counseling regardless of family history should be considered as many of these conditions (such as FIPA or MEN-1) have decreased penetrance and first-degree relatives that are carriers may not be affected. In cases of pediatric CD, genetic testing and counseling should be performed particularly if the clinical presentation is in keeping with a familial syndrome (e.g.: spotty pigmentation that may suggest CNC). The clinician may encounter an occasional patient with presumed sporadic

gigantism or CD that may harbor an underlying germline genetic alteration that predisposes to any of the familial syndromes in this review. In such cases, a low threshold for exploring genetic testing is important particularly if the clinical phenotype warrants it.

Figure 1 details an approach to screening in familial pituitary adenomas. Index cases or individuals with syndromic features should be offered targeted genetic testing (e.g.: *PRKAR1A* in CNC) for the syndrome in question. Index cases or individuals with negative targeted sequencing or those without a defined syndrome should be offered whole exome or genome sequencing. Screening should also be offered to a first-degree relative when a germline mutation has been identified. Additionally, the identification of a germline mutation should prompt periodic clinical, biochemical and radiological screening for the syndrome in question. Periodic (e.g.: every 2 years) reassessment of the medical literature and raw genetic data is encouraged to identify new genes or syndromes in individuals with a suspected syndrome and an unidentified genetic mutation.

Conclusions

Pituitary tumors are rare in children and adolescents but they could be, more often that in adults, associated with a tumor predisposition syndrome. Over the past three decades, advances in molecular genetics uncovered several molecular causes of pituitary adenomas changing the way these patients are approached by the clinicians. It is now imperative that genetic screening and counseling of affected or at risk individuals are offered to children and adolescents with pituitary tumors and an inherited tumor predisposition syndrome.

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Abbreviations

3PAs	pituitary adenoma association
cAMP	cyclic adenosine monophosphate
CNC	Carney’s complex
FIPA	familial isolated pituitary adenoma
GPCRs	G protein-coupled receptors
MAS	McCune Albright syndrome
MEN	Multiple endocrine neoplasia
NF 1	neurofibromatosis 1
PPNAD	primary pigmented micronodular adrenal disease
PRKAR1A	protein kinase A regulatory subunit type 1

X-LAG	X-linked acrogigantism

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Highlights

- X-linked acrogigantism (X-LAG) is a recently described pediatric disorder that is caused by an Xq26.3 genomic duplication and characterized by early-onset gigantism.
- A novel pituitary tumor-predisposing gene, *CABLES1*, has been uncovered in pediatric corticotropinomas.
- Somatic *USP8* gene mutations are a common cause of pediatric Cushing disease and associated with a higher likelihood of tumor recurrence.

