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Genetics of Adrenocortical Development and Tumors

Maya Lodish, MD, MHSc

Pediatric Endocrinology Fellowship, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Building 10, Room 9D42, 10 Center Drive, MSC 1830, Bethesda, MD 20892-1830, USA

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INTRODUCTION

This article links the understanding of the developmental physiology of the adrenal cortex to adrenocortical tumor formation. Many molecular mechanisms that lead to the formation of adrenocortical tumors have been discovered via next-generation sequencing approaches. The most frequently mutated genes in adrenocortical tumors are also factors in normal adrenal development and homeostasis, including those that alter the p53 and Wnt/ β -catenin pathways. In addition, dysregulated protein kinase A (PKA) signaling and *ARMC5* mutations have been identified as key mediators of adrenocortical tumorigenesis. The growing understanding of the genetic changes that orchestrate adrenocortical development and disease pave the way for potential targeted treatment strategies.

Adrenocortical carcinoma (ACC) has a bimodal age distribution with a peak in early childhood with a mean age of diagnosis at 3.2 years, and a peak in adulthood in the fourth and fifth decades.^{1, 2} ACC has an annual incidence of 0.7 to 2 per million.^{3, 4} The understanding of the pathophysiology of ACC is limited, and the disease carries a poor prognosis.⁵ Recent identification of genetic characteristics of ACC may lead to the development of novel therapeutic interventions. Several genes have been implicated as tumor drivers in sporadic ACC, including mutations in insulin-like growth factor 2 (*IGF2*), β -catenin (*CTNNB1* or *ZNRF3*), and *TP53*.^{6, 7} Importantly, germline variants of some of the same genes identified to be drivers of sporadic ACC are also associated with familial tumor syndromes characterized by ACC, including Beckwith-Wiedemann syndrome (BWS), familial adenomatous polyposis (FAP), and Li-Fraumeni syndrome.

Elevated cAMP signaling is related to most benign cortisol-producing tumors of the adrenal gland. The first human disease that directly linked cAMP signaling to cortisol-producing lesions was with the discovery more than 25 years ago that activating mutations in *GNAS1* caused adrenocortical tumors in infants with McCune-Albright syndrome (MAS). Mutations

in the regulatory subunit type 1 α (R1 α) of the cAMP-dependent protein kinase or PKA were then identified as the cause of another form of cortisol-producing hyperplasia, primary pigmented nodular adrenocortical disease (PPNAD). Inactivating mutations in inhibitors of the cAMP-signaling pathway (phosphodiesterases [PDEs]) were later identified as another cause of adrenocortical hyperplasia. Most recently, somatic activating mutations in the main catalytic subunit of PKA have been discovered in cortisol-producing adenomas. Put together, these findings provide convincing proof that increased cAMP signaling is key to adrenal tumor development. The implications of this finding lead to the search for targeted treatment strategies for adrenal tumors and hypercortisolism that act on the cAMP/PKA cascade.

A novel gene was recently identified that provides evidence that bilateral macronodular adrenal hyperplasia is frequently a genetic disorder. Germline mutations in the tumor suppressor gene *ARMC-5* lead to the development of an autosomal dominantly inherited form of Cushing syndrome (CS). Because this type of CS may present in a cyclical manner that may take many years to diagnose, the potential to identify individuals at risk for the development of CS based on genetic findings has the potential to lead to more timely diagnosis of CS. Recent advances in the understanding of adrenocortical signaling have taught that cortisol secretion within the adrenal gland is more complex than previously thought. It is now known that paracrine signaling via intra-adrenal secretion of corticotrophin is a factor in adrenal hyperplasia.

OVERVIEW OF ADRENOCORTICAL DEVELOPMENT

The adrenal cortex derives from components of the urogenital ridge, sharing a common origin with the kidney and gonads.⁸ The human adult adrenal cortex is separated into three distinct zones that may be characterized by their functionality and histology. The outermost layer, the zona glomerulosa, secretes aldosterone; the middle zona fasciculata secretes glucocorticoids; and the innermost zona reticularis produces sex steroid hormone precursors androstenedione and dehydroepiandrosterone (Fig. 1).

