Primary aldosteronism is the most common cause of secondary hypertension and is associated with a significant increase in cardiovascular and cerebrovascular morbidity. The most common forms of primary aldosteronism are aldosterone-producing adenomas (APAs) and idiopathic hyperaldosteronism with APA responsible for 30% to 50% of cases. Recently discovered somatic mutations of the potassium (K+) channel KCNJ5 gene coding for Kir3.4, a potassium inwardly rectifying channel, subfamily 1, member 5, were postulated to cause aldosterone-producing adenomas in 8 of 22 patients. Although crucial, the KCNJ5 mutations may not completely explain the histological and molecular findings in APAs; other events, or a “second hit,” may be involved.

Three familial hyperaldosteronism (FH) syndromes have been described. FH-I is defined as (glucocorticoid-remediable aldosteronism) a gene duplication from the crossover recombination of the promoter region of CYP11B1 and most of the coding region of CYP11B2 producing a chimeric gene expressed in the zona fasciculata. FH-II is defined as the presence of ≥2 close relatives having hyperaldosteronism (either having APA or idiopathic hyperaldosteronism), in whom genetic testing for the hybrid gene is negative. The etiology of FH-II is unknown, although there is a linkage with chromosomal region 7p22 in some patients. FH-III is defined as the phenotype of the patient with the T158A somatic mutation. Adrenal glands of the patients with the KCNJ5 mutation were normal by CT scan. The electro-physiological characteristics of cells transfected with the KCNJ5G151E cDNA were similar to those of cells transfected with the G151R and L168R, as described previously, and T158A, the germline mutation found in the original FH-III family. The phenotype of the patient with the T158A somatic mutation was similar to other patients in this cohort with APA and milder than that of the FH-III patients with the T158A germline mutation. This study demonstrates that the definition of FH-II is too broad and is composed of multiple etiologies.

The hypertension, hypokalemia, and hyperaldosteronism of the 2 patients with the newly described KCNJ5 mutation, G151E, were mild to moderate and easily controlled with low doses of mineralocorticoid receptor antagonists. In one, levels of 18-hydroxycortisol and 18-oxocortisol were normal; in the other they were within the range of patients with APA but significantly lower than patients with FH-I and in the FH-III family with germline T158A mutation. Adrenal glands of the patients with KCNJ5 G151E mutation were normal by CT scan. The electrophysiological characteristics of cells transfected with the KCNJ5G151E cDNA were similar to those of cells transfected with the G151R and L168R. Thus, FH-III caused by germline mutations of the KCNJ5 gene selectivity filter has variable phenotypes, whether because of the different mutation itself or as-yet-unknown factors.

Relatively few APAs have been sequenced, yet the frequency of somatic mutations of the KCNJ5 channel is very high, suggesting that this is a hot area for mutations, and more may be discovered. The reason for frequent somatic mutations in APA is unclear. Germline mutations...
the KCNJ5 gene are rare and were not found in an analysis of 1000 genomes.²

In rats, the ZG is distinct and forms a continuous zone of 3 to 10 cells wide depending on sodium intake. The unique enzyme in the synthesis of aldosterone, cyp11b2, is expressed only in this zone, and the number of cells expressing cyp11b2 increases with chronic sodium depletion.³ A chronically high sodium diet decreases the number of cells expressing the cyp11b2 in the rat ZG, but nests of cells strongly expressing it remain.⁴ The human adrenal exhibits areas of a variegated zonation with the ZG composed of small cells in a discontinuous pattern and subcapsular aldosterone-producing cell clusters (APCCs) expressing the CYP11B2 enzyme.⁵ It is likely that the discontinuous APCC pattern is analogous to that of a rat on a high-sodium diet, because most normal human adrenals are obtained from patients undergoing nephrectomy for renal cancer who are on a standard, relatively high sodium diet. This pattern of CYP11B2 expression suggests that aldosterone biosynthesis is regulated by the renin-angiotensin-aldosterone system in the regular and “discontinuous” ZG, whereas aldosterone production may be autonomous in the APCCs,⁶ which maybe analogous to the nests of cells expressing cyp11b2 in the ZG of rats on a high-sodium diet.⁷

The histopathology of APAs is complex. A large proportion of patients have peritumoral ZG hyperplasia and sometimes micronodules in addition to the adenoma.⁸ In most patients, in addition to expression in the APA, CYP11B2 is frequently expressed in APCCs distant to the adenoma.⁹,¹⁰ Depending on the patient, CYP11B2 expression varies from virtually 100% to only 40% of the cells in the APA.⁹ CYP11B1 enzyme expression in APAs varies between just a few to 20% of the cells; however, it appears that CYP11B1 and CYP11B2 are not expressed in the same cell, and within adrenomas there are cells that express neither enzyme. 17α-Hydroxylase is also expressed only in the cells expressing CYP11B1.¹¹ APCCs are frequently found in adrenals with cortisol-producing adrenomas in which the zona fasciculata and most of the ZGs are atrophic.¹²,¹³ These APCCs appear to function autonomously,¹⁴ but this remains to be proven.

In the original description of adenoma somatic mutations,² the KCNJ5 mutations comprised 33% and 29% of the reads in the exome sequencing used to detect mutations. It is not known whether the KCNJ5 mutations occur in all of the cells within an adenoma.²,⁶ In addition, whether the KCNJ5 mutations are responsible for increased cell proliferation resulting in adenoma formation is unclear.⁶,⁹ Genes linked to adrenal stem/precursor cells and to nuclear receptors that have a significant role in adrenal development were described recently for normal adrenals, as well as APAs and the peritumoral area. These include Sonic hedgehog (Shh), β-catenin, CD56, steroidogenic factor 1, and dosage-sensitive sex reversal-adrenal hypoplasia congenital critical region on the X chromosome, gene 1 (DAX-1).¹⁰ Although Sonic hedgehog is expressed in only a few cells beneath normal adrenal capsules, it is very highly expressed in the entire APA and hyperplastic per-tumoral ZG. Wnt/β-catenin signaling is also activated in both the APA and peritumoral cortex. It is tempting to hypothesize that mutations of the KCNJ5 gene occur relatively frequently in the activated adrenal stem cell/progenitor cells, causing the autonomous production of aldosterone and primary aldosteronism. The hyperplastic ZG and APCCs found at a distance from the adenoma suggest that the initial yet-unidentified event stimulates adrenal stem cell/precursors, followed by a somatic mutation in one of these stimulated cells, causing excessive production of aldosterone in addition to proliferation. This might explain the lack of suppression of aldosterone production by the contralateral adrenal, a very common finding of adrenal vein sampling to diagnose APA. One can postulate that adrenomas are caused by a second event within a hyperplastic ZG. It will be interesting to know whether suppression of aldosterone synthesis by the contralateral adrenal occurs in patients with an APA with a KCNJ5 mutation. Many APAS may represent a toxic adenoma within a hyperplastic adrenal ZG, analogous to a toxic nodule within a multinodular goiter, with 2 “hits” required to develop the APA.

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Mutations of the Potassium Channel KCNJ5 Causing Aldosterone-Producing Adenomas: One or Two Hits?

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