HHS Public Access

Author manuscript

Endocrinol Metab Clin North Am. Author manuscript; available in PMC 2019 June 01.

Published in final edited form as:

Endocrinol Metab Clin North Am. 2018 June ; 47(2): 275–297. doi:10.1016/j.ecl.2018.02.007.

Genetics of Cushing's syndrome

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Synopsis

The knowledge on the molecular and genetic causes of Cushing's syndrome (CS) has greatly increased in the recent years. Somatic mutations leading to overactivation of the 3′,5′-cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) and wingless-type MMTV integration site family (WNT)/beta-catenin (CTNNB1) pathways are the main molecular mechanisms underlying adrenocortical tumorigenesis causing CS. In the pituitary gland, corticotropinomas are characterized by resistance to glucocorticoid negative feedback, dysregulation of pathways controlling cell cycle progression and overexpression of pathways that sustain overactive ACTH production and secretion. Most of the patients with CS present sporadically, while isolated or syndromic familial forms of CS are quite infrequent. Nevertheless, recognizing the germline and somatic genetic defects behind corticotroph and adrenocortical tumorigenesis proves crucial for tailoring the clinical management of the patients and for designing strategies for genetic counselling and clinical screening to be applied in the routine medical practice.

Keywords

Cushing's syndrome; glucocorticoids; ACTH; corticotropinoma; pituitary adenoma; adrenal hyperplasia; cAMP; *USP8*

Introduction

Characterized by multisystemic manifestations of hypercortisolemia, endogenous Cushing's syndrome (CS) is caused in two-thirds of cases by an ACTH-secreting pituitary adenoma (corticotropinoma), and in up to one-quarter of cases by benign adrenal lesions, while other causes are more infrequent.[1] CS may have a familial presentation, as part of various syndromes of multiple neoplasia, or present sporadically in the presence of specific germline and/or somatic gene defects (Table 1). A vast progress has been achieved in the recent years

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Disclosure: The authors have nothing to disclose.

on identifying the molecular and genetic causes of CS of adrenal and pituitary (Cushing's disease, CD) origin. In this review, we have compiled and summarized the most relevant genetic causes of adrenal and pituitary CS so far described.

Genetic alterations in Cushing's syndrome of adrenal origin

Somatic activating *CTNN1B* mutations

In mice, beta-catenin (Ctnn1b) has an important role in driving embryonic adrenocortical cell proliferation, and its constitutive activation results in adrenocortical hyperplasia.[2] Nuclear and cytoplasmic accumulation of the CTNN1B protein are common findings in human benign and malignant adrenocortical tumors of various types, and these lesions often display somatic mutations in the *CTNNB1* gene (located on chromosome 3p22.1).[3–6] Within cortisol-producing adenomas (CPAs), the frequency of *CTNN1B* mutations is around 15%, while two-thirds of nonfunctioning adenomas and one-third of adrenocortical carcinomas carry these genetic defects, which are apparently associated with a more aggressive phenotype.[3, 4, 7] Most of the patients carry a missense mutation affecting the residue S45, which prevents phosphorylation of the protein by the "destruction complex" (see below), resulting in protein accumulation and activation of its target genes, and therefore resulting in constitutive activation of the wingless-type MMTV integration site family (WNT)/CTNNB1 pathway.[7] Beyond *CTNNB1* sequence mutations, CTNN1B accumulation may also be due to overactivation of the 3′,5′-cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) pathway, as it occurs in most adrenocortical lesions.[3]

Familial adenomatous polyposis

Germline loss-of-function mutations in the *APC* gene (on chromosome 5q22.2) are associated with adrenocortical adenomas or primary macronodular adrenal hyperplasia (PMAH) in patients with familial adenomatous polyposis; however, this gene does not seem to play a significant role in sporadic CS.[8, 9] *APC*-mutated tumors display cytoplasmic and nuclear CTNNB1 accumulation. The APC protein forms part, together with other tumor suppressors and protein kinases, of the "destruction complex", which regulates the WNT/CTNNB1 signaling pathway by targeting and directing CTNNB1 to proteasomal degradation.[2] Therefore, *APC* loss-of-function results in constitutive activation of the WNT/CTNNB1 pathway, in a way that is similar to that of *CTNNB1* mutations.