Adrenocortical cell precursors originate from the coelomic epithelium that, together with the gonadal cell precursors, forms the adrenogonadal primordium. The encapsulation of the adrenal primordium, creating the fetal adrenal gland, occurs by 9 weeks postconception.^{9, 10} By midgestation, the fetal adrenals are composed of two distinct cortical zones: the predominant fetal zone and the surrounding definitive zone. Shortly after birth, the adrenal cortex is remodeled and the fetal zone recedes. The establishment of the adrenal zona glomerulosa and zona fasciculata occurs in late fetal development; however, the zona reticularis is not completely established until adrenarche (Fig. 2). Corticotrophin is the primary regulator of development of the human fetal adrenal mediated through locally expressed growth factors including EGF, bFGF, and insulin-like growth factor (IGF)-I and -II.¹⁰ As the definitive cortex grows and the fetal cortex regresses, capsular cells give rise to steroid-producing adrenocortical cells.¹¹

ADRENOCORTICAL TUMORS: OVERVIEW OF GENETIC BASIS

Current understanding of normal adrenocortical development sheds light on the molecular pathways that, when altered, may stimulate abnormal proliferation and drive adrenocortical tumor formation. Adrenal tumors may be functional and lead to syndromes of hormone excess, hypercortisolism (CS), hyperaldosteronism (Conn syndrome), hyperandrogenism (virilizing syndrome), or mixed. CS may be caused by over-secretion of cortisol from adrenocortical hyperplasia, tumors, or cancer. Most (75%–90%) of these tumors are benign unilateral adenomas. ACC is infrequent, making up less than 5% of all ACTs. The remainder of the adrenal lesions (10%) are related to bilateral hyperplasia: PPAD and primary bilateral macronodular adrenal disease (PBMAD). Knowledge of the molecular pathways involved in adrenocortical tumorigenesis arises from the genetic basis of inherited syndromes that include adrenocortical tumors (Table 1), and from next-generation sequencing approaches of tumor and germline DNA (Table 2).

Several paracrine and endocrine signals are key players in adrenocortical development. Steroidogenic factor-1 (*SF-1*, *NR5A1*) and nuclear receptor subfamily 0 group B member 1 (*DAX-1*, *NR0B1*) are key transcription factors critical for adrenocortical development.¹² The sonic hedgehog pathway is central to adrenocortical development and has been implicated in ACC with up-regulation in adult ACCs, and downregulation in pediatric ACCs.¹³ The maintenance of the adrenal cortex involves the central migration of sonic hedgehog: positive progenitor cells where they differentiate into the cells making up the zona glomerulosa that later transition to zona fasciculata.¹⁴ The fibroblast growth factor (FGF) signaling pathway is integral to adrenal proliferation and differentiation. The four main signaling pathways downstream of FGF receptor activation are (1) Janus kinase/signal transducer and activator of transcription (Jak/Stat), (2) phosphoinositide phospholipase C (PLC γ), (3) phosphatidylinositol 3-kinase (PI3K), and (4) mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/Erk).¹⁵ FGFR1 and FGFR4 overexpression has been found in 65% of adrenocortical tumors and is associated with worse prognosis.¹⁶

INSULIN-LIKE GROWTH FACTOR SIGNALING PATHWAY

The IGF signaling pathway is involved in differentiation and growth of the adrenal cortex. IGF-2 is highly expressed in human fetal adrenal glands. The chromosomal location of IGF-2 is within an imprinted locus on 11p15.5 that also includes the cyclin-dependent kinase inhibitor 1 C (*CDKN1C*) and *H19*.¹⁷ The importance of IGF2 in adrenocortical development is illustrated by BWS, a pediatric overgrowth disorder with a predisposition to tumor development characterized by macroglossia and hemihypertrophy. BWS is caused by mutation, deletion, or hypermethylation of imprinted genes within the chromosome 11p15.5 region, encompassing *CDKN1C*, *H19*, *IGF2*, and *P57*.^{18, 19} Adrenal cytomegaly with cysts is the predominant adrenal phenotype in BWS; however, ACC occurs with increased frequency in patients with BWS as ACC occurs in 7% of patients.^{20, 21} Structural and functional abnormalities at 11p15 are also associated with sporadic adrenocortical tumors.²² Whole-genome, whole-exome, and/or transcriptome sequencing of 37 ACCs found that 91% show loss of heterozygosity of chromosome 11p; IGF2 on chromosome 11p was overexpressed in all tumors.²³

