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Adrenocortical Tumors and Hyperplasias in Childhood - Etiology, Genetics, Clinical Presentation and Therapy

Jennifer A. Sutter, MD[1] and **Adda Grimberg, MD, FAAP**[2]

1*Instructor of Pediatrics, University of Pennsylvania School of Medicine; Fellow, Division of Pediatric Endocrinology, The Children's Hospital of Philadelphia*

2*Assistant Professor of Pediatrics, University of Pennsylvania School of Medicine; Attending Physician, Division of Pediatric Endocrinology, The Children's Hospital of Philadelphia*

Abstract

Adrenocortical tumors are rare in children and are associated with a poor prognosis when malignant. The fund of knowledge regarding etiology, presentation and clinical outcomes remains limited. Evaluation of genetic disorders associated with the development of adrenocortical disorders has allowed researchers to identify a number of mutations that may be involved in tumorigenesis, including alterations in the GNAS1, PRKAR1A, TP53 and IGF2 genes. Clinical presentation in children is associated most commonly with young age, female gender and symptoms of virilization. Most children have localized disease at presentation which may be associated with a better prognosis when compared to adults. Surgical resection remains the only potentially curative treatment and mitotane, the most frequently used chemotherapeutic agent, has a poor response rate and is highly toxic. Broader participation in multi-center research, such as the International Pediatric Adrenocortical Tumor Registry, is needed to collect sufficient data to better guide our clinical management.

Keywords

Adrenocortical; Pediatric; AIMAH; PPNAD; Carcinoma; Adenoma; Hyperplasia; Mitotane

Adrenocortical neoplasms are rare in children and adolescents. Tumors account for less than 0.2% of all pediatric neoplasms and 1.3% of all carcinomas in patients less than 20 years old (1,2). Single tumors usually are benign unilateral adenomas and more rarely malignant carcinomas. Less commonly, patients can present with benign multinodular hyperplastic lesions including pigmented or non-pigmented micronodular adrenal disease and ACTH-independent macronodular adrenal hyperplasia (AIMAH). The latter is also known as massive macronodular adrenocortical disease (MMAD) (3-5). The purpose of this review is to highlight what is known about the etiology, clinical presentation and treatment of these disorders.

Etiology and Genetics

Little is known about the pathogenesis of these proliferative disorders. It would seem plausible that mutations in the normal signaling pathways that stimulate adrenal steroidogenesis would contribute to their development. The normal signaling pathways begin with the binding of ACTH to a G-protein coupled receptor. This leads to activation of the $G\alpha_s$ subunit followed by activation of adenylyl cyclase. This increases the concentration of cyclic adenosine 3′,5′-

Corresponding author: Dr. Adda Grimberg, Abramson Research Center - Room 802, 3615 Civic Center Boulevard, Philadelphia, PA 19104-4318, Tel: 215-590-3420, Fax: 215-590-1605, e-mail: grimberg@email.chop.edu

monophosphate (cAMP), thereby activating protein kinase A (PKA). PKA is a serine/threonine kinase that phosphorylates transcription factors such as cAMP response element modulator (CREM), cAMP response element binding protein (CREB), activating transcription factor-1 (ATF-1) and steroidogenic factor 1 (SF-1). These transcription factors bind to the cAMP response element (CRE) sequence or the cAMP responsive sequence (CRS) and modify the expression of steroidogenic genes (6-9). Investigations into familial syndromes that are associated with adrenocortical tumors or nodular disease have indeed identified mutations that affect this signaling pathway (**see** Figure).

ACTH is important for normal adrenal gland development and growth. It functions *in utero* as the principal stimulator of adrenocortical fetal zone growth. Afterwards, ACTH stimulates the differentiation, maintenance and hormonal secretion of glucocorticoids from the zona fasciculata, the middle zone of the adrenal cortex and androgens from the zona reticularis, the inner-most zone (10). ACTH hypersecretion, which can be seen with either Cushing's Disease or congenital adrenal hyperplasia (CAH), leads to bilateral adrenocortical hyperplasia and increased steroidogenesis (5,6,11,12). The size of the adrenal glands correlates with the plasma levels of ACTH and the duration of disease (13). Nodular transformation has been noted in a minority of patients with long standing hyperplasia (12,14).

