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EDITORIAL

Genetics of hyperaldosteronism and a wealth of new information on topics ranging from MEN1 to Cushing's disease and metabolic syndrome

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Hypertension (HTN) is one of the leading causes of overall morbidity and mortality worldwide [1]. Most patients are diagnosed with essential HTN, while secondary HTN accounts for up to 10% of cases and is mainly due to kidney disease, vascular abnormalities, and metabolic disorders, such as diabetes [2]. Primary aldosteronism (PA) is found in up to 6% of primary care patients with HTN and may be responsible for as much as 10 to 15% of referral cases with hard-to-control HTN [3]. In the last 30 years, genetic causes of PA have been identified, from the chimeric CYP11B1/CYP11B2 genes in glucocorticoid-remediable hyperaldosteronism to pathogenic variants in the *KCNJ5*, *ATP1A1*, *ATP2B3*, *CACNA1D*, *CACNA1H*, *CLCN2*, and *CTNNB1* genes, rarely in the germline and mostly in the somatic state (within the aldosterone-producing adenomas only) [4]. Yet, for the average patient with PA, i.e., those with apparently no damaging germline genetic variants in any of these genes, it is unknown what causes aldosterone excess; some individuals have a strong family history of HTN, but not all. Nevertheless, genetic background clearly plays a role, as recent studies have shown [5].

The leading article, by Mourtzi et al., published in this issue of *Hormones* attempts to partly fill this gap in our knowledge. Specifically, the investigators identified a distinct cohort of patients with known essential HTN and apparent normal adrenal glands (upon routine screening) and aldosterone concentrations at baseline that were within the normal ranges but exhibited hypersecretion under stress [6]. They went on to perform whole exome sequencing (WES) of peripheral DNA from the patients and identified known and previously unknown PA gene variants. The study is small, reporting the data on only 21 patients and, on this account, it might have been harder to publish in a first-rate genetics journal, a point also raised by some of the reviewers of the paper. However, as other reviewers argued, the study is not only remarkably well done (as far as methodology is concerned) but also pioneering in its concept, namely, the hypothesis that what causes aldosterone excess may not always be related to tumor formation, but instead to the impact of genetic variability on the regulation of aldosterone secretion. Additionally of great interest is the fact that, while some of the genes involved are well known, there are others, in the same or newly discovered pathways, that need to be studied for their possible involvement in inducing PA.

We all wish that the study were larger and included a range of control groups so that the data could be more generalizable. However, it represents a significant concept and reports valid observations, and, as such, we are delighted to publish it along with this commentary on it. Needless to say, *Hormones* always welcomes studies that report great science propelled by avant-guard concepts that test an attractive hypothesis, perhaps at the cutting edge of contemporary thinking. Is it not these so-called "small" studies that surprisingly frequently advance our knowledge more significantly than others that are much larger but report on already well-known observations? We value the latter (confirmatory studies), but we also look forward to seeing more of the former, these smaller, forward-looking ones that radically promote and strengthen science.

Along these lines, this issue has other great contributions, among them, the effect of androstenedione supplementation, a common practice, on other steroids and metabolism [7]; a number of articles on the metabolic syndrome [8–18]; a

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new mutation in the MEN1 gene [19]; medical treatment of hypercortisolemia in Cushing's disease [20]; new research on thyroid cancer [21] and its treatment [22]. We also have an article on multiple tumors of the pituitary gland, a relatively rare finding but an important one from the clinical standpoint (as well as the molecular pathways involved) [23].

The issue also contains two historical papers, on the name thyroid and another on the recognition of endocrine disruptors as narrated in Greek legends and based on two ancient myths concerning the spring of Salmacis and the curse of Hermaphoditus [24, 25].

This is yet another outstanding issue that we are proud to publish in *Hormones*, contributing once again to the advancement of endocrine science—from its ancient historical origins to current molecular and clinical research and to the very last word in genetics in hypertension and beyond!

Constantine A. Stratakis
Athens, November 1, 2022

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