Activating somatic *PRKACA* hotspot mutations

Adrenal CS is most often caused by CPAs and one to two-thirds of these tumors bear the somatic recurrent mutation p.L206R in the *PRKACA* gene (on chromosome 19p13.12), encoding the catalytic subunit alpha of PKA.[10–13] The functional effect of the L206R mutation is constitutive activation of the cAMP/PKA molecular pathway and therefore increased steroidogenesis, given that these mutations affect a site of the protein that is essential for its interaction with the regulatory subunits of PKA.[10, 11, 13] The mutation p.L199_C200insW, found in one CPA case, has a similar effect.[10] In addition, germline amplification of the 19p13.2-p13.12 chromosomal region was identified in five cases of CS from four different families.[10] In these patients, an apparent dosage-dependent effect on the phenotype was observed, as gene triplications were associated with a younger age at disease

onset, compared with duplications. These patients developed different types of adrenocortical lesions, including primary pigmented nodular adrenocortical disease (PPNAD), isolated micronodular adrenocortical disease (iMAD) and PMAH, and one patient developed breast cancer.[14]

Germline defects in phosphodiesterases

Phosphodiesterases are negative regulators of cAMP and 3′, 5′-cyclic guanosine monophosphate (cGMP)-dependent intracellular signaling, with multiple isoforms that display differential tissue and substrate specificity. A genome-wide association study identified germline inactivating mutations in the phosphodiesterase 11A gene (*PDE11A,* 2q31.2) in four patients with CS due to iMAD, including two affected individuals from the same kindred.[15] Later on, a germline missense mutation in the *PDE8B* gene was identified in an additional iMAD patient. PDE11A is a dual-specificity phosphodiesterase (i.e., it hydrolyzes both cAMP and cGMP), while PDE8B is cAMP-specific.[16] Both phosphodiesterases are highly expressed (although not exclusively) in the adrenal tissue, and the mutations found in iMAD lead to increased cAMP signaling, in a similar way than *PRKACA* gain-of-function and other cAMP defects identified in adrenal tumors.[17]

Germline and somatic *ARMC5* mutations

Loss-of-function mutations in the armadillo repeat containing 5 gene (*ARMC5*) are the most common genetic cause of CS due to PMAH. Around 26–55% patients bear *ARMC5* mutations (on chromosome 16p11.2) at both the somatic and the germline levels; within the PMAH tissue, different *ARMC5* mutations can be found in each nodule[18–21] *ARMC5* encodes a ubiquitously expressed pro-apoptotic protein, with an additional role as a regulator of steroidogenesis, as demonstrated *in vitro*.[18, 22] In mice, *Armc5* is required for gastrulation and its knockout is lethal, while haploinsufficiency leads to late-onset CS.[23] Presentation in *ARMC5* mutation-associated PMAH may be sporadic or familial (autosomal dominant).[24, 25] Patients with *ARMC5* mutations have higher midnight serum cortisol, as well as higher urinary 17-hydroxycorticosteroids and free cortisol levels during the 6-day test Liddle, and their nodules are larger and more numerous, compared with other PMAH patients.[19, 20]

Hereditary leiomyomatosis and renal cell carcinoma

Fumarate accumulation, as a result of fumarate hydratase (FH) deficiency, leads to pseudohypoxia, a well-known pro-tumorigenic stimulus.[26, 27] Loss-of function mutations in the *FH* gene (1q43) cause an autosomal dominant syndrome characterized by the association of cutaneous leiomyomatosis and renal cell carcinoma. Other tumors less frequently observed in these patients are leiomyosarcomas, uterine leiomyomas and papillary renal carcinomas, and, occasionally, PMAH (8% of patients).[28, 29] Loss of the normal allele has been demonstrated in the PMAH tissue, supporting the causative role of FH in these lesions; however, *FH* mutations have not been associated to sporadic PMAH.[8, 28]

Somatic *GIPR* microduplications

The finding of local ACTH production and aberrant GPCR expression as stimuli driving steroidogenesis in PMAH brings attention to the role of ectopic hormone signaling in adrenal tumorigenesis.[27, 30] Glucose-dependent insulinotropic polypeptide (GIP)-dependent CS is a rare condition in which ectopic GIP receptor (GIPR) expression in PMAH or CPA tissue leads to hypercortisolemia in response to the physiological posprandial release of GIP by the small bowel. A recent study identified somatic duplications of the 19q13.32 chromosomal region, including the *GIPR* gene, in 3/14 patients with GIP-dependent CS.[31] In two of these cases, rearrangements favoring the monoallelic expression of *GIPR* were identified, and among the genes contained in the amplified region, only *GIPR* was consistently overexpressed in the adrenocortical lesions. GIPR overexpression leads to increased steroidogenesis via overactivation of the cAMP/PKA pathway.

Gain-of-function germline *MC2R* mutations

A germline mutation (p.F278C), in the *MC2R* gene (on chromosome 18p11.21), encoding the ACTH receptor MC2R, was identified in a single patient with PMAH and resulted in constitutive receptor activation in vitro.[32] Two additional *MC2R* mutations (p.C21R and p.S247G) found in a patient with hypersensitivity to ACTH, had the same effect.[33] *MC2R* mutations appear to be a very rare cause of CS, if at all contributory.