AIMAH is a benign proliferative disorder of the adrenal cortex that presents with ACTH-independent Cushing 's syndrome. Histologically it is composed of nodules with two cell types, lipid rich cells with a clear cytoplasm and lipid poor cells with a compact cytoplasm. (4) Steroid hormone secretion by these cells is ACTH independent and associated with both undetectable plasma levels of ACTH and the inability to suppress cortisol secretion with high dose dexamethasone. (15) The cells, though, express the ACTH receptor and patients will respond to exogenous ACTH. (3,16) This is in contrast to primary pigmented nodular adrenocortical disease (PPNAD), adenomas and carcinomas, which are ACTH unresponsive. (3,17) The increased steroid hormone synthesis in AIMAH is thought to be due to the overall increase in adrenocortical mass rather than augmented synthesis within each cell (16).

The majority of patients with AIMAH present in the fifth decade of life with sporadic isolated disease (3). In children, though, AIMAH can be associated with McCune-Albright Syndrome (OMIM 174800), an autosomal dominant disorder characterized by polyostotic fibrous dysplasia, café-au-lait spots, precocious puberty and hyperfunctional endocrine glands. Hypercortisolism and AIMAH is found in 5% of patients with McCune-Albright Syndrome (18,19). The disorder is caused by an activating mutation in the *GNAS1* gene (chromosome 20q13.2, OMIM 139320), which encodes the $G\alpha_s$ subunit of the G-protein receptor. By inhibiting the protein's intrinsic GTPase function, *GNAS1* activating mutations lead to the constitutive activation of adenylyl cyclase, an increase in cAMP levels and enhanced intracellular signaling (19). AIMAH has also been found to be associated with ectopic expression of G-protein receptors for hormones other than ACTH, such as gastric-inhibitory peptide (GIP), vasopressin, catecholamines, luteinizing hormone and human chorionic gonadotropin. These receptors also activate adenylyl cyclase, and their over expression increases cAMP-mediated signaling. For example, food-dependent Cushing's Syndrome is characterized by low fasting cortisol levels and suppressed ACTH levels yet elevated cortisol and GIP levels after enteral meals (8).

Macronodular adrenocortical hyperplasia and adrenocortical nodules have also been reported in up to 36% of patients with the Multiple Endocrine Neoplasia Syndrome type 1 (MEN 1) with bilateral cortical hyperplasia present in 6-21% of patients (20,21). MEN 1 is an autosomal dominant tumor syndrome caused by an inactivating mutation of the MEN1 gene (chromosome 11q13;OMIM 131100) which encodes the tumor suppressor protein, menin (22). Menin is found mainly in the nucleus where it interacts with DNA processing and repair proteins and

transcription factors such as JunD. In binding JunD, menin suppresses its transcriptional activity and is necessary for JunD's action as a growth suppressor (22). MEN 1 is most commonly associated with pituitary, parathyroid and pancreatic tumors (11,18,22). In the vast majority of these patients their adrenal disease is hormonally silent (20).

PPNAD is another benign bilateral proliferative disorder. Histologically, it is characterized by small nodules, usually less then 4-6 mm in diameter, with a brown or black color due to large cells with a granular, pigment-containing cytoplasm. The internodular adrenal cortex is atrophic and disorganized and the adrenal glands retain normal weight and size (18,23). PPNAD can be seen in isolation, but is usually associated with the Carney Complex (OMIM 160980). This is an autosomal dominant syndrome that includes perioral, ocular or genital spotty skin pigmentation (lentiginosis), cardiac and peripheral myxomas, melanotic schwannomas, and endocrine over-activity. Affected patients often have tumors of two endocrine glands, most commonly PPNAD, but also including prolactin or growth hormone secreting pituitary tumors, thyroid adenomas or carcinomas, testicular large-cell calcifying Sertoli cell tumors or ovarian cysts (23,24,25). Clinically evident PPNAD is seen in 25-30% of patients with the Carney Complex and usually presents in childhood, late adolescence, or early adulthood (11,18,24). Germline inactivating mutations in the gene encoding the type 1α regulatory subunit of protein kinase A (*PRKARIA*), located on chromosome 17q22-24, have been found in 45-65% of the familial forms and 35% of the sporadic forms of Carney Complex (7,11,18,24,25). Somatic and *de novo* germline mutations of *PRKAR1A* are also found in isolated PPNAD (7,11). These mutations lead to decreased basal but increased cAMP-stimulated PKA activity (7,18,25). A second locus for Carney Complex (*CNC*2) was mapped to chromosome 2p16, but a causative gene has not been identified (26). These patients have been treated successfully with bilateral adrenalectomies (23).

