Genetic Adrenal Diseases

AACE Annual Meeting, Nashville, TN

May 13, 2014

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I. Introduction

In 2014, the AACE Adrenal Scientific Committee initiated a project of writing a series of articles to update members on the genetics of adrenal diseases. These consist of a case presentation, discussion of literature, table, and bullet points. The topics and authors are:

Primary aldosteronism: Anand Vaidya, Amir Hamrahian, & Richard J. Auchus

Congenital adrenal hyperplasia: Richard J. Auchus

Bilateral macronodular adrenal hyperplasia: Aarti Ravikumar & Alice C. Levine

Adrenal insufficiency: Elise M. Brett and Richard J. Auchus

Pheochromocytoma and paraganglioma: Karel Pacak & Sunil Wimalawansa

The complete papers are published in the April issue of Endocrine Practice. Today's lecture will highlight the key points from each paper.

II. Primary Aldosteronism

As the most common cause of secondary hypertension, primary aldosteronism (PA) is responsible for 5-13% of hypertension and up to 20% of resistant hypertension. The first genetic form of PA, or familial hyperaldosteronism type 1 (FHA1), is also known as glucocorticoid-remediable aldosteronism (GRA). GRA results from a hybrid gene between the *CYP11B1* (11-hydroxylase) and *CYP11B2* (aldosterone synthase) adjacent genes on chromosome 8q24.3. This hybrid gene allows the ACTH-dependent expression of an enzyme with aldosterone synthase activity in the zona fasciculata where cortisol is ordinarily made. The expression of this enzyme allows formation of aldosterone and also 18-oxygenated cortisol metabolites despite the suppression of plasma renin activity. The diagnosis of FHA1 is based on aldosterone suppression (<4 ng/dL) after dexamethasone (1 mg BID x 2 days or 8 mg overnight). Elevated production of 18-hydroxycortisol is also a feature but is not specific for FHA1. Genotyping for the hybrid gene is recommended for this autosomal-dominant disease. Treatment is either low-dose glucocorticoid such as dexamethasone (0.125 mg at bedtime), MR antagonist, or a combination of the two.

FHA2 was originally defined as FHA that was not glucocorticoid-suppressible. A few families have been described, but this disease remains poorly characterized. The genetic locus is 7p22, but the gene responsible for FHA2 has not been identified. FHA2 is inherited in an autosomal dominant manner, and some patients originally assumed to be FHA2 are now recognized as a third form, FHA3.

The genetic defect in FHA3 was defined in 2011 as *KCNJ5*, which encodes a potassium channel on the zona glomerulosa cells. The mutations impair the channel selectivity and allow sodium conductance, which depolarized the cell, allows calcium entry, and drives aldosterone production. Patients develop severe hypertension and hypokalemia in childhood. As in FHA1, the production of both aldosterone and 18-oxygenated cortisol metabolites is elevated. The adrenals can be of normal size or markedly enlarged. Treatment with MR antagonist is preferable, but if blood pressure and potassium cannot be normalized, bilateral adrenalectomy might be necessary. One of the most exciting aspects of FHA3 is that two recurring somatic mutations in *KCNJ5* are also found in 30% or more of aldosterone-producing adenomas. The mutations are different than those that cause FHA3 but also alter channel selectivity. This discovery has led to the identification of other somatic mutations in aldosterone-producing adenomas, including the sodium-potassium ATPase ATP1A1, the calcium ATPase ATP2B3, and the calcium channel CACNA1D.

<u>Key Points</u>:

- Primary aldosteronism is the most common form of secondary hypertension with an estimated prevalence of 1-10% among the general hypertensive population, and up to 15-20% among the resistant hypertensive population
- Early detection and treatment of primary aldosteronism may improve blood pressure, reduce reliance on blood pressure medications, and mitigate future cardiovascular disease risk.
- Heritable causes of primary aldosteronism should be considered in patients diagnosed at a young age, those with a family history of primary aldosteronism, early-onset hypertension, or cerebrovascular accident.

