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Cushing syndrome: old and new genes

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Abstract

Cushing syndrome (CS) describes the signs and symptoms caused by exogenous or endogenous hypercortisolemia. Endogenous CS is caused by either ACTH-dependent sources (pituitary or ectopic) or ACTH-independent (adrenal) hypercortisolemia. Several genes are currently known to contribute to the pathogenesis of CS. Germline gene defects, such as *MEN1*, *AIP*, *PRKAR1A* and others, often present in patients with pituitary or adrenal involvement as part of a genetic syndrome. Somatic gene defects, such as *USP8*, *TP53*, and others, also underlie a large percentage of patients with CS, and give insight in pathways involved in pituitary or adrenal tumorigenesis.

Keywords

Gene; pituitary; adrenal; Cushing; tumor

Introduction

Cushing syndrome (CS) refers to the constellation of signs and symptoms resulting from excessive levels of cortisol.(1) Although exogenous CS is a relatively common diagnosis, endogenous CS accounts for only 2.3–3.2 new cases per million people per year; 10% of those present in children.(2–4) The etiology of endogenous CS involves either an ACTH-dependent source, most commonly pituitary adenomas (PAs), described as Cushing disease (CD), or less often ectopic CRH and/or ACTH secretion, or ACTH-independent (adrenal-related) hypercortisolemia (Table 1).(1) Several subclassifications of the various types of CS exist based on their clinical, histological and macroscopic presentation (Table 1) and may give clues to their etiology.

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This review focuses on old and new germline or somatic gene defects of CS and provides a description of accompanying features in these patients (Table 2). These can be used for guidance in selecting appropriate genetic testing. Germline genetic defects in patients with CD are uncommon and explain less than 5% of all cases currently.(5) On the other hand, germline gene defects in patients with ACTH-independent CS may explain more than half of cases depending on the subtype of adrenal pathology identified. In either case, several lessons can be taught by the gene defects found about the possible pathways that may be affected and lead to hypercortisolemia. Malignant tumors, and specifically adrenocortical carcinomas, are not extensively reviewed. Other genomic mechanisms potentially involved in pathogenesis of CS, such as variable expression of components of certain pathways, methylation changes or miRNA changes, also contribute to the genetic background of CS.

Well established genetic causes of CS

Multiple Endocrine Neoplasia (MEN)—Multiple endocrine neoplasia (MEN) syndromes are commonly associated with CS.(6) MEN type 1 (MEN1) (OMIM#131100) is caused by genetic defects in *MEN1* which functions as a tumor suppressor gene at the endocrine tissues.(7) PAs present in 40% of patients with MEN1. However, ACTH-secreting pituitary tumors account for only 3–4% of them.(8, 9) They present at the third to fourth decade of life, although patients as young as 9 years of age have been reported.(8–10) Multiple synchronous or metachronous PAs of similar or different functional status may present in patients with MEN1, and clinicians should review carefully imaging and biochemical studies to avoid unnecessary interventions.(11)

Only few case reports of ACTH-secreting PAs have been reporting in the context of the other MEN syndromes, types 2 and 4 (MEN2 and MEN4, respectively): *RET* [MEN2A (OMIM#171400) and MEN2B (OMIM#162300)] and *CDKN1B* gene mutations [MEN4 (OMIM#610755)] suggesting that these syndromes play a less important role in pituitary tumorigenesis. (12–14)

Of note, patients with MEN syndromes may present with adrenal or ectopic CS.(15) In ACTH-independent CS, *MEN1* has been involved in the development of unilateral or bilateral adrenal disorders, including isolated nodules and carcinomas, or bilateral adrenocortical hyperplasia.(16) In studies where the adrenal presentation and function of patients with MEN1 was investigated, 20–50% of them were found to have abnormal radiographic presentation of adrenals, but only 2.5–5.5% patients presented with CS.(17–19) Ectopic CS in the context of MEN1 is not infrequent and most common sources are neuroendocrine tumors, thymic and others.(20, 21) In MEN2 and MEN4, ectopic CS may be associated with ectopic ACTH secretion from medullary thyroid carcinomas or pheochromocytomas, and rarely from other tumors.(22, 23)