WNT SIGNALING PATHWAY

The mammalian wingless-type MMTV integration site (Wnt) pathway is a central developmental regulator.²⁴ In the absence of Wnt signaling, β -catenin is in a complex with axin, APC, and GSK3- β . Within this complex, β -catenin is then phosphorylated and targeted for degradation. When Wnt signaling is activated, β -catenin is uncoupled from the degradation complex and translocates to the nucleus, where it activates target genes.²⁵ Constitutive activation of β -catenin drives adrenocortical tumorigenesis. Defects in Wnt pathway activation, including genetic loss of APC or gain-of-function mutations in *CTNNB1*, are known driver mutations of ACC.^{7, 26} In fact, Wnt signaling has been found to be the most frequently mutated pathway in ACCs.²⁷ *CTNNB1* mediates cell-cell adhesion and anchors the actin cytoskeleton, thereby regulating cell growth.²⁸ *CCNE1* encodes cyclin E, a regulatory subunit of cyclin-dependent kinase. Cyclin E is a key regulator of the cell cycle and is overexpressed in many human tumors.²⁹ Whole-exome sequencing of 41 matched ACC and normal tissues identified somatic mutations in *CTNNB1* in 10% of tumors.²⁷

The role of the Wnt/ β -catenin pathway in adrenocortical tumors is illustrated in the autosomal dominantly inherited syndrome FAP. Germline inactivating mutations of the tumor suppressor gene APC characterize FAP, leading to multiple colonic polyps, colon cancer, and adrenocortical tumors caused by dysregulated Wnt/ β -catenin signaling.²⁶ Gain-of-function mutations in β -catenin have been found in roughly 25% of benign and malignant adrenocortical tumors, highlighting the importance of activation of the Wnt signaling pathway.⁷ Exome sequencing of ACCs identified *ZNRF3*, encoding a cell surface E3 ubiquitin ligase, as a potential new tumor suppressor gene related to the β -catenin and Wnt signaling pathway.³⁰ A total of 19.3% of ACC samples out of 91 ACCs recently analyzed through the Cancer Genome Atlas were found to have alterations of *ZNRF3*.^{31, 32} Another large whole exome sequencing analysis of 41 tumors and matched normal samples found homozygous deletion at 22q12.1 including the Wnt repressors *ZNRF3* and *KREMEN1* in 9.8% and 7.3% of tumors, respectively.²⁷

CELL CYCLE REGULATORS

The transcription factor p53 on chromosome 17p13 is a tumor suppressor that regulates cell cycle arrest, apoptosis, senescence, metabolism, and DNA repair. In many cancers, activity of p53 is lost.³³ Whole-exome sequencing of 41 matched ACC and normal tissues identified somatic mutations in TP53 in 20% of ACC tumors.²⁷ Pediatric ACC is exceedingly rare and carries a poor prognosis; the most common germline alteration in pediatric ACC is caused by p53. Whole-genome, whole-exome, and/or transcriptome sequencing of 37 ACCs found TP53 mutations and chromosome 17 loss of heterozygosity in 76% of pediatric ACCs.²³ Li-Fraumeni syndrome is an autosomal-dominant cancer syndrome caused by heterozygous germline mutations in the p53 gene, and is associated with an increased risk of malignancies. Children with Li-Fraumeni syndrome are at an especially high risk of developing ACC.³⁴ The median age of ACC diagnosis among TP53 mutation carriers is 4.8 years of age.³⁵ Multiple endocrine neoplasia type 1 (MEN1) is another autosomal-dominant cancer syndrome involving dysregulation of the cell cycle. MEN1 is characterized by the