Genetic alterations common to Cushing's syndrome of adrenal and pituitary origin

Mosaic or somatic *GNAS* mutations

Early postzygotic mutations in *GNAS* (on chromosome 20q13.32) affecting the amino acid 201 of the best-known product of *GNAS,* the G stimulatory protein subunit alpha, cause the McCune-Albright syndrome (MAS).[34] MAS consists of monostotic or polyostotic fibrous dysplasia presenting together with one or more manifestations of endocrine hyperfunction (most frequently, primary precocious puberty) and/or dermal café-au-lait spots. Such mutations cause loss of the GTPase function of the protein, resulting in constitutively active GNAS (*gsp* oncogene).[35] Cushing's syndrome is an infrequent component of MAS (4% of patients), occurring most often in patients with multiple other manifestations of the syndrome.[34, 36] Hypercortisolism in this setting is due to bilateral primary bimorphic (diffuse/nodular hyperplasia and cortical atrophy with apparent *zona glomerulosa* hyperplasia) adrenocortical disease.[37] Besides MAS, somatic mutations in *GNAS* codons 201 or 227 (which have the same functional effects) can also be found as somatic changes in 4–15% of CPAs.[11–13] The same mutations are a common finding in sporadic pituitary adenomas, (mainly somatotropinomas), although they are rarely found in corticotrotropinomas, with only three cases reported so far.[38, 39]

Multiple endocrine neoplasia type 1

The syndrome of multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant condition characterized by the development of tumors in multiple endocrine and non-endocrine organs.[40] Primary hyperparathyroidism (the most constant feature of the

syndrome), gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and pituitary adenomas are the three main components or MEN1.[41] Eighty five percent of the MEN1 patients have familial presentation and penetrance is age and organ-specific, and almost complete by the fifth decade of life.[42] Ninety percent of the MEN1 cases bear loss-of-function germline mutations or deletions in the *MEN1* gene (on chromosome 11q13.1), encoding the tumor suppressor menin, a scaffolding protein that regulates the expression and function of proteins involved in transcriptional regulation, genome stability and cell proliferation.[43–46] In mice, *Men1* full knockout is lethal *in utero,* but hypomorphic models develop a syndrome resembling the human phenotype.[41]

CS in the setting of MEN1 can be due to a corticotropinoma (79%), primary adrenal disease (21%) or very, rarely, ACTH secretion from a GEP-NET (a few case reports).[47] Approximately 30–40% of MEN1 patients develop pituitary adenomas, and these tumors are the first disease manifestation in 17–29% of patients, usually arising at a young age.[48–50] Pituitary adenomas in MEN1 patients are significantly larger and more invasive than those occurring in non-MEN1 sporadic patients (76–85% are macroadenomas), but there is no increased prevalence of carcinomas.[48, 51] Two-thirds of the patients with clinically evident pituitary disease have prolactinomas, while corticotropinomas represent only 3–10% of the MEN1-related pituitary adenomas.[48, 50–52] Around 10% of MEN1 patients develop adrenal tumors (most of them nonfunctioning), but the incidence of adrenal enlargement is much higher; the prevalence of adrenal cancer is 1%. Nevertheless, CS is relatively infrequent (5% of MEN1 patients with adrenal tumors).[53]

Carney complex

Carney complex (CNC) is a rare syndrome composed of multiple endocrine neoplasia and cardiocutaneous manifestations, with autosomal dominant inheritance.[54, 55] Three-quarters of CNC cases are caused by loss-of-function mutations in the *PRKAR1A* gene (on chromosome 17q24.2), 6% are due to deletions in 17q24.2-q24.3, and a triplication of the *PRKACB* gene was identified as the cause of disease in a single patient, while other cases are linked to an uncharacterized defect in 2p16.[56–59] More than half of the cases display familial presentation, with almost full penetrance.[60] No germline or somatic *PRKAR1A* mutations have been identified in sporadic pituitary adenomas.[61–63] *PRKAR1A* loss-of-function causes unopposed activation of the cAMP/PKA pathway due to uncontrolled catalytic subunit activity.[55, 64] One-quarter of CNC patients develop CS due to PPNAD, although histological evidence of PPNAD has been detected in almost all CNC individuals at autopsy.[65] Patients develop hypercortisolism with insidious progression over the years, that characteristically displays a paradoxical rise during the six-day Liddle test.[66] Histologically, PPNAD consists of normal-sized or slightly enlarged adrenals with irregular contour, due to small subcapsular dark nodules and cortical atrophy.[67] So far, only three cases of CD have been reported among CNC patients, all of them with frameshift *PRKAR1A* mutations, although the corticotropinoma was highly suspected but not fully proven in one of the patients.[68, 69] Loss of heterozygosity (LOH) in the corticotropinoma tissue was demonstrated in two cases.[69, 70] In the setting of CNC, CD represents a diagnostic challenge in CNC, due to the possible coexistence of CS of adrenal origin.[57, 68]