Clinicians should follow carefully the diagnostic evaluation for the diagnosis and identification of the source of hypercortisolemia, without assuming a pituitary source in the case of elevated ACTH.(24, 25) Since PAs are infrequently associated with ACTH secretion, while non-functioning PAs are common, the presence of ACTH-dependent CS with the imaging identification of an adenoma, should be followed by workup for confirmation of

pituitary versus ectopic source, such as CRH stimulation test, high-dose dexamethasone suppression test or Bilateral Inferior Petrosal Sinus Sampling (IPSS) as appropriate.(25)

Familial Isolated Pituitary Adenomas (FIPA)/AIP—The term Familial isolated pituitary adenomas (FIPA) describes the presence of at least two family members with PAs, with or without other abnormalities.(26) Although the presence of family history and the inheritance pattern implies a genetic etiology for this syndrome, specific gene defects have been identified in half of the cases.(26) Fifteen percent of patients carry an aryl hydrocarbon receptor-interacting protein (*AIP)* gene mutation.(26–28) The AIP protein is probably involved in the synthesis of cAMP. Thus, *AIP* gene defects cause increased cAMP production leading to aberrant cell proliferation (29).

Approximately 5% of patient with FIPA have ACTH-producing adenomas, but most of them do not have an identified genetic background.(26, 30) Only few patients with CD and *AIP* mutations have been reported in either familial or sporadic cases, with the youngest patient presenting at 6 years of age. (31, 32) Other genetic causes of FIPA, such as *GPR101* (causing X-Linked Acrogigantism or X-LAG) are not found in patients with CD.(33, 34)

Carney complex and PKA in the pathogenesis of CS—Carney complex (CNC) presents with the constellation of myxomas, spotty skin pigmentation, and endocrine overactivity.(35) CNC is caused by mutations of the *PRKAR1A* gene in 70% of cases, whereas a second locus on chromosome 2p16 has been identified for some of the remaining cases.(36, 37) *PRKAR1A* encodes the type 1 alpha regulatory subunit of the protein kinase A (PKA), and gene defects lead to increased free catalytic subunits which lead to increased downstream activity of PKA. (35)

CNC presents with primary pigmented nodular adrenocortical disease (PPNAD) in approximately 60% of patients.(38) Patients may have radiographically normal-looking adrenals or adrenals with multiple nodules (often <1 cm in largest diameter).(39) CS in the context of PPNAD may be atypical or cyclical, but most patients have a pathognomonic paradoxical response to dexamethasone during Liddle's test when performed during the active state.(40)

More recently, two cases of corticotropinomas in patients with pathogenic variants in *PRKAR1A* have been reported, expanding the spectrum of the known pituitary involvement in CNC, previously limited to growth hormone and/or prolactin secreting PAs and somato(mamo)troph hyperplasia.(41, 42)

TSC and the mTOR//PI3K/Akt pathway—Tuberous sclerosis (TS) is an autosomal dominant syndrome presenting with hamartomas, mental retardation and epilepsy. Neuroendocrine tumors may be a rare presentation of TS and few cases of ACTH-secreting PAs have been reported in the literature. (43–45) Two genes are involved in the pathogenesis of the syndrome: *TSC1* (OMIM#191100) and *TSC2* (OMIM#613254). The genes are part of the mTOR/PI3K/Akt pathway that regulates cell growth and proliferation.(46) Of note, few cases of corticotropinomas with somatic mutations or amplifications of *PIK3CA*, another

component of the mTOR/PI3K/Akt pathway, have been reported especially in more aggressive tumors.(47, 48)