“three Ps” of primary hyperparathyroidism, pancreatic endocrine tumors, and pituitary adenomas; adrenal lesions may also occur. Loss of function mutations in *MENIN* disrupt cell cycle regulation and lead to cell proliferation. In approximately 20% to 40% of patients with MEN1, enlarged adrenals are found, with bilateral adrenal tumors in 1.3%.³⁶ In two recent studies reporting exome sequencing in ACC, between 4% and 7% of tumors had inactivating mutations in *MENIN*.³⁰ Finally, in the cell cycle during chromosome replication, telomeres are critical for maintaining genomic integrity. TERC, a protein that plays a key role in the protective activity of telomeres, has also been found to be amplified in ACC.^{31, 37}

cAMP-DEPENDENT PROTEIN KINASE PATHWAY

The cAMP-dependent PKA pathway plays a central role in controlling the development, function, and proliferation of adrenocortical cells. Breaking down the components of the cAMP/PKA pathway, first corticotrophin binds the MC2R G protein-coupled receptor, leading to the stimulation of adenylyl cyclase and release of cyclic-AMP. Next, cAMP activates PKA, a heterotetramer of two regulatory and two catalytic subunits; the PKA catalytic subunit (a serine-threonine kinase) then goes on to phosphorylate several targets, including those leading to cortisol synthesis. Four different genes encode four distinct isoforms of the regulatory subunits (R1 α , R1 β , R2 α , and R2 β).³⁸ In addition, four unique catalytic subunits of PKA are known (C α , C β , C γ , and PRKX). Following the binding of cAMP to PKA, the catalytic subunits dissociate from the regulatory subunits, allowing for the phosphorylation of PKA targets in the cytoplasm and the nucleus. Modifications in specific subunits of PKA, including, PRKAR1 α and PRKAC α , play a major role in adrenal physiology and pathophysiology (Fig. 3).^{39, 40}

MAS is the first disorder identified to connect cAMP/PKA pathway alterations to the growth of adrenal tumors. MAS is caused by postzygotic gain-of-function mutations in the alpha subunit of the gene for the stimulatory guanine-nucleotide-binding protein (Gsa) leading to constitutive activation of adenylyl cyclase.^{40–42} Clinically, patients present with the classic triad of fibrous dysplasia, cafe-au-lait skin pigmentation, and precocious puberty. CS is present in a subset of patients with MAS caused by activating mutations of Gsa.^{43, 44} Multiple nodules that develop from adrenocortical cells with fetal features characterize the adrenals in MAS affected by CS. In a small number of sporadic cortisol-producing adenomas, somatic mutations of GNAS have been identified.³

Carney complex is an autosomal-dominant MEN syndrome, including myxomas, endocrine tumors, and endocrine gland involvement.^{45, 46} Endocrine tumors associated with CNC include testicular large cell, calcifying Sertoli cell tumors, growth hormone–producing pituitary adenomas, thyroid nodules, and PPNAD. Germline inactivating mutations of the PRKAR1A gene coding for the regulatory 1- α (R1 α) subunit of PKA are the cause of for CNC in most patients.^{47, 48} PPNAD is found in 60% of patients with CNC.^{49, 50} A series of 212 patients with PPNAD found that in 20% of the cases adrenal tumors were isolated without any other manifestations of CNC, with a preponderance of females.⁴⁹ Somatic mutations in PRKAR1A and chromosomal loss of the region encompassing PRKAR1A have been identified in sporadic cortisol-secreting adenomas. One study of 44 sporadic