• Familial hyperaldosteronism type I (glucocorticoid remediable aldosteronism) is a rare autosomal dominant disorder due to a chimeric gene duplication resulting from unequal crossing over between the 11β-hydroxylase (CYP11B1) and aldosterone synthase genes (CYP11B2). Genetic testing confirms the diagnosis, and treatment with glucocorticoids can reduce ACTH-dependent aldosterone synthesis.
• Familial hyperaldosteronism type II is a heritable cause of primary aldosteronism defined by a family history of two or more affected family members with primary aldosteronism that are not glucocorticoid remediable or explained by another genetic mechanism. The molecular basis of this condition remains unknown.
• Familial hyperaldosteronism type III is a rare autosomal dominant form of primary aldosteronism caused by germline gain-of-fucntion mutations in the KCNJ5 gene; however, somatic mutations of KCNJ5 have been found in 40-60% of surgically resected aldosterone-producing adenomas.

III. Congenital Adrenal Hyperplasia

The congenital adrenal hyperplasias (CAH) are autosomal recessive deficiencies of any enzyme or cofactor protein involved in cortisol biosynthesis. The most common form is 21-hydroxylase deficiency (21OHD). The classic or severe form occurs in 1 in 16,000 births and features severe androgen excess beginning in fetal life, enough to virilize female fetuses, plus adrenal insufficiency. In the nonclassic form, cortisol production is normal, but precursor accumulation drives mild to moderate androgen excess. The diagnosis of 21OHD is fairly straightforward, based on the cortisol and 17-hydroxyprogesterone (17OHP) rise following cosyntropin injection. The other forms of CAH have their individual biochemical profiles (Table 2), depending on the location of the block, which steroids are deficient, which steroids accumulate, and what pathways these precursors can follow to active and inactive products.

In general, classic CAH is diagnosed in infancy, and the endocrinologist is providing management but not diagnosis. Among the notable exceptions is 17-hydroxylase deficiency, for which patients often do not present until the age of expected puberty with hypertension, hypokalemia, and pubertal failure. The nonclassic forms of CAH typically present in adolescence or early adulthood and can pose a diagnostic challenge. It is important to remember that the prevalence of nonclassic 21OHD is 1 in 1,000 and even more common in certain populations. The other types of CAH are far less common than 21OHD, and their nonclassic forms are even more rare. Thus, when evaluating a young woman for mild to moderate androgen excess, the only etiology that should be routinely considered is nonclassic 21OHD. The only time that less common forms on nonclassic CAH such as 11-hydroxylase deficiency need be considered is when significant childhood-onset androgen excess has been present and nonclassic 21OHD has been excluded.

<u>Key points</u>:
• Nonclassic 21OHD is common but diagnosed in the minority of cases
• Nonclassic 11OHD is very rare, and nonclassic 3βHSD deficiency is extremely rare
• Early pubarche with accelerated growth and bone maturation suggests NCAH
• Adults with NCAH are difficult to distinguish clinically from PCOS

• Hypertension and hypokalemia suggest classic 11OHD or 17OHD
• DSD and hypocortisolism are found in classic but not nonclassic forms of CAH
• Classic 3βHSD and POR deficiencies cause DSD in both sexes

IV. Bilateral macronodular adrenocortical hyperplasia

Adrenal cortical adenomas are common and are incidentally discovered on 1-9% of cross-sectional imaging studies done for other reasons. The adenomas that cause hypercortisolism tend to be relatively large, >2.4 cm. A much less common cause of nodular adrenal glands is macronodular adrenocortical hyperplasia (MAH). I think of MAH as a "goiter of the adrenal glands". Similar to thyroid goiters, MAH does not cause hypercortisolism until the glands are very large, indicating that cortisol biosynthesis is rather inefficient compared to the normal adrenal cortex.

A few genetic causes of adrenal adenomas such as familial adenomatous polyposis (FAP) and MEN1 are known, but these tumors rarely cause hypercortisolism. In the McCune-Albright syndrome, adenomas and macronodular hyperplasia can develop in the adrenal glands, and most often these nodules cause hypercortisolism in children. In the hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC due to fumarate hydratase mutations, MAH can be seen, but the frequency of adrenal nodules is so low that the association has been questioned. Somatic mutations in the catalytic subunit of protein kinase A (*PRKACA* gene) have been identified in highly functional cortisol-producing adrenal adenomas, but germline mutations in this gene have not been described.

