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

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The Aldosterone Secretagogues Angiotensin II, K^+ or Adrenocorticotropic Hormone Induce Adrenal Zona Glomerulosa (ZG) Cell Membrane Depolarization Through the Activation of K+ Channels, Resulting in the Opening of Calcium Channels and Stimulation of Calcium-Activated Signal Transduction Pathways, Increasing Expression of Enzymes of Aldosterone Synthesis, Thereby Increasing Aldosterone. Two Somatic Mutations in the K+ Selectivity Filter Sequence of the KCNJ5 Gene, G151R and L168R, Were Present in Approximately One Third of APA Patients. Three 3 Mutations Decrease K+ Channel Specificity and Increase Na+ Conductance and Membrane Depolarization, Resulting in Loss of Control of Aldosterone Synthesis.

Mulatero et al. reports results of a search for KCNJ5 mutations in 46 patients from 21 FH-II families. A new germline mutation, G151E, was identified in 2 related patients that was absent in 7 unaffected relatives. In addition, 3 somatic mutations were identified in adenomas from this cohort, 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 the KCNJ5 G151E mutation were normal by CT scan. The electrophysiological characteristics of cells transfected with the KCNJ5^G151E 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.\textsuperscript{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.\textsuperscript{7} 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.\textsuperscript{7} 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.\textsuperscript{8,9} 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,\textsuperscript{8} which maybe analogous to the nests of cells expressing cyp11b2 in the ZG of rats on a high-sodium diet.\textsuperscript{7}

The histopathology of APAs is complex. A large proportion of patients have peritumoral ZG hyperplasia and sometimes micronodules in addition to the adenoma.\textsuperscript{9} In most patients, in addition to expression in the APA, CYP11B2 is also activated in both the APA and peritumoral cortex. It is required to develop the APA.

Disclosures

None.

References


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9. Gomez-Sanchez and Gomez-Sanchez KCNJ5 Mutations: 1 or 2 Hits 197

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