adrenocortical tumors found somatic 17q22 to 24 losses were seen in 23% of adenomas and 53% of adrenal cancers. In three tumors, somatic, PRKAR1A-inactivating mutations were identified, leading to protein truncation.^{51, 52} More recently, in whole exome sequencing from 84 ACCs, seven (8%) cases were found to have inactivating PRKAR1A mutations, and three additional cases had homozygous deletions of PRKAR1A, increasing the role of PKA signaling in ACC.³¹ In addition, this finding leads to a potential relationship between benign and malignant adrenocortical tumors.⁵³ PPNAD and micronodular adrenocortical hyperplasia have both been associated with genetic defects in cAMP-binding PDEs. The role of PDEs is to lower cAMP levels after stimulation of the cAMP/PKA pathway; inactivating mutations of PDE cause buildup of cAMP and stimulation of the PKA signaling cascade. PDE11 A and PDE8B mutations have been found in patients with PPNAD and iMAD, and PDE8B have also been shown to be associated with predisposition to iMAD.^{47, 54, 55} Constitutive activation of the catalytic subunit of PKA, PRKACA, has been found to be a common cause of CS.^{40, 56–59} PRKACA-activating mutations are responsible for 42% of sporadic CS.^{40, 56–59} Activating PRKACA mutations obstruct the interaction of the regulatory subunit with the catalytic subunit, leading to constitutive activation of PKA, increased cortisol production, and altered tumor growth.⁵⁹ Genetic copy number gains encompassing PRKACA on chromosome 19p13.2p13.12 locus are another described cause of CS related to activation of the PKA pathway.^{40, 60} Most recently, ACC has been found to be associated with somatic mutations of PRKAR1A.³¹ All of these findings have led to a search for novel targeted treatment strategies with PRKACA inhibitors for management of adrenocortical tumors.^{56, 58}

Genetics of Primary Bilateral Macronodular Adrenal Disease

PBMAD may be seen in multiple tumor syndromes MEN-1 and FAP and also include hereditary leiomyomatosis and renal cell carcinoma (HLRCC, caused by fumarate hydratase gene [*FH*] mutations). In HLRCC, inactivating mutations of *FH* lead predominantly to hereditary leiomyomatosis and renal cancer; however, in approximately 8% of patients adrenal lesions are found.⁶¹ A single case of clinical CS associated with PBMAD in the context of HLRCC has been described, in which loss of heterozygosity for *FH* was found in the adrenal lesion.⁶²

ARMC5 is another armadillo-containing protein with homology to β -catenin and APC that is involved in adrenocortical pathophysiology. Inactivating ARMC5 mutations have been found in more than half of cases of primary bilateral macronodular adrenal hyperplasia.⁴² Additional studies have confirmed the high frequency of ARMC5 mutations in this disorder.^{63–66} ARMC5 is a putative tumor suppressor that regulates apoptosis. ARMC5 has also been shown in vitro to directly interact with PKA subunits, linking ARMC5 to the PKA/cAMP pathway.⁶⁷ Intra-adrenal corticotrophin secretion by clusters of adrenocortical cells is a paracrine signaling pathway found to occur in PBMAD.⁶⁸ Abnormal G-protein-coupled receptors expressed by adrenocortical cells themselves, including receptors for vasopressin, catecholamines, luteinizing hormone, serotonin, and glucose-dependent insulinotropic peptide, may also serve to regulate cortisol secretion.^{69–72} Intra-adrenal production of corticotrophin may offer a potential therapeutic target for CS in certain types

of adrenal hyperplasia through the application of corticotrophin receptor inhibitors (melanocortin type 2 receptor antagonists).⁷³

Genetics of aldosterone producing adenomas

Aldosterone-producing adenomas may be caused by somatic mutations in genes that regulate intracellular calcium concentration. Somatic mutation of two ATPases, ATPA1A (encoding the alpha subunit of the sodium/potassium ATPase) and ATP2B3 (encoding the plasma membrane calcium-transporting ATPase3) have been found in aldosterone-producing adenomas.⁷⁴ KCNJ5 mutations, a gene that encodes a potassium channel, have also been found in 40% of aldosterone-producing adenomas.^{75, 76} Mutations in KCNJ5 alter the channel's permeability to potassium ultimately leading to activation of the calcium-calmodulin-dependent protein kinase II.⁷⁷ Germline ARMC5 variants may also be associated with primary aldosteronism.⁷⁸