Genetic alterations in Cushing's disease

Somatic gain-of-function *USP8* mutations

Mutations in the exon 14 of the *USP8* gene (15q21.2), encoding the ubiquitin-specific protease 8, have been reported in 31–60% of corticotropinomas occurring in children and adults in tumor-extracted DNA, accounting for the most common somatic gene alteration in CD.[71–74] Such gene defects affect highly conserved residues localized in a hotspot within the 14-3-3 binding motif (residues 715–720). Under physiological conditions, USP8 binds and deubiquitinates target ubiquitinated proteins to prevent their proteasomal degradation. Cleavage of USP8 at a site immediately upstream to the 14-3-3 binding motif by still unknown proteases results in enhanced deubiquitinase activity from a C-terminal 40-kDa protein fragment.[72] Phosphorylation and binding to 14-3-3 proteins regulates USP8 function by preventing cleavage, but loss of such interaction results in unrestricted protein function. A key target protein for USP8 in corticotroph cells is the epidermal growth factor receptor (EGFR), and *USP8* gain-of-function mutations are translated into continuous EGFR recycling, and therefore increased EGFR signaling, resulting in increased *POMC* transcription.[72, 73, 75] Along these lines, corticotropinomas carrying *USP8* mutations are usually microadenomas that strongly express POMC.[76]

Although EGFR overexpression is not a consistent finding in *USP8* mutation positive tumors, *in vitro* studies have proven that USP8 mutants inhibit the degradation of the ligand-bound EGFR in EGF-stimulated cells.[72, 76] Expression of the somatostatin receptor type 5 (SSTR5) and O-6-methylguanine-DNA methyltransferase (MGMT) are increased in *USP8*-mutated tumors, suggesting that such tumors might be responsive to the pharmacological treatment with pasireotide, but not with temozolomide.[76] The frequency of *USP8* mutations is higher in females in all the cohorts reported so far, but there are discrepancies among studies regarding other clinical and biochemical features.[71–73, 76] Interestingly, the frequency of *USP8* mutations in a recently reported cohort of patients with Nelson's syndrome (45%), was not higher than what has been reported for CD, although such mutations were associated with lower frequency of ACTH normalization after surgery.[77]

Somatic *RASD1* mutation

Originally identified as a gene induced by dexamethasone treatment of AtT20 cells, *RASD1* encodes a glucocorticoid-inducible Ras guanosine triphophatase (RAS GTPase) that might have a physiological role in the glucocorticoid negative feedback in corticotrophs, where it inhibits cAMP-stimulated secretion.[78, 79] By interacting with G inhibitory proteins, RASD1 exerts a context-dependent activation or suppression of MAPK signaling.[80, 81] *RASD1* is also expressed in other tissues, where it might mediate local responses to glucocorticoids; it displays a circadian rhythm of expression in the hypothalamus and has a role as a mediator of the photic response of the circadian clock.[78, 82] A novel missense mutation in the *RASD1* gene was detected in a small allelic fraction by whole exome sequencing in corticotropinoma tissue from a young adult CD female; a coexistent hotspot *USP8* mutation was identified in the same tumor.[83] It was hypothesized that, in this genetically heterogeneous tumor, the *RASD1* mutation could contribute to cell proliferation and ACTH secretion in a small subpopulation of cells.

Somatic *TP53* mutations

Only three CD cases have so far been associated with somatic inactivating missense *TP53* mutations, including two patients with ACTH-secreting pituitary carcinomas (one heterozygous and one not specified) and one patient with an invasive corticotropinoma with high Ki-67 index and a homozygous mutation.[84, 85] Immunostaining for TP53 was positive in the three cases, and particularly high for carcinomas (60 and 90% of positive cells). Interestingly, accumulation of TP53 protein has been observed in 50% of corticotropinomas, suggesting that alternative mechanisms should have a role in the overexpression of this tumor suppressor.[86]

Somatic and germline *N3CR1* mutations

Mutations in the *N3CR1* gene, encoding the glucocorticoid receptor, have been identified by direct sequencing in two cases of CD: a patient with a frameshift somatic mutation and Nelson's syndrome and a case of CD with generalized glucocorticoid resistance and a dominant-negative *de novo* germline mutation.[87, 88] Whole-exome sequencing of 12 corticotropinomas demonstrated an additional case with a somatic nonsense mutation.[73] Loss of function of *N3CR1* in the corticotroph cells impairs the response to the negative adrenal feedback, rendering the cells resistant to the antiproliferative and antisecretory effects of glucocorticoids. Other studies failed to identify further mutations, indicating that *N3CR1* gene defects are a rare cause of CD.[89, 90]

