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CACNA1D- and KCNJ5-Mutant Aldosterone-Producing Adenomas (APAs) Have Opposite 2-Year Clinical Outcomes from Adrenalectomy: Prospective Trial Findings Explained By Different Cells-Of-Origin

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In a recent trial, adrenalectomy achieved complete clinical success at 6 months in only 30% of 78 patients with unilateral primary aldosteronism (PA) (Nat Med 2023 29:190). We have now compared influence of common APA genotypes on success at 2 years, and sought different cells of origin to explain the result. **Methods:** Home BP, plasma aldosterone and renin were re-measured 2 years after surgery. APA genotype and transcriptome were analysed by RNAseq. Single-nucleus (Sn) RNAs from 17 fresh-frozen adrenals and 9 APAs (3 each with *CACNA1D* or *KCNJ5*-mutation), were quantified by 10x Chromium, and cells with mutations identified by targeted amplicon analysis. Unusual cells were confirmed by immunofluorescence (IF), and their origin sought in published datasets for other tissues. **Results:** 14/18 patients with *KCNJ5*-mutation, but 0/20 with *CACNA1D*, had BP <135/85 mmHg off treatment at 2 years (p=0.03, logistic regression on genotype, age, gender, ethnicity). Biochemical success rate was also lower in *CACNA1D*-mutant patients. The most upregulated gene in *CACNAID* vs *KCNJ5*-mutant APAs was the endothelial-progenitor *CCM2L* (33-fold, $p=10^{-26}$), followed by neuronal and adrenomedullary genes e.g. *PTPRZ1, SLC35F1, UNC79*, by 13-17-fold, $p=10^{-}[1]^{0\text{-}}[1]^{2}$). Transcripts of these genes, in Sn analyses of 85203 nuclei from 17 non-tumour samples, clustered in *CYP11B2*-expressing cells, along with genes characteristic of aldosterone-producing micronodules (APM). The APM cluster was downstream of medulla on pseudotime analysis. In Sn analysis of 9 APAs, *CCM2L* was highly differentiated in *CYP11B2*$^{+}$ cells from 3 *CACNA1D*- vs 3 *KCNJ5*-mutants ($p=10^{-}[1]^{06}$) along with *PTPRZ1 (*$p=10^{-232}$), *SLC35F1* (p=0) and many other neuronal/medullary transcripts. UMAPs of APAs and adjacent adrenal both revealed a cluster of hybrid cells expressing *CCM2L* or other endothelial genes, plus *CYP11B2* and other zona glomerulosa (ZG) or APM-selective transcripts. The proportion of hybrid cells was higher in *CACNA1D*-mutant APAs (236/803) and adjacent adrenal (37/946) than *KCNJ5*-mutant (101/954) and adjacent tissue (8/766). By contrast, *CYP11B2*$^{+}$ cells from *KCNJ5*-mutant APAs were enriched for transcripts in the *CYP11B2*$^{-}$ ZG-cell cluster of adjacent adrenal. Amplicon analysis of APAs detected *CACNA1D* mutation in multiple cells of the endothelial cluster. IF confirmed cells expressing *CYP11B2* and endothelial transcripts. Mining of GTEX, and Human Cell Atlas led to a cluster of *CD34*$^{+}$*RENBP*$^{+}$ endothelial progenitors in spleen as likely source of CCM2L^{+} cells (Gen Biol 2019 21:1). **Conclusion:** Somatic genotype influences long-term outcome after adrenalectomy for PA, reflecting origin of *CACNA1D*-, but not *KCNJ5*-, mutant APAs from APMs. Bilateral APMs have been inferred from their occurrence in most PA adrenals (Nat Rev Neph 2023 19:788). This is supported by our finding of *CCM2L*$^{+}$*CYP11B2*$^{+}$ hybrid cells, with a likely circulatory origin from spleen.

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