Adrenocortical carcinomas—Although this review is mainly focused on non-malignant causes of CS, since cancerous causes often have multiple genetic gene defects as well as chromosomal rearrangements that render them aggressive and malignant, it is important to mention the main genetic regulators of adrenocortical carcinomas. One of the most important genes involved in adrenocortical tumorigenesis is *TP53* which is identified in up to 70% of cases, especially in children.(49, 50) *TP53* is a tumor suppressor gene coding for p53 protein which regulates cell cycle. Li Fraumeni syndrome (LFS) is an autosomal dominant condition caused by germline defect of *TP53* gene represents one is the extreme of the spectrum of the p53 defects. Patients with LFS have predisposition for several tumors, including soft tissue sarcomas, osteosarcomas and adrenocortical carcinomas.(51)

Wnt signaling pathway/b-catenin—Beta-catenin is part of the Wnt signaling pathway, involved in cell differentiation and several cancers. Wnt signaling is activated during development and later downregulated. Activation of the canonical Wnt pathway through binding to Frizzled receptor leads to decreased degradation of intracellular b-catenin which after accumulation in the cytoplasm translocates to the nucleus to activate TCF/LEF-type transcription factors of several genes involved in cell cycle regulation (such as cyclins and *c-MYC*).(52)

Activation of the Wnt signaling pathway has been reported as a frequent event in adrenocortical carcinomas and adenomas. Somatic mutations of b-catenin gene (*CTNNB1*) explain up to half of the these cases where Wnt signaling is found increased.(53) *APC* gene, responsible for familial adrenomatous polyposis (FAP) when mutations are present in the germline, is another member of the Wnt pathway and regulates the ubiquitination of b-catenin acting as a suppressor of its effects.(54) Inactivation of *APC* has been reported in cases of adrenocortical adenomas and hyperplasia.(55)

Neonatal CS in the context of genetic syndromes—CS in the neonatal period is extremely rare.(56) When present, its association with underlying genetic syndromes is common. Of the identified genetic causes of neonatal CS, McCune-Albright syndrome (MAS) and Beckwith-Wiedemann syndrome (BWS) may be associated with neonatal ACTH-independent CS.(57, 58) MAS is caused by postzygotic somatic mutations of the *GNAS* gene, which codes for the Gsa subunit of G-protein coupled receptor, leading to constitutive activation and increased intracellular cAMP.(59) Most cases of neonatal CS and MAS are caused by unilateral or bilateral adrenocortical hyperplasia. BWS is caused by defects of the 11p15 locus involving *IGF2*, *H9* and *CDKI* genes.(60) Patients with BWS present with adrenocortical tumors or bilateral adrenocortical hyperplasia. Of note, *GNAS* gene defects and BWS have been recently reported in association with CD, expanding our understanding of the effects of these genes.(61–65)

In 2014, de Kock *et al* published an important paper reinvestigating the cause of previously reported cases of neonatal CD. The authors reported that the reported tumors actually fit the histologic diagnosis of pituitary blastomas.(66) They further identified *DICER1* variants in

the available samples, with or without loss of heterozygosity at the tumor level.(66) *DICER1* codes for a small RNA processing endoribonuclease that is involved in siRNA and miRNA production.(67) DICER1 syndrome involves among other presentations pleuropulmonary blastomas, cystic nephromas, Sertoli-Leydig cell tumors, multinodular goiter and other tumors.(68)

Ectopic Cushing syndrome—Ectopic CS may present in the context of various cancers including breast, colon, pancreas and others, however the genetic cause of aberrant *POMC* expression and ACTH secretion has not been extensively studied.(69) Most of the cases of ectopic CS with an identified genetic cause correspond to *MEN1* or *RET* gene mutations. Some additional causes of ectopic CS that have been reported in the literature include *BRAF* and *TP53* mutations, in neuroendocrine tumors of the colon, and a case report of ectopic CS in the context of a pancreatic neuroendocrine tumor in a patient with *VHL* mutation. (70, 71)

