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Mutations in KCNJ5 gene cause hyperaldosteronism

Commentary on:

K⁺ Channel Mutations in Adrenal Aldosterone-Producing Adenomas and Hereditary Hypertension

Choi et al

Science. 2011;331:768-772.

Summary: "A new report in *Science* finds that a few somatic KCNJ5 mutations explain a subset of aldosterone-producing adenomas, the most frequent secondary cause of arterial hypertension.

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Primary aldosteronism (PAL) is the most common secondary form of arterial hypertension with an estimated prevalence between 6 and 10% and as high as 20% in patients with resistant hypertension¹⁻². It is due in the majority of cases to either an adrenal producing adenoma (APA) or a bilateral adrenal hyperplasia (also known as idiopathic hyperaldosteronism)³. However, the molecular mechanisms underlying aldosterone hypersecretion and/or nodulation of the adrenal cortex are still largely unknown. In this paper⁴, Lifton's group opens a completely new area by establishing the concept that recurrent somatic mutations at the *KCNJ5* gene coding for the potassium channel Kir3.4 could account for a substantial proportion of APAs, but also that a germinal *KCNJ5* mutation cause a very rare autosomal dominant and early-onset form of PAL, characterized by bilateral massive adrenal hyperplasia and referred to as FH-3⁵⁻⁶.

Using whole exome sequencing on four APA-blood pairs from unrelated subjects, the authors have identified somatic mutations of the *KCNJ5* gene in two tumors; sequencing of other 18 APA identified six additional cases with *KCNJ5* mutations. Remarkably, only two recurrent mutations were found, G151R and L168R, affecting two residues in and near the selectivity filter of the Kir3.4 potassium channel. A similar heterozygous inherited germinal mutation, T158A, located in the same conserved region, was also found in the previously described FH-3 kindred⁵. *KCNJ5* encodes the inwardly rectifying K⁺ channel Kir3.4 that exists both as homotetramers and heterotetramers with Kir3.1⁷. Using electrophysiological studies, the authors clearly demonstrated that these mutations result in loss of channel selectivity, with increased sodium conductance leading to membrane depolarization. Importantly, in zona glomerulosa cells, the site of aldosterone production in the adrenal cortex, membrane depolarization leads to opening of voltage-activated Ca²⁺ channels, with activation of the calcium signaling pathway, the major mediator of aldosterone production. From their results the authors conclude that *KCNJ5* mutations are involved in inherited and acquired aldosteronism with cell autonomous proliferation and that they are sufficient for both constitutive aldosterone secretion and cell proliferation.

These results are of utmost importance since they open the possibility that a hormonal adrenal disease affecting millions of individuals worldwide could be due in part to one single mechanism, i.e. somatic adrenal mutations affecting a potassium channel. As such, this revolution in the endocrine and cardiovascular fields raises some questions.

One surprising finding is that similar *KCNJ5* mutations lead either to APA formation, in the case of somatic mutations, or to massive bilateral adrenal hyperplasia without nodulation when inherited. Indeed, the three affected family members carrying a germline T158A *KCNJ5* mutation all underwent bilateral adrenalectomy which showed diffuse hyperplasia of the zona fasciculata and no evidence of nodularity⁵. These results are in contradiction with what would be expected from a gene predominantly expressed in the zona glomerulosa⁴, but are in line with observations in transgenic animals inactivated for TASK1 and TASK3 channels, the major contributors to the maintenance of background potassium conductance⁸. TASK1 knock-out mice present a complex phenotype of severe sex-dependent hyperaldosteronism due to abnormal expression of aldosterone synthase in the adrenal zona fasciculata, whereas removal of an important background K⁺ current in TASK1/TASK3 double knock-out animals leads to autonomous aldosterone production. Remarkably, this phenotype is not accompanied by any alteration of adrenal gland morphology and zonation. These results may imply that in addition to increased Ca²⁺ signaling, activation of other, as yet unknown pathways is required to promote zona glomerulosa autonomous cell proliferation and nodulation in APA. They also suggest that more subtle germinal mutations of the *KCNJ5* gene may be responsible of bilateral adrenal hyperplasia, the other main cause of PAL.

Another surprise is the absence of extra-adrenal manifestations in the previously described FH3 family ⁵ since Kir3.4 as well as its dimerization partner Kir3.1 are highly expressed in other tissues, especially the heart. Recently *KCNJ5* missense mutations have been identified in a patient with atrial fibrillation ⁹ and in a family with autosomal dominant long QT syndrome, a hereditary disorder that leads to sudden cardiac death secondary to fatal cardiac arrhythmias ¹⁰. Although these mutations result in a loss of channel function, the functional consequences of altered channel selectivity and membrane depolarization in extra-adrenal tissues, and notably on cardiac function, probably deserve further investigation in FH-3 carriers of inherited *KCNJ5* mutations.