MAH also occurs in families in an autosomal-dominant form. Recently, three groups identified the responsible gene as *ARMC5*, which encodes the armadillo-repeat containing 5 protein. *ARMC5* is a tumor-suppressor gene, and loss of the wild-type allele leads to nodule formation. In a given adrenal gland, the germline mutation is always the same, but the somatic alteration in the originally wild-type allele can be different among the various nodules. The mechanism of nodule formation from loss of ARMC5 is not know, but ARMC5 is a component of the wnt/β-cateinin signaling pathway, which is known to be important in adrenal development.

<u>Key points</u>:
• Adrenal nodules are common, reportedly detected on abdominal imaging in 4-7% of cases with approximately 10% that are bilateral.
• The commonest secretory syndrome associated with adrenal cortical nodules is mild hypercortisolism. UFC is often normal or only modestly increased and therefore the best confirmatory tests for the presence of mild hypercortisolism are the loss of diurnal variation of cortisol using the late night salivary cortisol or the inadequate suppression of serum cortisol after 1 mg dexamethasone overnight.
• ACTH-independent bilateral macro nodular adrenal hyperplasia (AIMAH) presents later in life, and hypercortisolism only manifests once the nodules are quite large, as they inefficiently produce steroids.
• AIMAH has long been suspected to be a heritable disorder. Recent studies demonstrate inactivating mutations in a putative tumor suppressor gene, ARMC5, in patients with AIMAH. Germline mutations in ARMC5 were detected in younger, first

degree relatives of index cases that were associated with previously unsuspected bilateral adrenal nodular hyperplasia and in some, modest degrees of hypercortisolism.
• Less common genetic causes of AIMAH include McCune-Albright syndrome (GNAS1 mutations) and MEN1 (MEN1 mutations).
• AIMAH is probably not "AI" (ACTH-independent) as ectopic expression of ACTH was recently demonstrated in the hyperplastic adrenal tissue. This disorder is therefore more properly referred to as BMAH (Bilateral Macronodular Hyperplasia).

V. Adrenal insufficiency

Primary adrenal insufficiency (AI) is itself a rare disease, with a prevalence of about 1 in 10,000. The most common form in Western societies is autoimmune adrenalitis, whereas infectious causes were dominant in Addison's day. The CAH disorders are all genetic forms of AI and are discussed above. Autoimmune AI can be part of the autoimmune polyglandular syndrome type 1 (APS1), also known as APECED syndrome for autoimmune polyendocrinopathy, candidiasis and ectodermal dystrophy. In APS1, hypoparathyroidism and mucocutaneous candidiasis usually develop before the adrenal insufficiency, which itself has a peak onset in the second decade. The disease is caused by mutations in the autoimmune regulator gene (*AIRE*), which is a transcriptional regulator essential for the removal of autoreactive T-cells and self-tolerance. APS2 or Schmidt syndrome also features adrenal insufficiency and has some familial clustering, but it has not been shown to be a monogenic disease.

Other genetic forms of adrenal insufficiency that involve additional organ-systems include adrenoleukodystrophy (ALD), adrenal hypoplasia congenital (AHC), and Allgrove syndrome or triple-A syndrome. ALD is an X-linked condition due to mutations in the fatty acid transporter ABCD1. Patients often present in adolescence or early adulthood with adrenal insufficiency and/or neurologic manifestations, but the disease varies from adrenal insufficiency alone to rapidly progressive neurologic deterioration. AHC results from mutations in the *NR0B1* gene encoding the transcription factor DAX1, which is also X-linked. DAX1 balances the transcriptional activity of steroidogenic factor 1 (SF1), which is essential for the development and function of the steroidogenic cells in the adrenal and gonads. Patients with AHC have primary adrenal insufficiency with hypogonadotropic hypogonadism. In contrast, patients with mutations in the *NR5A1* gene encoding SF1 nearly always have gonadal dysgenesis with elevated gonadotropins and occasionally also have primary adrenal insufficiency. The triple-A syndrome stands for alachrima, achalasia, and adrenal failure due to ACTH resistance; neurologic dysfunction is also a feature of the syndrome. Autosomal-recessive mutations in the *AAAS* gene encoding the protein ALADIN are responsible for triple-A syndrome. ALADIN is a WD-repeat protein and a component of the nuclear pore complex involved with nuclear protein import.

The other major group of genetic adrenal insufficiency disorders is the familial glucocorticoid deficiencies (FGD), which all show autosomal-recessive inheritance. One variant is actually a nonclassic form of lipoid congenital adrenal hyperplasia due to partial defects in the steroidogenic acute regulatory protein (StAR). The most common variants are ACTH resistance states, which can be due to mutations in the ACTH receptor itself (*MC2R* gene) or its accessory protein (*MRAP* gene).