Newly identified genes in the germline or somatic state

USP8—The *USP8* gene codes for a deubiquitinase protein involved in the recycling of epidermal growth factor receptor (EGFR). In 2015, two independent groups reported somatic variants in the *USP8* gene in corticotropinomas.(72, 73) All variants were located in a hot spot, the 14–3-3 binding motif (between amino acids 713 and 720), and led to gain of function activation of the gene. Increased deubiquitinase activity led to increased EGFR levels and consequently elevated proopiomelanocortin (*POMC)* gene expression. Since then additional groups have reported a frequency of 20–60% of *USP8* mutations in CD, and have studied potential implication in patient prognosis, with some reporting a more aggressive behavior of these tumors.(74–77) Recently, Cohen *et al* reported the first patient with a germline *USP8* gene defect. The patient presented with recurrent severe CD, and multiple other medical problems that highlight the involvement of USP8 in several tissues. (78)

USP8-negative corticotropinomas have been recently linked to somatic variants in other genes of the MAPK pathway (*USP48* and *BRAF*), which may explain up to 20% of all cases. (79, 80)

ARMC5—In 2013, Assie *et al* reported the association of *ARMC5* with the pathogenesis of massive macronodular adrenocortical disease (MMAD). *ARMC5* gene defects were identified in 55% of all cases.(81) Biallelic inactivation was present in all cases, with patients carrying a germline mutation and a second “hit” (another inactivating variant or deletion at the other allele) occurring at the tumor level.(81) ACRM5 protein is involved in dedifferentiation and apoptosis signaling of adrenocortical cells, resulting in reduced steroidogenesis and mass formation.(81, 82) The end result of this defect is cell overgrowth and mass production, leading to excessive hormone secretion and CS.(82)

PKA subunits and Phosphodiesterase (PDE)—The description of *PRKAR1A* gene defects in adrenal CS and the involvement of abnormal cAMP-PKA activity in several adrenal disorders leading to excess cortisol production, led to identification of additional genes of the cAMP-PKA pathway which are causative or contributory to adrenal-related hypercortisolemia.(83) *PDE11A* (and possibly *PDE8B*) mutations contribute to a variety of

pathologic adrenal lesions.(84, 85) Phosphodiesterases (PDEs) are enzymes involved in the hydrolysis of cAMP and defects in these genes lead to increased levels of cAMP and aberrant PKA signaling (Figure 1). Amplifications and activating mutations of the *PRKACA* gene, coding for the C alpha catalytic subunit of PKA, have also been involved in the pathogenesis of adrenal CS, caused by either isolated cortisol producing adenomas (CPAs) or adrenocortical hyperplasia.(86, 87)

***TP53* in CD—**After initial reports of rare *TP53* mutations in PAs and their association mainly with aggressive tumors, a recent study and metanalysis of corticotropinomas changed this assumption and reported that up to 12% of tumors may have a somatic *TP53* mutation. (88–90) Authors reported *TP53* mutations in 33% of *USP8*-negative tumors and hypothesized that p53 protein is important for regulation of apoptosis (one of the main pathways affected in corticotropinomas) or the BRCA1 mediated DNA-repair in corticotroph cells.(80, 91) Further studies are needed to 245 confirm this finding.

SDH—The “three P association” or 3PAs describes the combination of pituitary adenomas, pheochromocytomas (PHEO) and/or paragangliomas (PGL) at members of the same family. (92) Most cases are caused by SDH-related genes *(SDHA, SDHAF2, SDHB, SDHC, SDHD)*, while additional genes have been more recently reported (*VHL*, *MEN1*, *RET* and *MAX).* Succinate dehydrogenase (SDH) is part of the complex II of the mitochondria involved in energy production and the respiratory chain. (93) Although PAs is a mandatory component of the syndrome only one case of a patient with ACTH-secreting adenoma has been reported in the literature.(94) Of note, SDHx genes may be associated with adrenocortical carcinomas which commonly present with ACTH-independent Cushing syndrome. (95)