Multiple endocrine neoplasia type 2

Activating mutations in the rearranged during transfection protooncogene (*RET*, 10q.11.2) are associated with the syndrome of multiple endocrine neoplasia type 2, an autosomal dominant entity that includes three distinctive clinical presentations: familial medullary thyroid carcinoma (MTC), MEN2A (association of MTC, pheochromocytomas, hyperparathyroidism), and MEN2B (MTC, pheochromocytomas, characteristic facies, marfanoid habitus, ocular abnormalities, musculoskeletal manifestations and generalized ganglioneuromatosis).[91] *RET* encodes the tyrosine kinase membrane receptor for the glial-derived neurotrophic factor, expressed by the neural crest during embryogenesis. Activating mutations result in constitutive RET function and activation of pro-proliferative molecular pathways, including the RAS/RAF proto-oncogene serine/threonine-protein kinase (RAF)/mitogen-activated protein kinase (MAPK)/phosphoinositide 3-kinase (PI3K)/RAC-alpha serine/threonine-protein kinase (AKT) pathway.[91, 92] Pituitary adenomas are not a classical component of MEN2, but an association between pituitary adenomas and *RET* mutations has been reported in four different patients. Three patients presented with an MEN2A-like phenotype; the fourth patient presented as MEN2B; among them, two CD cases have been associated with *RET* mutations.[93–96] Other patients with similar phenotypes have been described in the literature, although genetic testing was not available or was negative for *RET* mutations.[97] Although rarely, MEN4 patients can also develop CS due to ectopic ACTH secretion from MTC.[91]

Multiple endocrine neoplasia type 4

Human germline mutations in the cyclin dependent kinase inhibitor 1B gene (*CDKN1B*, 12p13.1) cause about 2% of the cases of *MEN1* mutation-negative multiple endocrine neoplasia.[98–100] These patients display a heterogeneous phenotype, referred to as multiple endocrine neoplasia type 4 (MEN4), encompassing parathyroid and pituitary adenomas, neuroendocrine tumors and various benign and malignant neoplasms.[98] MEN4 is an autosomal dominant disorder with incomplete penetrance, therefore it can present clinically as familial or sporadic cases.[101] The most common component of the syndrome is hyperparathyroidism, while renal angiomyolipoma, adrenal non-functional tumor, uterine fibroids, gastrinoma and gastric carcinoma, GEP-NETs, non-functioning pancreatic endocrine neoplasm, neuroendocrine cervical carcinoma, bronchial carcinoid and papillary thyroid carcinoma have also been described as part of the syndrome.[98–100, 102–107]

Pituitary tumors have been reported in eight MEN4 patients so far, only one of them with CD.[100, 101, 107] This female patient carrried a frameshift *CDKN1B* mutation (p.K25fs) and was diagnosed with CD at the age of 46 years; loss of the normal allele was demonstrated in the tumor tissue. She also developed a small-cell neuroendocrine cervical carcinoma and hyperparathyroidism. Although the association of *CDKN1B* mutations with human corticotropinomas is rare, CDKN1B plays a crucial role in the control of corticotroph proliferation. In addition, *Cdkn1b* knockout mice develop, among other phenotypic abnormalities, ACTH-secreting hyperplasia or adenomas of the pituitary *pars intermedia* with full penetrance.[108–110] Given that *CDKN1B* gene defects are infrequent, other gene regulatory mechanisms might play a role in the impaired CDKN1B function often observed in corticotropinomas.

Three P association (3PAS)

The association of a pituitary adenoma with a pheochromocytoma or paraganglioma (pheo/PGL) in a single patient, recently defined as the “Three P Association” (3PAs), is a very infrequent phenotype, with only 82 cases identified in the literature.[97, 111–121] Out of the cases with a known genetic cause, twenty one are due to germline loss-of-function mutations in genes that are known to be causative of pheo/PGL: *SDHB, SDHD, SDHC* and *SDHA* genes (*SDHx* genes), in nine, six, two, two and one cases, respectively, while an *SDHAF2* and a *MAX* mutation were reported in one case each.[111–115, 117, 120, 122–126] A few other cases presenting with this phenotype represent variants of classic syndromes of multiple endocrine neoplasia: three cases with *RET* mutations (MEN2A), two cases with *MEN1* mutations (MEN1) and one with a *VHL* mutation (Von Hippel-Lindau disease).[93, 95, 119, 127] Four cases of Cushing’s disease presenting with 3PAs phenotype have been reported in the literature, one of them carrying a *RET* mutation (see “Multiple endocrine neoplasia type 2”). Genetic screening failed to identify causative mutations in two patients.[117, 118] One patient was not genetically tested but had a family history compatible with MEN2A.[128] Although it is feasible that mutations in other pheo/PGL-related genes could lead to CD, this has not been demonstrated so far.