Malignant adrenocortical carcinomas that develop in children can be either sporadic or associated with Li-Fraumeni Syndrome (OMIM 151623), a dominantly inherited familial cancer syndrome. Patients with this syndrome may develop a number of cancers that typically include soft tissue sarcomas, osteosarcomas, breast cancer, brain tumors, leukemia and lymphoma, and adrenocortical adenomas and carcinomas (27,28). Clinical criteria for diagnosing a family with classic Li-Fraumeni Syndrome include: (1) a proband with a sarcoma diagnosed under 45 years of age; (2) a first-degree relative with one of the associated tumors diagnosed under 45 years of age and (3) a first or second degree relative with any cancer diagnosed under 45 years or with a sarcoma diagnosed at any age (29,30,31). Adrenocortical tumors usually occur during the first decade of life and second primary tumors develop in up to 15% of patients (28,32). Germline mutations in the gene encoding the tumor suppressor p53 located at chromosome 17p13.1 (*TP53*) are found in 70% of affected families (33,34). These germline mutations have also been found in 50-80% of children with sporadic adrenocortical carcinoma in two small studies in North America and Europe (32,35). In southern Brazil, there is a fifteen-fold greater incidence of isolated pediatric adrenocortical carcinoma compared to other populations. These children have a unique germline missense mutation of *TP53* (R337H) that affects the protein's oligomerization domain, leading to pH-dependent instability, and predisposes them to develop adrenocortical tumors (36,37,38,39). The reason for this increased frequency in southern Brazil was unclear, as a founder effect was initially thought to be unlikely given the pattern of two intragenic and two flanking polymorphic markers (36,40). However, Pinto et al. recently demonstrated an identical *TP53* haplotype in 95% of 22 apparently unrelated Brazilian patients with adrenocortical tumors carrying the R337H p53 mutation, suggesting that it originated from a single common ancestor. The same haplotype was also found in all the tumor DNA, usually compounded by loss of the normal *TP53* allele (41). Normally the p53 protein is activated by cellular stress like DNA damage, irradiation, hypoxia and oncogenic stress and, through transcriptional activation, repression and protein-protein interactions, stimulates cell cycle arrest, apoptosis or senescence. p53 is therefore important

in protecting the body from the proliferation of damaged and dangerously aberrant cells (42, 43). Loss of heterozygosity at *TP53* or the loss of a normal allele within tumor DNA that unmasks an inherited mutant allele, has also been associated with an increase in the incidence of malignancy and recurrence in adults (11,44). Germline mutations in the human checkpoint kinase 2 (*hCHK2*) gene, at chromosome 22q12.1, have also been reported in patients with Li-Fraumeni syndrome who do not harbor *TP53* mutations. *hCHK2* is a serine/threonine kinase that phosphorylates and activates p53. However, there have been no reports of adrenocortical carcinoma in patients with hCHK2 mutations (29).

