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

Mourtzi N[1], Sertedaki A[1], Markou A[2], Piaditis G.P[2], Katsanis N[3], Traeger-Synodinos J[4], Tsigos C[5], Charmandari E[1]

[1]Division of Endocrinology, Metabolism and Diabetes, National and Kapodistrian University of Athens Medical School, "Aghia Sophia" Children's Hospital, Athens, 11527, Greece
[2]Department of Endocrinology and Diabetes Center, G. Gennimatas General Hospital, Athens 11527, Greece
[3]Departments of Pediatrics and Cellular and Molecular Biology, Northwestern University School of Medicine, Chicago, IL, USA
[4]Laboratory of Medical Genetics, National and Kapodistrian University of Athens Medical School, Choremeio Research Laboratory, 'Aghia Sophia' Children's Hospital, Athens, 11527, Greece
[5]Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio University, Athens, 17671, Greece

ESPE 2021
The 59th Annual Meeting Online
22-26 September 2021

HELLENIC REPUBLIC
National and Kapodistrian University of Athens
EST. 1837

INTRODUCTION

Compelling evidence suggests that Primary Aldosteronism (PA) is much more prevalent than previously thought, accounting for more than 20% of patients with resistant hypertension[1]. 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 understood[1]. In previous studies[2], 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 function[3].

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

1. N. Mourtzi, A. Sertedaki, A. Markou, G. P. Piaditis, and E. Charmandari, "Unravelling the Genetic Basis of Primary Aldosteronism," Nutrients, 2021; 13(3):875.
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): 2857–2864.
3. A. Sertedaki et al., "Functional characterization of two novel germline mutations of the *KCNJ5* gene in hypertensive patients without primary aldosteronism but with ACTH-dependent aldosterone hypersecretion," Clin Endocrinol 2016; 85(6):845-851.

CONTACT INFORMATION

Evangelia Charmandari,
MD, MSc, PhD, MRCP(UK), CCT(UK)
Professor of Pediatrics – Pediatric and Adolescent Endocrinology
Email: evangelia.charmandari@googlemail.com