Additional genes responsible for FGD kindred include mini chromosome maintenance-deficient 4 homologue (*MCM4*) among the Irish traveler population; nicotinamide nucleotide transhydrogenase (*NNT*), which encodes an antioxidant protein of the inner mitochondrial membrane; and thioredoxin reductase 2 (*TXNRD2*), a selenoprotein that catalyzes the reduction of oxidized thioredoxin, in a Kashmiri kindred.

Key points:
• Many causes of adrenal insufficiency can now be attributed to a single gene defect
• Some of these conditions previously thought to present only in childhood have also presented in adulthood with variable phenotypes
• Testing for many of these gene defects is now commercially available
• Identification of a genetic cause of adrenal insufficiency may alert the clinician to the need for early treatment or surveillance for associated conditions
• Identification of a genetic cause of adrenal insufficiency can be critical for family planning and screening of family members based on the known pattern of inheritance

VI. Pheochromocytoma and paraganglioma

Pheochromocytoma (PC) and paraganglioma (PGL) are tumors of the autonomic nervous system, which includes the adrenal medulla. Intra-adrenal tumors are the PCs, and these are almost always functional, producing catecholamines. PGLs can be sympathetic or parasympathetic, and the sympathetic-derived PGLs often produce catecholamines as well. The catecholamine excess leads to the hypertension and tachycardia characteristic of these tumors, and the episodic bursts of catecholamines leads to paroxysms of palpitations, headache, severe hypertension, pallor, and diaphoresis. Additional manifestations include cardiomyopathy, fatty liver, diabetes, weight loss, tremor, and orthostasis. These tumors are usually large (>3 cm) before symptoms occur, but about 5% are now discovered as incidental adrenal nodules. Diagnosis is based on measurement of plasma or urine metanephrines and imaging studies. Since Dr. Pacak will review these conditions in detail during his lecture, I simply include his table of PC-PGL genetics from his paper.

Key points:
• 19 genes are known to cause hereditary PHEO/PGL
• Paternal transmission is known for SDHD, SDHAF2, and MAX genes
• Careful family history, even if negative in 1st degree relatives and concomitant neoplasm (especially renal cell carcinoma, GIST) may point to the presence of a hereditary PHEO/PGL, especially with SDHx mutations
• Many hereditary PHEOs/PGLs have a specific biochemical phenotype; elevated methoxytyramine is most often associated with the presence of SDHx mutations
• Using metoclopramide (Reglan) and antidepressants must be avoided in patients with PHEO/PGL

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Gene / Locus	Adrenal Histopathology	Genetics	Clinical Clues
ARMC5 (16p11.2)	BMAH (Type 2)	Likely autosomal dominant 1 germline and 1 somatic mutation consistent with Knudson's two-hit hypothesis of tumorigenesis	Metabolic Syndrome Mild Hypercortisolism
MEN1 (11q13)	Multiple Endocrine Neoplasia 1 BMAH (Type 1 or Type 2)	Autosomal dominant	Parathyroid Adenomas (95%) Pancreatic Tumors (45%) Pituitary tumors (40%) Adrenal Lesions (20%) – most non-functional, rarely primary aldosteronism.
APC (5q22.2)	Familial Adenomatous Polyposis BMAH (*Type 1 or Type 2*)	Autosomal dominant	Early colon cancer Hundreds – thousands of colonic polyps
GNAS1 (20q13.3)	McCune Albright Syndrome BMAH (*Type 1*) with Frequent coexistence of micronodules and macronodules	Postzygotic activation mutation	Adrenal hypercortisolism in young children Café au-lait spots Polyostic fibrous dysplasia
FH (1q42.1)	Hereditary leiomyomatosis and renal cell cancer syndrome BMAH (*Type 2*)	Autosomal dominant	Uterine fibroids Renal cell carcinoma

Table 1: Genetics of Bilateral Macronodular Hyperplasia. *Type I* refers to BMAH with *atrophic* internodular cortex, *Type 2* refers to BMAH with *hyperplasia* of both nodular and internodular tissue.

Table 1: Clinical presentations of pheochromocytoma/paraganglioma associated with various genetic mutations.