Adrenocortical carcinomas have also been associated with Beckwith-Wiedemann Syndrome (OMIM 130650), an overgrowth disorder characterized by macrosomia, macroglossia, organomegaly and abdominal wall defects. This syndrome can occur either sporadically or in an autosomal dominant pattern and patients are predisposed to developing embryonal tumors such as Wilms' tumors, neuroblastomas, hepatoblastomas and adrenocortical carcinomas (11,45). Over expression of IGF-II is thought to contribute to tumorigenesis in Beckwith-Wiedemann Syndrome (46,47). The IGF2 gene, located on chromosome 11p15.5, is normally expressed from only the paternal allele due to imprinting, or the expression of only one parent's allele (in this case, the father's) while the other parent's allele (the mother's) is silenced (11, 18,47). Over expression of IGF-II can be caused by paternal isodisomy, in which the maternal allele is lost and the paternal allele is duplicated, or by maternal inheritance of microdeletions of the imprinting center such that the maternal allele is no longer silenced (47). IGF-II stimulates cell survival and proliferation by binding and activating the type 1 IGF receptor (46,48) and transcription of both the *IGF2* and *IGF1R* genes can be repressed by p53 (42). IGF-II over expression was also found in NCI-H295R cells, which are derived from a human adrenocortical tumor (49) and in approximately 90% of malignant adrenal tumors in studies reviewed by Fottner *et al.* (46) Loss of heterozygosity at the *IGF2* locus in tumor DNA is also associated with an increased incidence of malignancy and recurrence in adults with adrenocortical tumors. (50)

Bioavailability and action of the IGFs are modulated by the six high-affinity IGF binding proteins (IGFBPs), some of which have been shown to also carry IGF-independent functions (51). In addition to IGF-II, significantly elevated levels of IGFBP-2 are seen with malignant adrenocortical carcinomas (52). The significance of this elevation in IGFBP-2 is unclear. It was initially thought that IGFBP-2 negatively regulates cell growth by sequestering IGFs, but there is growing evidence that IGFBP-2 may actually promote tumor growth through IGF-independent mechanism(s) (53,54).

Presentation of Single Adrenal Tumors

There are very few studies evaluating the clinical characteristics and treatment outcomes for adrenocortical tumors in children due to the rarity of the condition. The largest to date presents data from 254 patients with either adenomas or carcinomas enrolled in the International Pediatric Adrenocortical Tumor Registry (IPACTR). This population has a predominantly Brazilian contribution (79.5%), but it also includes patients from the United States (13%) and nine other countries (7.5%). The patients were entered into the database if they were reported by their primary physician(38). Two additional studies retrospectively evaluated a series of 54 patients from France(55). and 30 patients from Turkey (56). The median age at diagnosis for these three studies was 3-4 years, with a range of 0-19 years(38,55,56). There appears to be two peak times for presentation, during the first 2 years of life, with 60% of children in the IPACTR presenting before 4 years, and peripubertally between 12-14 years(38,55). There also appears to be a greater incidence of adrenocortical tumors in female patients, with an overall predominance of 1.6:1(38,56). In the IPACTR this difference was seen in children aged ≤3

years (1.7:1) and ≥ 13 years (6.2:1) but not between 4-12 years(38). In the Turkish study, the gender difference was greater for children with adenomas (4:1)(56).

Adrenocortical tumors can be either functional or non-functional. In children most tumors are functional, with 80-90% having endocrine manifestations at diagnosis and up to 94% secreting excess hormones on further evaluation(38,55,56). Most children (50-84%) present with virilization (pubic hair, accelerated growth and skeletal maturation, an enlarged penis or clitoris, hirsutism and acne) due to excess androgen secretion(38,55,56). Less frequently, children present with Cushing's Syndrome (15-40%) with hypertension, obesity and decreased linear growth due to excess glucocorticoids, feminization (7%) or gynecomastia due to excess estrogens, signs of hyperaldosteronism (1-4%) including hypertension and hypokalemia, or a mixture of symptoms (38,55,56). Cushing's Syndrome appears to occur more frequently in adrenocortical carcinomas, larger tumors (>10 cm), and older children (38,55,56). Non-functional tumors also tend to occur more frequently in older children (38). An abdominal mass could be palpated in approximately half of the patients in the two retrospective studies (55, 56). There often is a delay between the onset of symptoms and diagnosis with a median time of 5-8 months (38,55,56) Children, though, seem to be diagnosed earlier than adults, possibly due to the relative ease with which virilization can be recognized before puberty, when androgen levels are normally very low; during puberty, sex steroid production normally increases and results in phenotypic changes, such that any additional androgen production by a tumor is often masked (55).