Familial isolated pituitary adenoma

Familial isolated pituitary adenoma (FIPA) is defined by the presence of pituitary adenomas in two or more members of the same family in the absence of other clinical features, with autosomal dominant inheritance and incomplete penetrance, and accounts for about 2.5% of all pituitary adenomas.[129, 130] One-fifth of the FIPA cases are due to germline loss-of-function mutations in the *AIP* gene (11q13.2).[131, 132] *AIP* mutations are also detected in a subset of sporadic pituitary adenomas affecting young patients, and in one-third of cases of gigantism.[133, 134] In the somatotroph cells, AIP has a complex effect as a negative regulator of the cAMP/PKA pathway and of the downstream effects of a Gi protein-coupled receptor, probably an SSTR.[135, 136] Ninety-three percent of the *AIP* mutation positive patients have macroadenomas and the clinical phenotype is growth hormone excess in 80% of the cases.[132, 133] Only three cases of CD associated with *AIP* mutations have been described so far in one pediatric and two young adult patients with missense mutations (p.K103R in the pediatric case and p.R304Q in the adults), all of them with apparently sporadic presentation.[137, 138] Nevertheless, the variants found in these patients have displayed inconsistent experimental results, therefore their pathogenic potential is uncertain (reviewed in [139]).

FIPA with undetermined genetic cause represents a heterogeneous group of patients regarding pituitary tumor types, although half of these patients develop GH excess.[140] Six percent of these patients have CD, and FIPA families with exclusively cases CD have only been reported in the absence of *AIP* mutations.[133, 141] X-linked acrogigantism, an infrequent form of gigantism with very young onset caused by *GPR101* (Xq26.3) gene amplification, occasionally has a familial presentation and is included by some, but not all authors as part of FIPA. Nevertheless, *GPR101* gene defects have not been implicated in CD as yet.[142]

CD associated with *CABLES1* mutations

The negative cell cycle regulator *CABLES1* is a direct target gene for glucocorticoids in the corticotroph cells, therefore acting as a mediator of the regulatory adrenal-pituitary feedback loop.[143] CABLES1 stabilizes and prevents the degradation of cell cycle regulators and interacts with TP53 and TP73 to trigger apoptosis; such tumor suppressor activity is inhibited by 14-3-3 or AKT-mediated phosphorylation [144, 145] CABLES1 expression is lost in a variety of human cancers, and *CABLES1* gene inactivation promotes cell proliferation and survival, as well as tumor formation *in vitro,* and replicates the human neoplasms in mouse models.[144] We have recently identified four CD patients with loss-of-function *CABLES1* missense mutations, accounting for 2% of the patients tested.[146] The four patients had young-onset macroadenomas that were large and aggressive. The mutations were demonstrated at the germline level in two of the patients, while only tumor-derived DNA was available in the other two cases; one of the germline mutations was demonstrated in an apparently unaffected parent. These mutations displayed reduced ability to block corticotroph cell proliferation in response to dexamethasone stimulation *in vitro*. None of the patients had somatic *USP8* mutations, and immunohistochemistry revealed variable CABLES1 with very low nuclear CDKN1B staining. Given its function, *CABLES1* could provide a link between two of the main molecular mechanisms disrupted in corticotropinomas: dysfunction of the CDK/cyclin-dependent cell cycle regulation and

EGFR activation of the epidermal growth factor receptor (EGFR) pathway, which uses AKT1 as one of its main effectors.[145, 147, 148]

DICER1 syndrome

The DICER1 syndrome or pleuropulmonary blastoma (PPB) familial tumor and dysplasia syndrome consists of the association of PPB, ovarian sex cord-stromal tumors, cystic nephroma and thyroid gland tumors such as multinodular goiter, adenomas, and differentiated thyroid cancer together with other less common benign and malignant tumors.[149, 150] This syndrome is caused by loss-of-function mutations in the *DICER1* gene (14q32.13), and has autosomal dominant presentation, with very low penetrance. Eighty percent of the mutations are inherited and 20% present *de novo* and only one-third of the mutation carriers have a known familial history of *DICER1*-related tumours.[150] DICER1 is a multidomain enzyme with important functions in micro RNA (miRNA) processing; the RNaseIIIa and RNaseIIIb domains, located at the C-terminal half, constitute the catalytic core of the enzyme. Somatic *DICER1* loss-of-function variants have been reported in *DICER1*-related tumors, most of them affecting the RNase IIIb catalytic domain, in the presence or absence of germline mutations.[151]