SUMMARY AND FUTURE CONSIDERATIONS

The most frequently mutated genes in adrenocortical tumors are also factors involved in normal adrenal development and homeostasis. A better understanding is being gained of the molecular genetics of adrenocortical tumor development. The most common somatic alterations in ACC are mutations or deletions of *TP53* and *ZNRF3* or *CTNNB1*, altering either the p53 or the Wnt/ β -catenin pathway. The PKA/cAMP signaling pathway plays a crucial role in adrenocortical physiology and pathophysiology; activating mutations of pathway regulators and inactivating mutations of pathway inhibitors both lead to cortisol excess. Germline mutations of *PRKARIA* lead to PPNAD and CS in adolescence or early adulthood. Somatic *PRKACA*-activating, *PRKARIA*-inactivating, or *GNAS*-activating mutations may cause cortisol-secreting adenomas. Recently, whole-genome expression profile of normal adrenals was compared with *PRKARIA* and *GNAS*-mutant adrenal glands, and it was shown that although activation of certain oncogenic signals were shared between these two lesions, others including Wnt signaling were differentially expressed depending on the lesion.⁷⁹ These discoveries offer the possibility to target molecular alterations in this pathway with novel mechanisms to treat cortisol excess in CS, and highlight the importance of genetic testing in adrenocortical tumors.

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KEY POINTS

- Current understanding of normal adrenocortical development sheds light on the molecular pathways that, when altered, may stimulate abnormal proliferation and drive adrenocortical tumor formation.
- Knowledge obtained from inherited syndromes that are characterized by adrenocortical tumors and next-generation sequencing of adrenocortical tumors have helped find causative mutations for these lesions.
- Recent studies have identified cyclic AMP-dependent protein kinase A (PKA) signaling as a key mediator of cortisol secretion by the normal adrenal cortex. It therefore follows that mutations in genes that involve dysregulated cAMP/PKA pathway components are implicated in adrenocortical pathology.
- ARMC5 is a recently discovered gene that is associated with bilateral macronodular adrenocortical hyperplasia.

Fig. 1.

The anatomy and structure of the adrenal glands. The adrenal glands are located at the upper poles of the kidneys. In humans, the adrenal gland has three distinct cortical zones (1) the zona glomerulosa, (2) the zona fasciculata, and (3) the zona reticularis. The inner part of the adrenal gland is the medulla, responsible for catecholamine synthesis. ZF, zona fasciculata; ZG, zona glomerulosa; ZR, zona reticularis.

Fig. 2.

Early adrenal development. The adrenal cortex develops from a thickening of the coelomic epithelium at the intersection of the urogenital ridge and the dorsal mesentery. This group of cells is called the adrenogonadal primordium, and these cells express the transcription factors SF-1 and NR5A1. The chromaffin cells form the medulla, and the adrenal primordium cells form the fetal adrenal gland, which is surrounded by the definitive adrenal gland. The fetal adrenal cortex differentiates into a definitive zone and a fetal zone after 9 weeks' gestation. The transitional zone appears after 24 weeks' gestation. After birth the fetal adrenals involute, and the adult adrenals form. By 6 months of age the adult adrenal cortex consists of the zona glomerulosa and the zona fasciculata. During adrenarche (age 6–7) the zona reticularis is formed. ZF, zona fasciculata; ZG, zona glomerulosa; ZR, zona reticularis.

Fig. 3.