Disease stage at diagnosis is important because smaller tumors are associated with better surgical outcome and complete surgical resection is the only known curative treatment for adrenocortical carcinoma (55). The staging system that is employed may vary slightly between studies, but it usually divides tumors into local, regional or metastatic disease. Most children (~75%) present with local disease, either stage I (<5 cm or ≤200g with complete resection) or stage II (>5cm or >200g with complete resection). A smaller percentage (~10%) present with regional invasion to adjacent areas such as lymph nodes, the kidney and the inferior vena cava or have residual tumor after resection (stage III). Another small percentage (~15%) present with distant hematogenous metastasis to the lungs, liver or both (stage IV) (38,55). In one study, all of the children with adrenocortical adenomas had localized disease and were cured by total resection (56). For adrenocortical carcinoma, local disease with a smaller tumor burden (<10cm) appears to be associated with an improved prognosis (55).

In adult adrenocortical tumors, the Weiss score, a microscopic diagnostic score, and other immunohistochemical properties are used to determine malignant potential and prognosis. The Weiss score looks at nuclear grade, mitotic rate and atypia, vascular and capsular invasion and necroses to predict malignancy. An increased mitotic rate has the greatest predictive value (57). In addition, antibody staining for increased expression of the proliferation antigen Ki67 (58) and defining altered gene expression by cDNA micorarrays, including increased expression of IGF-II, appear to be promising techniques in differentiating carcinomas from adenomas (59,60). Unfortunately, histological classification in pediatric adrenocortical tumors has been unreliable and classification based on existing systems does not predict prognosis. In a retrospective study of 33 pediatric adrenocortical tumors, clinical and surgical factors proved prognostic, while none of the immunohistochemical markers or histopathologic criteria were significantly associated with outcome (61)

Therapy and Prognosis of Single Adrenal Tumors

The prognosis for children with malignant adrenocortical tumors remains poor. The 5-year overall survival rate is 49-55% with an event- or disease-free survival rate of 46-54% (38, 55). Complete surgical resection is the only effective and potentially curative treatment for

adrenocortical carcinoma (38,55,56). Surgical resection can include an adrenalectomy alone or be more extensive involving a nephrectomy, partial hepatectomy, splenectomy, or the removal of an intracaval thrombus depending on the disease stage (62). In one study, complete macroscopic resection was initially achieved in 45 of 54 children, but 40% of those with apparently complete resection still had disease recurrence after a median disease-free survival time of 7 months (55). Patients with microscopically complete resection were found to fare better with a 5-year overall survival rate of 70% compared to 7% in those children in whom it was not achieved (55).

Chemotherapy is often used before or after tumor resection to either reduce the tumor burden to enable a more complete resection, prevent recurrence or to treat recurrence if it occurs. The most common agent is mitotane (O,P'-DDD), an insecticide derivative that inhibits the conversion of cholesterol to pregnenolone and 11-deoxycortisol to cortisol and induces necrosis in adrenal tumors and metastases (38,55,56,63-65). Mitotane use in children continues to be controversial due to modestly low response rates (25-30%) and well documented toxicity which includes gastrointestinal complaints, hepatotoxicity, fatal adrenal insufficiency making glucocorticoid replacement mandatory, growth failure and neuropsychiatric symptoms such as weakness, confusion, lethargy and ataxia (55,63,66-68). Damage to the developing central nervous system leading to permanent developmental delays is one of the greatest concerns regarding the use of mitotane in young pediatric patients (63). Studies in adults suggest that achieving plasma levels greater than 14mg/L are necessary for a therapeutic response (69, 70), but that levels less than 20mg/L limit toxicity (70,71). Additional chemotherapeutic regimens include different combinations of fluorouracil, doxorubicin, cisplatin and etoposide (38,55,56). Little is known about the efficacy of these medications for adrenocortical carcinoma due to their limited use. In one study, children who achieved complete remission with these chemotherapeutic agents relapsed in only two to five months after stopping the medications (55). A more recently published study using etoposide, doxorubicin and cisplatin plus mitotane in adult patients with advanced disease shows promising results with improved response rates and overall survival (72). Radiation therapy for the treatment of metastases, incomplete local resection or local recurrences is now being studied as well (38,55,62,67).