Gene	Age at Primary Diagnosis	Primary Tumor Location	Biochemical Phenotype	Metastatic Potential	Other Tumors and Important Findings
VHL	30s	Adrenal (bilateral)	NE or NE & DA	Low	Retinal hemangiomas, CNS hemangioblastomas, clear cell renal carcinoma
RET	30s	Adrenal (bilateral)	EPI or EPI & NE	Low	Medullary thyroid carcinoma (MEN2A & MEN2B), hyperparathyroidism (MEN2A & MEN2B), marfanoid habitus (MEN2B), mucosal ganglioneuromas (MEN2B)
NF1	40s	Adrenal	EPI or EPI & NE	1-5%	Café-au-lait spots, neurofibromas, hamartomas, carcinoids, pancreatic neuroendocrine tumors, duodenal somatostatinomas, peripheral nerve sheath tumors, gliomas
SDHA	27-77	Head and neck, adrenal, extra-adrenal	?	?	Clear cell renal carcinoma, GIST, pituitary adenoma
SDHB	30s	Extra-adrenal	NE or DA or NE & DA or nonsecretory	High	Clear cell renal carcinoma, GIST, pituitary adenoma, breast and thyroid cancer (?), neuroblastoma pulmonary chondroma
SDHC	40s	Head and neck,	NE or nonsecretory	Low	Clear cell renal carcinoma

		mediastinum			
SDHD	30s	Head and neck (bilateral, multifocal) or extra-adrenal	NE or DA or NE & DA or nonsecretory	Low	Clear cell renal carcinoma, GIST, pituitary adenoma, pulmonary chondroma
SDHAF2	30s	Head and neck (multiple); adrenal	?	Low	None described
TMEM127	40s	Adrenal (bilateral)	NE & EPI	Low	None described
MAX	30s	Adrenal (bilateral)	NE & EPI	Moderate	None described
HRAS	31-76	Adrenal	NE or EPI	Low	None described
HIF2α	17-35	Extra-adrenal, less commonly adrenal	NE	Low	Polycythemia, duodenal somatostatinoma, often multiple
PHD1 and *PHD2*	14-39	Adrenal (bilateral); extra-adrenal (multiple)	NE	?	Polycythemia
FH		Adrenal, extra-adrenal, head and neck	NE	Moderate	Papillary renal cell carcinoma, uterine fibroids, cutaneous leiomyoma

Abbreviations: DA = dopamine, CNS = central nervous system, EPI = epinephrine, GIST = Gastrointestinal stromal tumor, NE = norepinephrine; "?": not known. Adapted from Martucci et al. (reference 2).

TABLE: Genetics of Primary Hyperaldosteronism

Syndrome Classification	Molecular Mechanism	Inheritance	Prevalence of Germline Genetic Inheritance	Prevalence of Somatic Mutations	Lab Findings	Adrenal gland morphology	Genetic Testing	Treatment
Familial Hyperaldosteronism type I *(Glucocorticoid Remediable Aldosteronism)*	Chimeric fusion of CYP11B1/CYP11B2 genes resulting in ACTH-dependent aldosterone synthesis in zona fasciculata	AD	Very rare	-	Normal to high ARR Normokalemia common Elevated 18-OH-F &18-oxo-F	Normal Unilateral or bilateral nodularity	Germline sequencing to detect chimeric gene	Glucocorticoids and/or MRA
Familial Hyperaldosteronsim type II	Unknown	AD	-	-	High ARR Hypokalemia common	APA or BAH	None	MRA or adrenalectomy
Familial Hyperaldosteronism type III	Gain of function mutation of GIRK4 channel (*KCNJ5*) increases Na^+ conductance, depolarizes cell, and opens voltage-gated calcium channels to increase aldosterone synthesis	AD	Very rare	~ 40%	High ARR Hypokalemia common Elevated 18-OH-F &18-oxo-F	APA or BAH, often with pronounced adrenomegaly	Germline sequencing of *KCNJ5*	MRA or adrenalectomy
-	Gain of function mutations of voltage-gated calcium channel (*CACNA1D*) resulting in increased intra-cellular calcium signaling and aldosterone synthesis	AD	Very rare	~10%	High ARR	APA	Germline sequencing of *CACNA1D*	MRA or adrenalectomy
-	Loss of function mutations in adrenal Na^+/K^+ ATPase alpha subunit (*ATP1A1*) resulting in reduce pump activity, and lower depolarization threshold		Somatic only	~5%	High ARR	APA	-	MRA or adrenalectomy
-	Loss of function mutation in adrenal Ca^{2+} ATPase (*ATP2B3*) resulting in intra-cellular calcium accumulation and lower depolarization threshold.		Somatic only	~2%	High ARR	APA	-	MRA or adrenalectomy