Food-dependent CS—Food-dependent CS is a rare variant of ACTH-independent CS, where cortisol secretion is stimulated by the post-prandial state, most probably by the effect of glucose-dependent insulinotropic polypeptide (GIP).(96, 97) Although ectopic GIP receptors (GIPRs) in adrenal tumor cells were described many years ago, it was in 2017 when researchers identified the genetic basis of this rare variant of adrenal CS, and reported somatic duplications in chromosome 19q13.3 containing *GIPR* gene in 3 patients with food-dependent CS.(96, 98) In 2/3 cases there was chromosomal rearrangement that moved the *GIPR* gene under the effect of glucocorticoid-responsive elements, leading to increased expression of GIPR in tumor cells which then react with increased hormone production under the effect of meals.(98)

Other genes—*CABLES1* was recently identified as a rare cause of corticotropinomas.(99) The gene codes for a protein that interacts with cyclin-dependent kinase, and inactivating mutations of the gene result in aberrant cell proliferation.(99)

Recommendations for genetic testing of patients with CS

When considering offering genetic testing to patients outside the research setting, practitioners should understand the diagnostic yield of the test and the effect on treatment options, if any. We always review carefully every patient’s personal and family history for

evidence of diagnoses that could provide clues to a specific genetic syndrome. Specifically, personal history of other medical diagnoses (such as cancer, especially in young age), physical characteristics (such as freckling or other birthmarks) or pertinent family history (members of the family with pituitary or adrenal disorders, history of nephrolithiasis or calcium problems, type and age at diagnosis of cancers in the family, early onset obesity or diabetes and others) form our pretest probability for an underlying genetic defect. If we suspect a well characterized genetic syndrome, we discuss with patient and/or parents (if children) the value of the test. For certain conditions (like MEN), there are already established guidelines on diagnosis and genetic screening.(100) For newer conditions, advise on genetic screening should be provided by physicians familiar with the conditions and able to provide appropriate counseling.

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Practice points

- The etiology of endogenous CS involves either an ACTH-dependent source, most commonly pituitary adenomas (PAs), described as Cushing disease (CD), or less often ectopic CRH and/or ACTH secretion, or ACTH-independent (adrenal-related) hypercortisolemia
- Germline genetic defects in patients with CD are uncommon and explain less than 5% of all cases. On the other hand, germline gene defects in patients with ACTH-independent CS may explain high percentage of cases depending on the subtype of adrenal pathology identified.
- Patient's phenotyping, family history and histologic evaluation of the source of hypercortisolemia provide necessary clues to direct targeted genetic testing whenever possible.

Research agenda

- Currently available extensive genetic testing may provide more data on the underlying genetic causes of CS, but challenges present with the volume of data produced from these techniques and the capacity of bioinformatic analysis.
- Additional genomic mechanisms, such as methylation and miRNA changes, potentially contribute to the pathogenesis or the variable phenotype of patients with CS.