Somatic point mutations and chromosomal rearrangements play a key role in transforming normal cells into proliferating cells. Previous studies have shown a relative low change in genetic aberrations, i.e. loss of heterozygosity (LOH), in small adenomas compared to adrenocortical cancers ¹¹. Among the 22 adrenal samples analyzed by Choi et al., all somatic *KCNJ5* mutations occurred in the adrenals with few or no LOH. A selection process could thus be involved in which a *KCNJ5* mutation would favor hyperplasia without the need of - or even counterselecting - other tumoral processes. Basic cellular research is needed to understand at which step of the adrenal cortical cell lineage these mutations occur, as well as the remarkable recurrence of very few *KCNJ5* mutations that could be present at a frequency as high as 30% in surgical APAs. Genomic studies performed on larger collections should give a better estimate of all somatic events and their consequences on gene expression and pathophysiology. It is conceivable that APA will be seen in the near future not as one entity, but rather as a heterogeneous disorder caused by different somatic mutations (point mutations or LOH) (Figure 1), molecular events that may help defining clinical subsets of PAL as well as to address new therapeutic options.

Finally, it is remarkable that almost 20 years after having identified the genetic cause of rare monogenic glucocorticoid remediable aldosteronism, also called FH1 ¹², Dr Richard Lifton and his group have now identified not only the molecular cause of another very rare familial PAL, FH3, but also paved the way for the understanding of a large proportion of sporadic cases of Conn's adenomas. These very innovative results should stimulate further genetic and basic research in that field and help to decipher the mechanisms involved in other familial and sporadic PAL.

LEGEND TO FIGURE 1

TITLE : GENETIC MECHANISMS UNDERLYING FAMILIAL AND SPORADIC PAL

Three inherited forms have been described, FH-2 being probably the most common but without gene identified yet. Other mendelian forms (FHx) may exist.

For the most common sporadic forms of primary aldosteronism, no mutation has been identified for BAH (bilateral adrenal hyperplasia) whereas two recurrent *KCNJ5* mutations have been identified in APAs (aldosterone producing adenomas). Other genes with point mutations as well as causative genomic rearrangements with loss of heterozygosity (LOH) have yet to be described.

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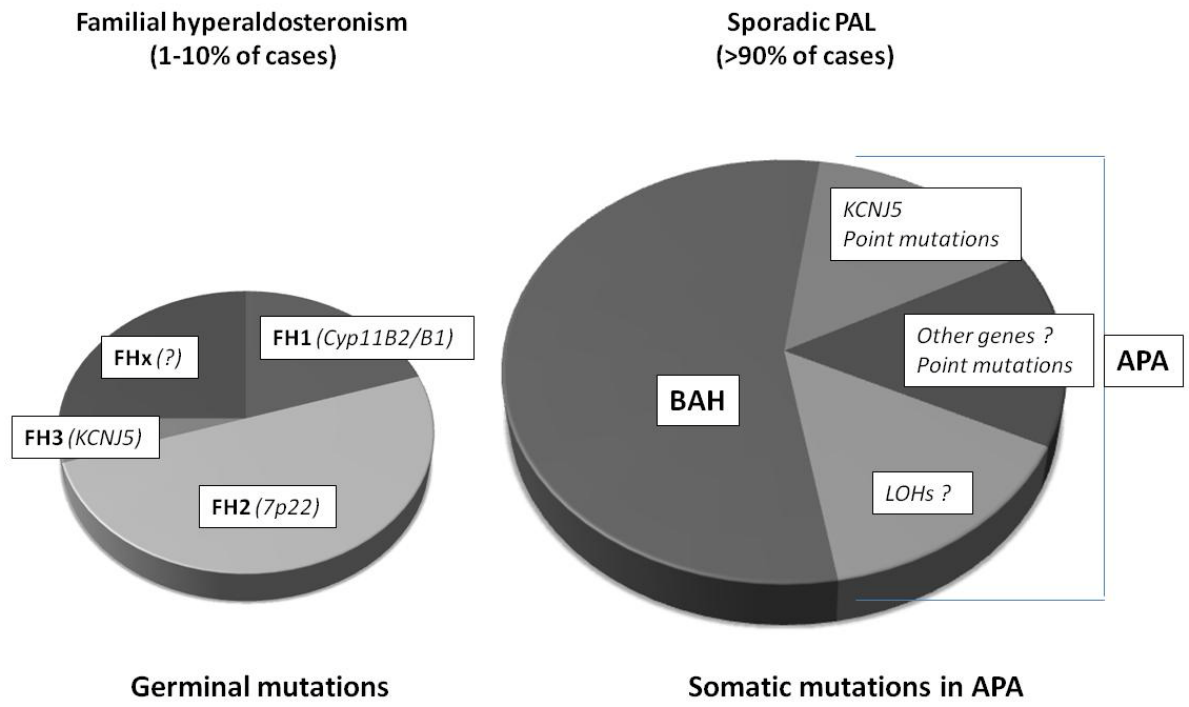


Figure 1.