# Genetic disorders in primary aldosteronism - familial and somatic: an explanatory attempt

Aldosterone is the steroid hormone secreted from the adrenal gland in response to sodium deficiency, blood volume loss or potassium loading. It acts on the kidney and the colon to retain sodium and excrete potassium, in a feedback loop the return to status quo. If aldosterone is secreted – and sodium retained - outside this normal feedback loop the result is primary aldosteronism (PA). Primary is medical for ‘we’re not sure what causes this’.

Familial genetic disorders are due to defective genes in sperm or egg, transmitted to offspring and thus found in all cells. Somatic mutations, on the other hand, result from accidental damage to a cell in a particular organ. In both cases, the mutation gives some advantage to that cell, so it multiplies faster than normal, and in the adrenal makes aldosterone not ‘turned off’ by the normal feedback mechanisms. The result is hypertension and a greater risk of heart attack/stroke/ atrial fibrillation than age-, sex-, and blood pressure matched essential hypertensives. Essential is an alternative medical word for ‘we don’t really know what causes this’.

Primary aldosteronism can be the result of one-sided overproduction from an adenoma (a benign tumor) or bilateral adrenal hyperplasia. Five years ago 8 of 22 aldosterone producing adenomas were shown to have a mutation in the gene coding for KCNJ5, a component of a potassium ‘channel’ in the cell membrane, leading to aldosterone overproduction. This was followed by a much larger study, on over 300 patients, confirming and extending the first; subsequently a number of other mutations – in enzymes (sodium ATPases, calcium ATPases), calcium channels, and a key intracellular protein - have been discovered and described. Over 60% of all APA examined to date show one of the mutations, and are negative for the mutation in other tissues.

Familial hyperaldosteronism (FH) is a fascinating mixed bunch. FH-1 was first described over 50 years ago, and 25 years ago the molecular mechanisms clarified. The enzyme CYPIIB1 is responsible for making cortisol while CYBIIB2 makes aldosterone. The genes encoding CYPIIB1/B2 lie next to one another, and when sperm and egg combine they may not line up right, which produces a composite gene – front end CYPIIB1, back end CYPIIB2, which makes aldosterone out of control by the normal homeostatic loop. The ‘chimeric’ gene from the ancestral misalignment is transmitted, and gives young people severe (but fortunately, very rare, and easily treated) hyperaldosteronism.

FH-II is defined as two first degree relatives – parent/child, siblings – having PA. The best study puts the prevalence at 6% of hypertensives, a conservative figure. Family sizes are smaller, intergenerational time longer, people are more mobile – all making finding two family members with primary aldosteronism less likely. Secondly, and lamentably, fewer than 1% of hypertensives are ever screened for PA…

FH-III is rare, and caused by inherited mutations in KCNJ5. These vary in severity – from requiring bilateral adrenalectomy at a young age, to adequately treated by an antagonist of aldosterone at mineralocorticoid receptors.

Why is this important? Hypertension is the most important cause of cardiac damage in developed countries, and PA may in fact account for closer to 50% than 10% of hypertension. If this is the case, FHII may be either very much more common (or a non-starter). We are used to just looking at disease, and doing clinical trials to see what helps: getting down to pathways and mechanisms provides new insights and the promise of rational, evidence based treatment for high blood pressure and cardiovascular disease.

***John Funder**, AC, MD, PhD, FRCP, FRACP*
*Hudson Institute of Medical Research and Monash University, Clayton, Victoria, Australia*

## Publication

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