Little is known about prognostic factors in children with adrenocortical tumors. Factors significantly associated with survival in patients with localized disease (Stage I or II) in the IPACTR include a smaller tumor burden or stage I disease (complete resection and ≤200 g), presentation with virilization alone, or age less than 4 years even when children with adrenocortical adenomas were excluded. Children less than 4 years of age had a 5-year survival rate of 85.6% compared to 59.9% for children aged 4-12 years and 38.1% for children aged 13-20 years. The researchers did not evaluate prognostic factors for those with regional or metastatic disease given the small numbers and extremely poor 5-year survival (38). These findings agree with an earlier study in which survival rates were significantly improved when tumors were revealed by endocrine symptoms (60%) or if the tumor was less than 10 cm at presentation (70% vs. 32%). A significant age effect was not found in this study, but the sample size was much smaller (55).

Management Issues for Endocrinologists

The clinical management of children with adrenocortical tumors is best handled by a multi-disciplinary team including an endocrinologist, oncologist and surgeon. Below you will find a number of issues that should be addressed by the patient's primary endocrinologist after the diagnosis of an adrenal tumor is confirmed:

1. Pre-operatively, it is imperative that a full panel of adrenocortical hormones and their precursors be measured to identify any potential tumor markers (67,68).

2. Patients should receive empiric stress dose glucocorticoid treatment perioperatively for tumor resection. Glucocorticoid coverage for stressful situations should be continued throughout treatment until normal adrenal function is confirmed. Mitotane use requires glucocorticoid replacement therapy due to its inhibition of cortisol synthesis.
3. Within a week post-operatively, a repeat hormone panel should be obtained to confirm that any tumor markers, or levels that were abnormally high pre-operatively, normalize or dramatically decrease after tumor resection.
4. Monitor for evidence of recurrence with hormonal testing every 2 months during the first year followed by every 4 months during the second year. Afterwards, this can then be spaced to every 6 months (62).
5. Obtain imaging studies to evaluate for recurrent disease. An international consensus conference of physicians and researchers held in September of 2003 recommended imaging studies only if hormonal abnormalities exist (62). However, other groups have advocated routine imaging for at least five years even with a normal hormone profile (73). CT scans or MRI can be used to assess for adrenal masses, but MRI is superior to document vascular invasion. CT scans of the abdomen and thorax should be used to detect metastases in the liver or lungs (67,68).
6. Follow clinically for potential secondary effects of excess hormone secretion. For example, if a patient presents with signs of virilization and an advanced bone age, she/he may subsequently develop hypothalamic-pituitary activation and central precocious puberty. Such patients may benefit from treatment with a gonadotropin-releasing hormone (GnRH) agonist to delay further pubertal progression.
7. A careful family history should be elicited. If suspicious for a familial tumor syndrome, genetic testing may be offered, but only in the context of thorough genetic counseling. Family discussion with the oncologist is strongly recommended.
8. Due to the rarity of pediatric adrenocortical tumors, collecting sufficient patients to enable rigorous study that will advance our understanding will require collaboration by as many clinicians as possible. Try to contribute to on-going research, such as referring all patients to the IPACTR:

Raul C. Ribeiro, MD Director, International Outreach Member, Hematology/ Oncology Department St. Jude Children s Research Hospital 332 North Lauderdale Street Memphis, TN 38105 Phone: 901-495-3694 or 901-495-5318; Fax: 901-495-3122 E-mail: raul.ribeiro@stjude.org

Summary and Future Directions

In summary, adrenocortical tumors are rare in children and are associated with a poor prognosis when malignant. Little is known about their etiology and the clinical outcomes of their treatment. Evaluation of genetic and familial disorders associated with the development of adrenocortical proliferative disorders has allowed researchers to identify a number of possible mutations that may be involved in tumorigenesis. These include mutations in the *GNAS1*, *PRKAR1A* and *TP53* genes, as well as *IGF2* over-expression from loss of its normal imprinting controls. The clinical presentation of adrenocortical tumors in children is associated most commonly with young age, female gender and symptoms of virilization. Most children have localized disease at presentation. This is associated with a better prognosis when compared to adults because microscopically complete resection is more easily achieved. Surgical resection

remains the only potentially curative treatment and mitotane, the most commonly used chemotherapeutic agent, has a poor response rate and is highly toxic.