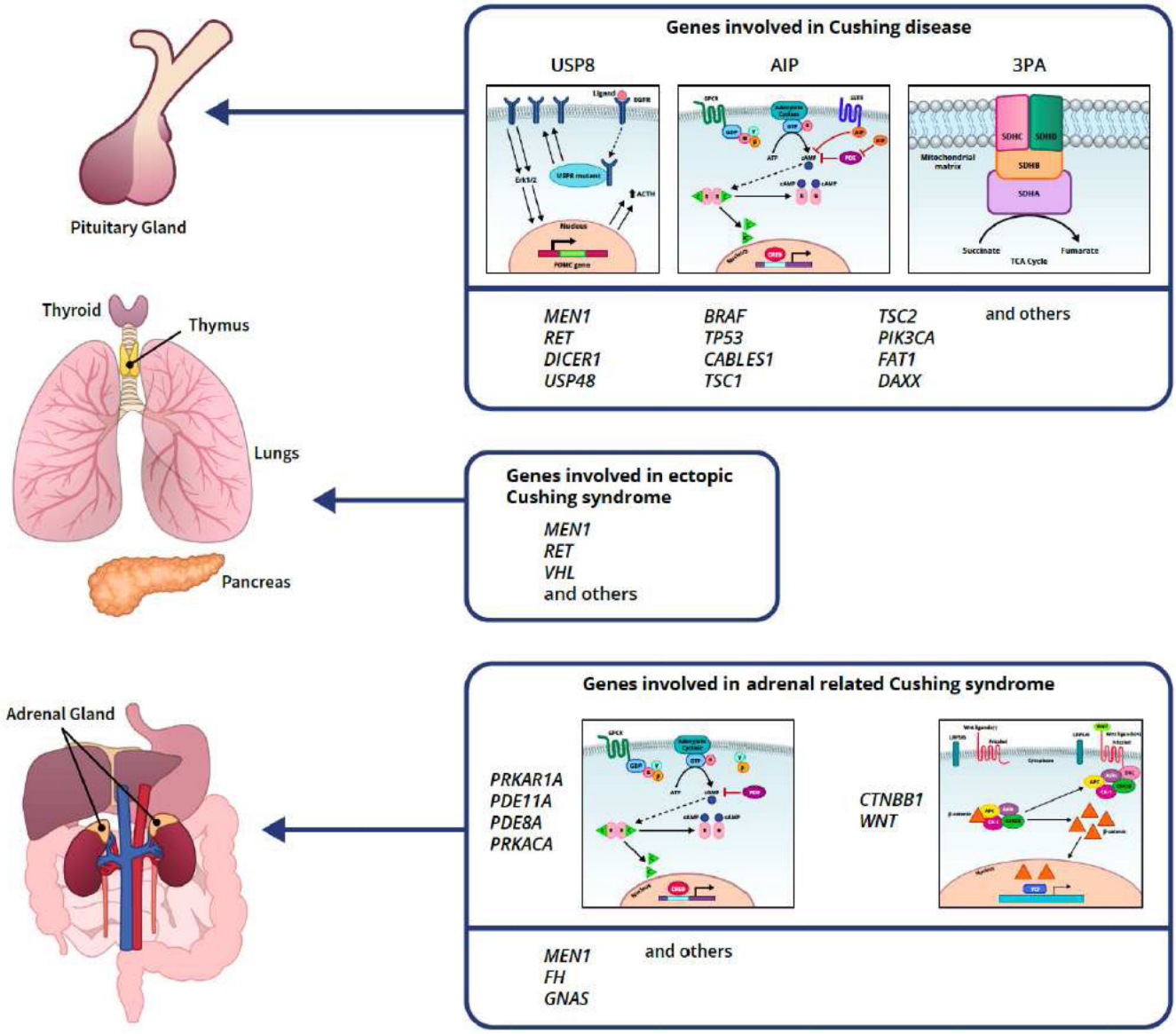

Figure 1.
Genes involved in various subtypes of CS. (Graph credit to Nichole Jonas)

Table 1.

Classification of types of Cushing syndrome.

Etiology		Mechanism
Exogenous	Iatrogenic	Exogenous administration of supraphysiologic doses of glucocorticoids as part of therapeutic scheme for a medical condition (autoimmune, rheumatologic, malignant etc)
Endogenous	ACTH-dependent	Pituitary ACTH secreting tumors (ACTH-secreting pituitary adenomas or carcinomas, pituitary blastomas)
		Ectopic ACTH and/or CRH secretion (bronchial, thymic, or pancreatic neuroendocrine tumors, and others)
	ACTH-independent	Adrenocortical carcinomas
		Cortisol-Producing Adrenocortical adenomas (CPAs)