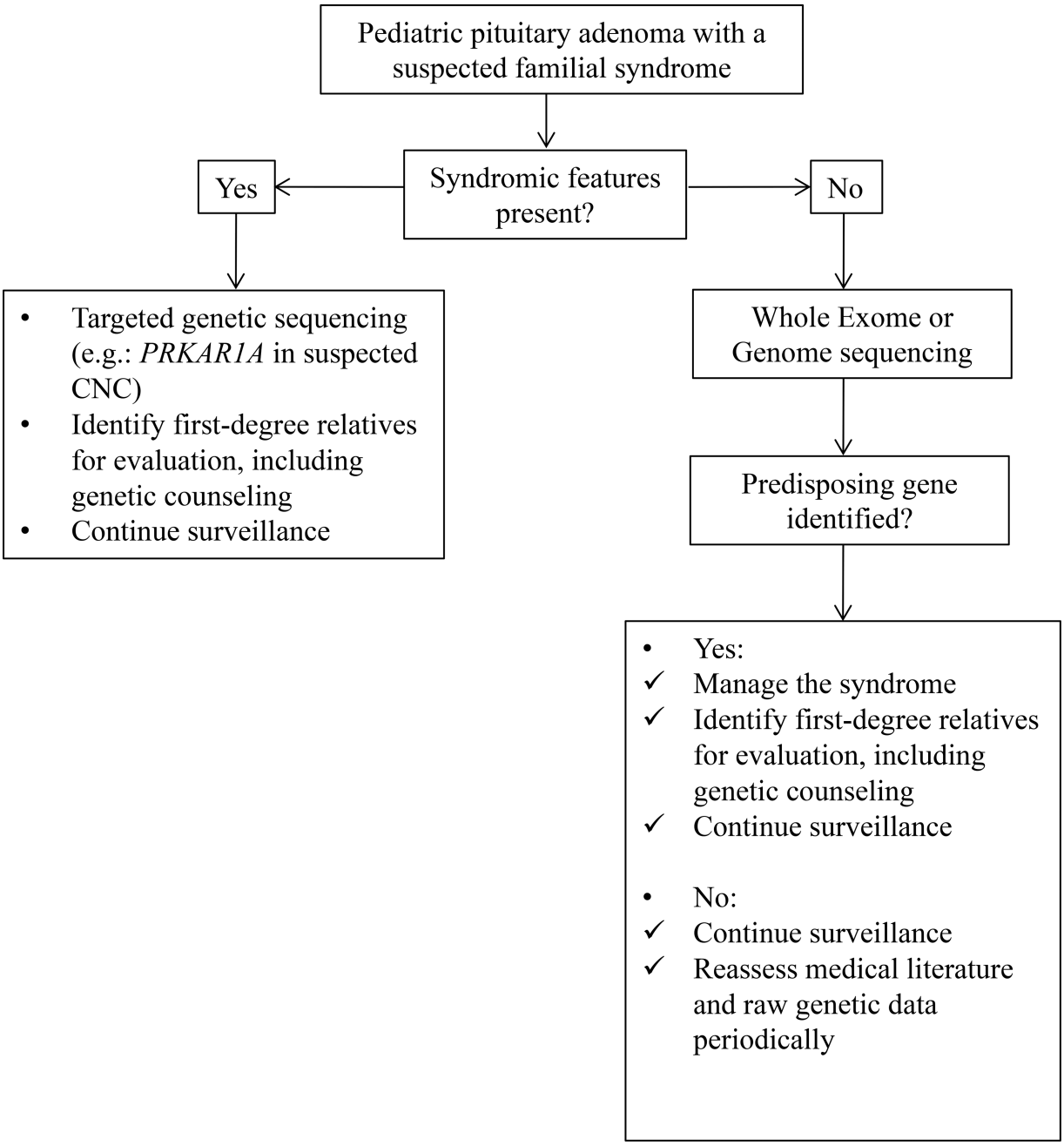

Figure 1.

An approach to screening in familial pituitary adenomas. Index cases or individuals with syndromic features should be offered targeted genetic testing for the syndrome in question. Index cases or individuals with negative targeted sequencing or those without a defined syndrome should be offered whole exome or genome sequencing. Screening should also be offered to a first-degree relative when a germline mutation has been identified. Additionally, the identification of a germline mutation should prompt periodic clinical, biochemical and radiological screening for the syndrome in question.

Table 1

Genetic syndromes associated with familial pituitary adenomas.

Syndrome	Gene	Chromosome	Function	Inheritance	Pituitary tumor type
Familial isolated pituitary adenoma (FIPA)	*AIP*	11q13.3	Tumor suppressor	AD	Somatotropinoma Somatomammotropinoma Corticotropinoma Non-functional Prolactinoma
X-linked acrogigantism (X-LAG)	*GPR101*	Xq26.3	Unknown function	Sporadic, X-linked dominant	Somatotropinoma Somatomammotropinoma
Carney complex (CNC)	*PRKAR1A*	17q24.2	Tumor suppressor	AD	Somatotropinoma Somatomammotropinoma Corticotropinoma
Multiple endocrine neoplasia type 1 (MEN-1)	*MEN1*	11q13.1	Tumor suppressor	AD	Somatotropinoma Somatomammotropinoma Corticotropinoma Non-functional Prolactinoma
Multiple endocrine neoplasia type 2A (MEN-2A)	*RET*	10q11.21	Oncogene	AD	Corticotropinoma
Multiple endocrine neoplasia type 2A (MEN-2B)	*RET*	10q11.21	Oncogene	AD	Corticotropinoma
Multiple endocrine neoplasia type 4 (MEN 4)	*CDKN14*	12p13.1	Tumor suppressor	AD	Somatotropinoma Corticotropinoma Non-functional Prolactinoma
DICER1 syndrome	*DICER1*	14q32.13	Tumor suppressor	AD	Corticotropinoma
McCune Albright Syndrome (MAS)	*GNAS1*	20q13.32	Oncogene	Sporadic (mosaicism)	Somatotropinoma Somatomammotropinoma

Syndrome	Gene	Chromosome	Function	Inheritance	Pituitary tumor type
Tuberous sclerosis complex (TSC)	*TSC1*	9q34.13	Tumor suppressor	AD	Corticotropinoma
	TSC2	16p13.3			
Paraganglioma, pheochromocytoma, and pituitary adenoma association (3PA)	*SDHA*	5p15.33	Tumor suppressor	AD, sporadic	Somatotropinoma
	SDHB	1p36.13			
	SDHC	1q23.3			
	SDHD	11q23.1			