Table 1: Forms of Classic and Nonclassic (NC) Congenital Adrenal Hyperplasia (CAH)

Disease	Gene(s)	Prevalence	Clues	Diagnosis, CST Results
Lipoid CAH	*STAR*, *CYP11A1*	Rare	Hypogonadism Enlarged adrenals	All steroids low
NC Lipoid CAH	*STAR*	Very rare	Cortisol deficient	Low cortisol, normal ratios
21-Hydroxylase Deficiency	*CYP21A2*	1:16,000	Androgen excess Hypotension	High 17OHP/cortisol
NC 21-Hydroxylase Deficiency	*CYP21A2*	>1:1,000	Androgen excess	High 17OHP/cortisol
11β-Hydroxylase Deficiency	*CYP11B1*	<1:100,000	Hypertension + Androgen excess	High 11-deoxycortisol/cortisol
NC 11β-Hydroxylase Deficiency	*CYP11B1*	Very rare	Androgen excess	11-Deoxycortisol >1800 ng/dl Normal cortisol
17-Hydroxylase Deficiency	*CYP17A1*	<1:100,000	Hypertension + Sexual infantilism	High DOC/cortisol Low androgens, DHEAS
3β-HSD Deficiency	*HSD3B2*	Rare	DSD in both sexes Hypotension	High 17OHPreg/cortisol
NC 3β-HSD Deficiency	*HSD3B2*	Extremely rare	Androgen excess	17OHPreg >3000 ng/dl Normal cortisol
P450-Oxidoreductase Deficiency	*POR*	Rare	DSD in both sexes +/- Antley-Bixler	High progesterone, low cortisol Variably high 17OHP, DOC

CST = Cosyntropin stimulation test; 17OHP = 17-hydroxyprogesterone; HSD = Hydroxysteroid dehydrogenase; DOC = 11-deoxycorticosterone; 17OHPreg = 17-hydroxypregnenolone; DSD = Disorder of sex development

Table: Genetic causes of adrenal insufficiency

Disease	Gene	Inheritance pattern	Associated	Laboratory
[1]AAA	*AAAS*	Autosomal recessive	Alacrima, achalasia	
[2]ALD	*ABCD1*	X-linked recessive	Neurologic, hypogonadism	Men - high VLCFA
[3]AHC	*NR0B1*	X-linked recessive	Hypogonadotropic hypogonadism Delayed puberty	Low gonadotropins and testosterone
Adrenal Insufficiency with Gonadal Dysgenesis	*NR5A1*	Autosomal dominant More common 46,XY	Gonadal dysgenesis Undervirilization	High gonadotropins Low testosterone
[4]APS-1	*AIRE*	Autosomal recessive	Mucocutaneous candidiasis hypoparathyroidism	Positive 21-hydroxylase antibodies
[5]CAH: 21-Hydroxylase	*CYP21A2*	Autosomal recessive	Variable- salt wasting, simple virilizing, females with ambiguous genitalia	Elevated 17OH-progesterone, basal or stimulated
[5]CAH: 3β-Hydroxysteroid Dehydrogenase	*HSD3B2*	Autosomal recessive	Male - undervirilization Female - mild virilization	Elevated 17OH-pregnenolone Elevated DHEA
Lipoid [5]CAH	*STAR*	Autosomal recessive	XY sex reversal	All steroids low
[6]FGD	*MRAP* *MC2R* *NNT* *MCM4* *TXNRD2*	Autosomal recessive	Glucocorticoid only Hyperpigmentation	Elevated ACTH, normal renin and aldosterone

[1]AAA- Triple A syndrome, Allgrove Syndrome
[2]ALD- adrenoleukodystrophy
[3]AHC- adrenal hypoplasia congenita
[4]APS-1 autoimmune polyglandular syndrome type 1
[5]CAH- congenital adrenal hyperplasia
[6]FGD- familial glucocorticoid deficiency