Physicians treating children with adrenocortical tumors are handicapped by a paucity of data when making difficult clinical decisions. Given the overall poor prognosis of adrenal carcinomas and the known toxicities of treatment, the ability to distinguish adenomas from carcinomas would be a crucial piece of information when considering the risk-benefit analysis for an individual patient. Unfortunately, markers for risk stratification, such as histologic and molecular markers that identify adenoma versus carcinoma, are not yet well defined. Thus, the IPACTR has evolved from just collecting data on the clinical course of patients to also collecting tumor samples for a tumor bank. They aim to use these samples to study gene expression and the p53 pathway to correlate molecular data with clinical and outcome data to hopefully identify useful prognostic markers that will help guide treatment decisions. Broader participation in collaborative research, like the IPACTR, is needed to increase our understanding of this disease process in order to develop more targeted therapies and improve the survival rates for children who develop adrenocortical tumors.

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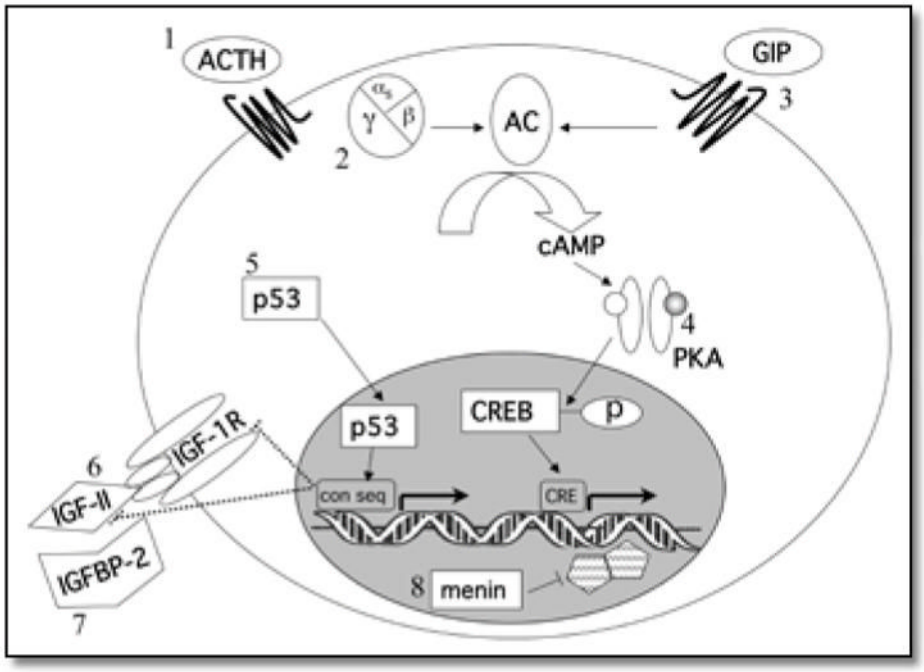

Figure.

Alterations in signaling pathways thought to be involved in the development of adrenocortical tumorsor or hyperplasias. 1. Excessive ACTH secretion in Cushing's Disease or CAH, 2. GNAS1 activating mutations in McCune Albright Syndrome, 3. Ectopic expression of G-protein associated receptors, 4. Mutations in PRKAR1A leading to increased cAMP stimulated PKA activity in PPNAD and the Carney Complex, 5. TP53 mutations associated with Li-Fraumeni Syndrome and adrenocortical carcinomas in Brazil, 6. IGF-II over-expression in Beckwith-Wiedemann Syndrome, 7. IGFBP-2 over-expression, and 8. Inactivating mutations of MEN1 in Multiple Endocrine Neoplasia type 1. Con seq = p53-binding consensus sequence; CRE = cAMP response element.