Pituitary blastoma is a very rare and aggressive apparently congenital pituitary tumor presenting clinically as CD early in infancy.[152] A recent study reported thirteen cases of DICER1 syndrome with pituitary blastoma, and nine out of ten infants tested were positive for heterozygous *DICER1* mutations. Somatic *DICER1* mutations were detected in seven cases, and two cases displayed LOH in the tumor, accounting for a total of nine patients with somatic alterations; seven of these cases were also positive for germline mutations.[152] This series, together with a recent case report, account for a total of 14 genetically screened cases of this neoplasm reported to date.[153] The first manifestation of disease appeared early in childhood, and in most cases (9/14) pituitary blastoma was the only manifestation of the syndrome; five out of the patients died within 0–26 months of the first surgery.[152, 153] At the histopathological examination, pituitary blastomas resemble the human fetal adenohypophysis at the age of 10–12 gestational weeks, when corticotrophs and somatotrophs are already differentiated, and alpha-glycoprotein subunit starts to emerge, but other cells types are not yet evident.[154] Aside of pituitary blastoma, it remains uncertain whether *DICER1* could also play a role in CD due to pituitary adenomas.

Tuberous sclerosis complex

Tuberous sclerosis complex is a syndrome characterized by multiple hamartomatous lesions affecting brain, skin, heart, lungs and kidneys, associated with neurological manifestations such as seizures, autism and cognitive disability. This syndrome is due to loss-of-function mutations in either the *TSC1* (9q34.13) or the *TSC2* (16p13.3) gene, whose protein products (hamartin and tuberin) act as negative regulators of the mammalian target of rapamycin complex1 (mTORC1), therefore inhibiting cell growth.[155] Pituitary adenomas are not a common feature of the tuberous sclerosis complex, but CD has been described in two of such patients so far: a pediatric patient with a *TSC2* mutation and a young adult who was not genetically tested; both patients presented with other coexistent manifestations of TSC.[63, 156, 157]

X-linked congenital adrenal hypoplasia

The clinical association of adrenal hypoplasia with glucocorticoid and mineralocorticoid deficiency and hypogonadotropic hypogonadism is due to loss of function mutations in the *DAX1* gene (Xp21.2), encoding an orphan nuclear receptor.[158] A single case of a corticotropinoma associated with a germline frameshift *DAX1* mutation has been described.[159] The patient had preexisting adrenal insufficiency, primary hypothyroidism and hypogonadotrophic hypogonadism and was diagnosed with a CD at the age of 33 years, due to an invasive corticotropinoma. Maternal inheritance of the genetic defect was proven, but no other affected family members were identified.

Summary

Great progress has been done in the recent years to elucidate the genetic defects underlying CS of adrenal and pituitary origin. Frequent molecular abnormalities in adrenal lesions include cAMP/PKA and WNT/CTNN1B signaling overactivation, while glucocorticoid resistance, abnormal expression of cell cycle regulators and overexpression of membrane receptors predominate in corticotropinomas. Although most of the patients present sporadically, CS is part of a growing number of syndromes of familial isolated CS or multiple endocrine and non-endocrine neoplasia. Moreover, it should be kept in mind that CS of adrenal and pituitary origin can coexist in the setting of some syndromic presentations, complicating the diagnosis. Further research efforts are required to unveil other molecular abnormalities in CS, which will hopefully lead to novel therapeutic targets.

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Key Points

- Cushing's syndrome (CS) of pituitary or adrenal origin usually presents as a sporadic entity and is most commonly due to somatic gene defects.
- Cortisol-producing adenomas are the most common cause of adrenal CS and these lesions are frequently caused by somatic activating mutations in the *PRKACA* gene.
- Somatic gain-of-function mutations in the *USP8* gene constitute the most common genetic defect in corticotropinomas.
- Although infrequent, familial forms of CS may present either isolated or in association with various familial syndromes of multiple endocrine and non-endocrine neoplasia.
- Understanding the genetic defects that drive corticotroph and adrenocortical tumorigenesis should lead to unraveling novel therapeutic targets, which will hopefully be translated into more efficient strategies for the medical treatment of patients with CS.