cAMP/PKA signaling in adrenocortical tumors. (A) In the resting state, PKA exists as an inactive tetramer comprising a dimer of regulatory subunits bound to catalytic subunits. PDEs act as inhibitors of the pathway by degrading cAMP to regulate signal transduction. Adenylyl cyclase catalyzes the conversion of ATP to cAMP, and elevation in cellular cAMP levels leads to activation of PKA, release of the catalytic subunits, and phosphorylation of downstream targets, including the transcription factor cAMP response-element binding protein (CREB). (B) In McCune-Albright syndrome, activating mutations in the *GNAS* gene, which encodes the stimulatory guanine nucleotide-binding protein ($G_{\alpha s}$) subunit, lead to constitutive activation of the $G_{\alpha s}$ protein subunit that couples hormone receptors to intracellular generation of cAMP. Mutations in $G_{\alpha s}$ lead to prolonged activation of $G_{\alpha s}$ and its downstream effectors. In Carney complex, inactivating mutations in the regulatory subunit 1α of PKA ($R1\alpha$) subunit of PKA lead to suppression of its inhibitory action, release of the catalytic subunits, and transcription of downstream targets. Inactivating mutations in PDEs lead to accumulation of cAMP and dysregulated activation of the cAMP-PKA pathway. Activating mutations in the catalytic subunit of PKA result in up-regulation of the PKA pathway and phosphorylation of downstream targets. AC, adenylyl cyclase; $C\alpha$, catalytic subunit of PKA; GPCR, G-protein-coupled receptor.

Table 1

Genetic syndromes associated with adrenal hyperplasia/neoplasia

Syndrome	Gene	Locus	Function of the WT Protein	Associated Manifestations
Primary bilateral macronodular adrenocortical disease	<i>ARMCS</i>	16p11	Potential role in regulation of apoptosis and steroidogenesis	Meningioma?
Multiple endocrine neoplasia type 1	<i>Menin</i>	11q13	Regulator of gene transcription, cell proliferation, apoptosis, and genome stability	Multiple endocrine neoplasia type 1 hyperparathyroidism, pituitary adenomas, pancreatic neuroendocrine tumors
Hereditary leiomyomatosis and renal cell cancer	<i>FH</i>	1q42	Krebs cycle, amino acid metabolism	Hereditary leiomyomatosis and renal cell carcinoma
Li-Fraumeni syndrome	<i>TP53</i>	17p13.1	Cell cycle regulator	Breast cancer and soft tissue sarcomas, brain tumors, osteosarcoma, leukemia, and adrenocortical carcinoma
McCune-Albright syndrome	<i>GNAS1</i>	20q13	Stimulation of adenyl cyclase, activation of the cAMP/protein kinase A pathway	Fibrous bone dysplasia, cafe-au-lait spots, precocious puberty, acromegaly, toxic multinodular goiter
Gardner syndrome	<i>APC</i>	5q12-22	Prevent b-catenin accumulation, inhibition of the Wnt/ β -catenin pathway	Familial adenomatous polyposis: colon adenomas and carcinomas, pigmented retinal lesions, desmoid tumors, other malignant tumors as adrenocortical carcinomas
Beckwith-Wiedemann syndrome	<i>IGF2</i>	11p15 imprinting	Growth factor	Hemihypertrophy, macroglossia, ear pits, hypoglycemia, aisceromegaly, abdominal wall defects, Wilms tumor, hepatoblastoma, adrenocortical carcinoma
Carney complex	<i>PRKARIA</i>	17q22-24	Activation of the cAMP/protein kinase A pathway	Lentigines, pituitary adenomas, cardiac myxomas

Table 2

Driver genes in adrenocortical carcinomas

Gene	Cytogenetic Location	Gene Name	OMIM
<i>TERF2</i>	16q22.1	TELOMERIC REPEAT-BINDING FACTOR 2	602027
<i>ZNRF3</i>	22q12.1	ZINC FINGER AND RING FINGER PROTEIN 3	612062
<i>TP53</i>	17p13.1	TUMOR PROTEIN p53	191170
<i>CTNNB1</i>	3p22.1	CATENIN, BETA-1	116806
<i>PRKAR1A</i>	17q24.2	PROTEIN KINASE, cAMP-DEPENDENT, REGULATORY, TYPE 1, ALPHA	188830
<i>CCNE1</i>	19q12	CYCLIN E1	123837
<i>IGF2</i>	11p15.5	INSULIN-LIKE GROWTH FACTOR II	147470
<i>FGFR1</i>	8p11.23	FIBROBLAST GROWTH FACTOR RECEPTOR 1	136350
<i>FGFR4</i>	5q35.2	FIBROBLAST GROWTH FACTOR RECEPTOR 4	134935
<i>RB1</i>	13q14.2	RB1 GENE	614041