		Bilateral adrenocortical hyperplasia (BAH)
		- Micronodular (most nodules < 1cm)
		• Pigmented
		  • Primary Pigmented Nodular Adrenocortical Disease (PPNAD) in the context of Carney complex
		  • Isolated Primary Pigmented Nodular Adrenocortical Disease (PPNAD)
		• Isolated Micronodular Adrenocortical Disease (iMAD)
		- Macronodular (most nodules > 1cm)
		• Bilateral Macroadenomatous hyperplasia (BMAH): adenomas with internodular atrophy
		• Massive Macronodular Adrenocortical Disease (MMAD): adenomas with internodular hyperplasia

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Table 2

Characteristics and presentation of patients with genetic syndromes associated with Cushing syndrome.

Genetic syndrome	Type of CS	Gene(s)	Gene locus	Approximate frequency of CS in patients with the genetic syndrome	Clinical presentation
Multiple Endocrine Neoplasia type 1 (MEN1)	Cushing disease, ACTH-independent CS or ectopic CS	*MEN1*	11q13.1	Cushing disease: 1% ACTH-independent CS: 2.5–5.5%	Tumors of anterior pituitary gland, parathyroid glands, pancreatic islet cells and others
Multiple Endocrine Neoplasia type 2A/2B (MEN2A/2B)	Cushing disease or ectopic CS	*RET*	10q11.21	Rare case reports	Medullary thyroid carcinoma with pheochromocytoma and hyperparathyroidism (MEN2A) or mucosal neuromas and intestinal ganglioneuromas (MEN2B)
Multiple Endocrine Neoplasia type 4 (MEN4)	Cushing disease	*CDKN1B*	12p13.1	1 case reported	MEN1-like syndrome
Familial Isolated Pituitary Adenomas (FIPA)	Cushing disease	*AIP* (15–30% of cases)	11q13.2	5% of FIPA patients	Presence of at least two family members with PAs, with or without other abnormalities
Carney complex (CNC)	ACTH-independent CS, rare cases of Cushing disease	*PRKAR1A*	17q24.2	ACTH-independent CS: 60% CD: Rare case reports	Myxomas, spotty skin pigmentation, endocrine overactivity and other tumors
McCune-Albright (MAS)	ACTH-independent CS, rare cases of Cushing disease	*GNAS*	20q13.32	Up to 7%	Polyostotic fibrous dysplasia, café-au-lait macules, and precocious puberty, and other endocrine disorders
Beckwith-Wiedemann syndrome (BWS)	ACTH-independent CS, rare cases of Cushing disease	*IGF2*, *H9* and *CDKI*	11p15	Rare case reports	Hemihypertrophy, macrosomia, macroglossia, predisposition to embryonic tumors and others
Li-Fraumeni syndrome (LFS)	ACTH-independent CS	*TP53*	17p13.1	6–13% of patients (frequency referring to adrenocortical carcinomas)	Predisposition to various tumors at early age, including soft tissue sarcoma, osteosarcoma, brain tumors, breast cancer, melanoma and others
DICER1	Cushing disease	*DICER1*	14q32.13	Rare	Pleuropulmonary blastomas, cystic nephromas, Sertoli-Leydig cell tumors, multinodular goiter, and other tumors
3 P association (3PA)	Cushing disease	*SDHx*, *VHL*, *MEN1*, *RET* and *MAX*	Various	1 case reported	3Ps: Pituitary adenomas, Pheochromocytomas and/or Paragangliomas
Tuberous sclerosis (TS)	Cushing disease	*TSC1*, *TSC2*	9q34.13 (TSC1) 16p13.3 (TSC2)	Rare case report	Hamartomas, epilepsy and mental retardation
USP8 germline syndrome	Cushing disease	*USP8*	15q21.2	1 patient reported (100% penetrance hypothesized)	Cushing disease, developmental delay, dysmorphic features, skin defects, chronic lung disease, chronic kidney disease, dilated cardiomyopathy with congestive heart failure (CHF) and others