Table 1

Causes of endogenous Cushing's syndrome and their genetic bases

Origin	Lesion type	General molecular mechanisms	Clinical presentation	Known genetic causes
Cushing's disease (60–70% of cases)	Corticotropinoma	Resistance to glucocorticoid negative feedback, cell cycle dysregulation, overexpression of membrane receptors (arginine-vasopressin receptors, epidermal growth factor receptor)	Sporadic Cushing's disease, no associated manifestations	Somatic *USP8* GOF hotspot mutations
				Somatic *GNAS* GOF mutations (codon 201 or 227)
				Somatic *RASD1* LOF mutation
			Carney complex	Germline *PRKAR1A* LOF mutations/ deletions, uncharacterized defect in 2p16, *PRKACB* amplification
			Familial isolated pituitary adenoma	Germline *AIP* LOF mutations/deletions, unknown genetic defect in 80% of cases
			Familial CD with very low penetrance?	Germline *CABLES1* LOF mutations
			Multiple endocrine neoplasia type 1	Germline *MEN1* LOF mutations/ deletions
			Multiple endocrine neoplasia type 2	Germline *RET* LOF mutations/deletions
			Pheocromocytoma/paraganglioma and pituitary adenoma	
			Multiple endocrine neoplasia type 4	Germline *CDKN1B* LOF mutations/ deletions
			Tuberous sclerosis	Germline *TSC1* or *TSC2* LOF mutations
Ectopic ACTH secretion (5–10% of cases) and ectopic CRH secretion (very rare)	Medullary thyroid carcinoma	Production of ACTH or CRH by tumoral neuroendocrine tissue	Isolated medullary thyroid carcinoma	*RET* LOF mutations
			Multiple endocrine neoplasia type 2	
	Other malignant neuroendocrine tumors (bronchial endocrine tumor, small cell lung cancer, others)		Isolated small cell lung cancer	Loss of 3p23-p21, somatic *TP53* and *RB1* LOF mutation, others
			Multiple endocrine neoplasia type 1	Germline *MEN1* LOF mutations/ deletions
	Benign neuroendocrine tumors (pheochromocytoma, others)		Multiple endocrine neoplasia type 2	Germline *RET* LOF mutations/deletions
			Neurofibromatosis type 1	Germline *NF1* LOF mutations
			Von Hippel-Lindau disease	Germline *VHL* LOF mutations
			Isolated paraganglioma/pheochromocytoma	*SDHA, SDHB, SDHC, SDHD, SDHAF2, FH, MAX, TMEM127* LOF mutations
Adrenal (primary) (20–30% of cases)	Cortisol-producing adenoma	Overactivation of the cAMP and WNT/ CTNNB1 pathways, overexpression of steroidogenic enzymes	Sporadic Cushing's syndrome, no associated manifestations	Somatic *PRKACA* GOF hotspot mutations, somatic CTNNB1 LOF mutations

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Origin	Lesion type	General molecular mechanisms	Clinical presentation	Known genetic causes
			Multiple endocrine neoplasia type 1	*MEN1* LOF mutations/deletions
			Familial adenomatous polyposis and Gardner's syndrome	Germline *APC* LOF mutations
	Primary multinodular adrenal hyperplasia (PMAH)	Ectopic GPCR and ACTH expression, overactivation of the cAMP and WNT/CTNNB1 pathways, overexpression of steroidogenic enzymes	Sporadic Cushing's syndrome, no associated manifestations	Germline and somatic *ARMC5* LOF mutations
				Somatic *GIPR* amplification
				Somatic *MC2R* mutations
				Germline *PRKACA* amplification
	Primary pigmented nodular adrenocortical disease (PPNAD)	Overactivation of the cAMP pathway	Sporadic Cushing's syndrome, no associated manifestations (isolated PPNAD)	Germline *PRKAR1A* LOF mutations/deletions, uncharacterized defect in 2p16, germline *PDE11A* LOF mutations
			Carney complex	Germline *PRKAR1A* LOF mutations/deletions, uncharacterized defect in 2p16, *PRKACB* amplification
	Isolated micronodular adrenal disease (iMAD)		Sporadic Cushing's syndrome, no associated manifestations	Germline *PDE8B* LOF mutation
				Germline *PDE11A* LOF mutations
				Germline *PRKACA* amplifications
	Primary bimorphic adrenocortical disease		McCune-Albright syndrome	Mosaic *GNAS* GOF mutation (codon 201)
	Adrenocortical carcinoma	Impaired *TP53/RB1* signaling and chromatin remodeling, overactivation of the WNT/CTNNB1 pathway	Familial adenomatous polyposis	Germline APC LOF mutations
			Sporadic Cushing's syndrome, no associated manifestations	Somatic *ZNRF3, APC, CTNNB1, CDKN2A, CDK4, RB1, MDM2, TP53, MEN1, DAXX,* and *ATRX* mutations
			Beckwith-Wiedemann syndrome	11p15.5 maternal rearrangements, paternal uniparental disomy, abnormal methylation, germline *CDKN1C* and *WTX* LOF mutations
			Li-Fraumeni syndrome	Germline *TP53* LOF mutations
			Multiple endocrine neoplasia type 1	*MEN1* LOF mutations/deletions
			Rubinstein-Taybi syndrome	Germline *CREBBP* or *EP300* LOF mutations

See references in text. GOF, gain-of-function; GPCR, G protein-coupled receptor; LOF, loss-of-function.