The genetic etiology of ACTH-dependent aldosterone hypersecretion in hypertensive patients without Primary Aldosteronism

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INTRODUCTION

Compelling evidence suggests that Primary Aldosteronism (PA) is much more prevalent than previously thought, accounting for more than 20% of patients with resistant hypertension1. Although, major advances have been made in the field of genetics underpinning sporadic and familial forms of PA, the etiology of mild forms of PA is poorly understood1. In previous studies2, we identified a distinct cohort of patients without PA who exhibited ACTH-dependent aldosterone hypersecretion. Following sequencing of KCNJ5 gene, we detected two novel variants in two patients of this cohort, which were shown via electrophysiological studies to impact KCNJ5 function3.

AIM

To examine if genetic variation in genes implicated in aldosterone synthesis/secretion play a role in ACTH-mediated aldosterone hypersecretion.

METHOD

Whole Exome Sequencing (WES) on NovaSeq 6000 platform (Illumina), was performed in 21 hypertensive patients without PA, who exhibited ACTH-dependent aldosterone hypersecretion. Variant calling was performed following the GATK guidelines and we extracted the genetic variation of 25 genes associated with PA. Considering the pivotal role of ion channel genes in the pathogenesis of PA, we also filtered for variants residing in ion channel genes. Qualifying variants had a gnomAD frequency < 1% and were deemed as pathogenic by in-silico tools.

RESULTS

Nine patients of our cohort (9/21, 42.9%) carried potentially damaging variants in genes implicated in the pathway of aldosterone biosynthesis. In particular, in seven patients we detected seven rare and potentially damaging variants in six genes previously associated with PA (KCNK9, KCNK5, ATP13A3, SLC26A2, CACNA1H, CACNA1D). The variant detected in KCNK9 (p.V221M) gene was novel. We also report two variants in two novel candidate susceptibility genes for mild forms of PA, KCNK16 (p.P255H) and CACNA2D3 (p.V557I).

CONCLUSIONS

Genetic variations in aldosterone synthesis/secretion-regulating genes may contribute to aldosterone hypersecretion under conditions of stress by priming the adrenal cortex to respond to ACTH. We also identified two novel candidate susceptibility genes for a mild form of PA, KCNK16 and CACNA2D3, and one novel variant in KCNK9.

REFERENCES

2. A. Markou et al., “Stress-induced aldosterone hyper-secretion in a substantial subset of patients with essential hypertension,” J Clin Endocrinol Metab. 2015; 100 (8): 2867–2864.

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