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Maternally inherited essential hypertension:

adding further complexity to an already complex condition

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Hypertension is a complex clinical condition characterized by raised blood pressure. Apart from personal and environmental factors a genetic component of hypertension is well recognised. Heritability is estimated at 15 to 40 % [1].

In order to unravel the genetic factors that contribute to blood pressure regulation, and hence to hypertension, a multitude of strategies have been employed, driven by advances in understanding of our genetic make-up, technology and our understanding of pathophysiology. Candidate gene approaches were among the first, in hindsight slightly naïve, attempts to study the genetic component of hypertension. They were based on the assumption of strong effects of genetic variants on blood pressure, and the simplistic conception that genetic variation will be limited to or at least focused on major effectors such as vasoactive substances and their receptors. At a time when technology allowed first genome-wide approaches to undertake unbiased studies [2,3], there was considerable disappointment that "blood pressure genes" were not readily detected [4]. We have since learned that effect sizes are much smaller than originally thought, that there are hundreds if not thousands of genetic variants associated with blood pressure regulation, and that they often affect genes that encode signalling and regulatory proteins, or are located in parts of the genome that do not directly relate to a specific gene or exon [5].

However, there have been other strategies. Mendelian forms of hypertension allowed researchers to better understand the mechanisms of blood pressure regulation, and in particular the role of the kidneys. Renal electrolyte transport has long been recognised as being tightly linked to blood pressure, and sequencing the genes that encode transporter proteins has indeed led to the discovery of new genetic variants that would not have been detected by genome-wide association studies [6]. Similarly, in patients with some forms of

secondary hypertension such as those with aldosterone-producing adenomas, studies of somatic mutations has led to better understanding of the genotype/phenotype association and thereby pathophysiology [7]. These approaches are often based on clinical observations, thorough examination of patients and careful work-up of genetic material from index patients and their family members.

In this issue of the *Journal*, Hao Guo and colleagues [8] describe two novel mitochondrial DNA variants that are associated with maternally inherited essential hypertension. They studied a family across three generations including the index patient, her three siblings and their offspring. The index patient came to the authors' attention because of onset of severe hypertension at young age, associated with metabolic changes including high triglyceride and LDL-cholesterol and low HDL-cholesterol levels. Magnesium levels were found to be low, and there were additional cardiovascular phenotypes including arterial stiffening, changes in left ventricular function and impaired exercise tolerance. There were further cases of such unusual hypertension in the family, and the pedigree suggested that the trait is being passed on from mothers to their offspring, implying mitochondrial inheritance. Sequencing of the entire mitochondrial genome led to the discovery of a potentially pathogenetic variant in the *MT-TP* gene (m. 15992 A>G) and a non-synonymous variant in the *MT-CYB* gene (m. 15077 G>A) that acts in synergism and could explain the observed phenotype. The former gene encodes the mitochondrial tRNA that transfers proline in protein synthesis, and the variant has the potential to reduce proline recognition efficiency of this tRNA.

The mitochondrial genome is unique in that it encodes some of the key players involved in mitochondrial function, namely energy generation, but that it relies on the cell's complex apparatus to complete the cycle from genetic information to transcription and translation into

protein [9]. Numerous variants in the mitochondrial genome that are associated with maternally inherited essential hypertension have been described, and many of them affect genes encoding for tRNAs [10].

tRNAs are complex molecules that in the first instance enable protein biosynthesis by decoding the transcript and translating it into amino acids. Depending on the position of a genetic variation within tRNAs the efficiency of protein biosynthesis can be altered in numerous ways, with the potential to even result in altered amino acid sequence [10]. However, it has been increasingly recognised that tRNAs play roles beyond translation of mRNA into protein, and these include regulatory functions akin (yet mechanistically different) to those of non-coding RNA species such as microRNAs [11]. This explains why the effects of changes in tRNAs are not entirely predictable and to some extent occur at random, depending on changes in protein sequence and the regulatory functions of tRNAs. It is also not surprising that in the family characterised by Guo *et al.* [8] the key variant m. 15992 A>G is modified by another variant (m. 15077 G>A). And equally unsurprisingly, the clinical phenotypes associated with tRNA mutations can include a wide range of different traits.

Patients in the family studied by Guo *et al.* [8] not only have early onset hypertension but also reduced exercise tolerance and left ventricular remodelling. Whether these are genuine effects of the genetic alterations or secondary to severe hypertension remains unclear. More strikingly, a metabolic phenotype characterized by an unfavourable lipid profile in these patients could well be related to changes in mitochondrial function and has been found in other patients with mitochondrial DNA mutations [10]. Patients are also characterized by hypomagnesaemia and while the mechanisms linking the genetic variants to magnesium

homeostasis remain unclear the key role of Mg^{2+} for mitochondrial function [12] and the pathophysiological links between Mg^{2+} transporters and hypertension [13] are evident.

Variants in tRNAs remind us of the complex nature of protein biosynthesis and that the link between a gene and the resulting protein is less tight than originally proposed. With defects in the protein synthesizing machinery, genetic code cannot be translated correctly into protein. Moreover, we have also learned about the role of posttranslational modifications of proteins that affect their structure, trafficking and function. Such modifications can be altered as a result of variants within the gene encoding the protein but also as a result of other processes that lead to glycosylation, oxidation, palmitoylation or other changes to proteins. For example, we recently demonstrated different forms of uromodulin in the urine of normotensive and hypertensive pregnant rats [14] and there are good reasons to believe that this protein undergoes posttranslational modifications that lead to impaired trafficking, sorting and ER stress [15]. Obviously the picture becomes even more complicated with tRNA variants that affect proteins already during biosynthesis.

Where does the paper by Guo *et al.* [8] lead us? To be honest, probably not very far. They describe yet another mitochondrial DNA variation and another possible explanation for maternally inherited essential hypertension. The exact functional consequences of the described variants remain as unclear as those of the myriad nuclear DNA variants that have been discovered by genome-wide association and DNA sequencing studies. The authors remind us, however, that hypertension is far more than simple changes in vasomotor function or volume homeostasis. Compared to the already impenetrable model of hypertension that Arthur Guyton drew in 1972 [16] we begin to realise that hypertension is considerably more complex. Mitochondrial tRNA variants are yet another piece in this ever evolving jigsaw.

On a more general note, the paper by Guo *at al.* [8] is the result of careful clinical observation and meticulous work-up of clinical and molecular characteristics of members of a large family. Many of us, including myself, will ask themselves if they would have detected this constellation in their own practice. With all the pressures on clinical services, the assumption that hypertension is a straightforward condition that can generally be managed in primary care, and the impression of stakeholders and funding bodies that hypertension is not as "trendy" as other cardiovascular conditions, who would have the time to draw a detailed pedigree to recognize an unusual pattern of inheritance? And who would have the resources to phenotype family members and dissect the underlying genetic variant? The study by Guo *et al.* [8] underscores that it important and satisfying to remain curious, and that hypertension is anything but boring.

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