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EDITORIAL

Genes and hypertension: stepping into the secret through the arterial wall

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This editorial refers to 'Genetic aetiology of blood pressure relates to aortic stiffness with bi-directional causality: evidence from heritability, blood pressure polymorphisms, and Mendelian randomization', by M. Ceceljaa *et al.*, doi:10.1093/eurheartj/ehaa238.

Arterial hypertension is still associated today with the heaviest burden in terms of mortality, and healthcare and socioeconomic costs worldwide. In spite of a substantially general agreement on the diagnosis and clinical management of arterial hypertension, it is disappointing to admit the paradox of the failure in identifying its aetiology. In fact, the large majority of patients are still labelled as having 'essential hypertension'. Numerous hypotheses have been proposed over the last 90 years on the aetiology of hypertension which in contrast still appears well concealed. Since the first aetiopathogenic theory , identifying hypertension as an extreme of the Gaussian distribution of normal blood pressure (BP) values in the population,[1] several attractive hypotheses have been advanced, often identifying the kidney as the leading actor in the pathogenesis of arterial hypertension.[2,3] On the other hand, according to the 'mosaic' theory originally developed by Irvine Page *et al.*,[4] multiple factors, including genetic and environmental factors, may contribute to the abnormal and persistent rise of BP levels. Over time, especially thanks to the data available on secondary forms of arterial hypertension characterized by a specific monogenic mutation, e.g. Liddle syndrome or primary hyperaldosteronism, the contribution of the heritable component of BP level has gained the centre of the stage.[5] At the same time, over the past few decades, there has been a rapid change in the way we look at the genome. Indeed, in the case of arterial hypertension, which is characterized by >30–50% heritability,[6] in the form of polygenic mutations, we moved from the earliest study showing linkage of the angiotensinogen gene locus in hypertensive siblings,[7] to numerous case–control association studies, testing the role of mutations in candidate genes encoding proteins involved in the regulation of BP, to the most recent approach of the genome-wide association study (GWAS).[8] The GWAS allows the search for all alleles in random positions throughout the genome that are associated with the development of hypertension. Since the first Wellcome Trust Case Control Consortium study in 2007,[9] numerous GWAS, largely affected by bias regarding the selection of the cases and controls, have led to the identification of >1000 single nucleotide polymorphisms (SNPs), associated with the development of arterial hypertension. Many of the previously identified SNPs fall within genes related to systems or pathophysiological mechanisms known to be involved in the regulation of BP, such as angiotensinogen, components of the natriuretic peptide family,[10] the ionic channels of the kidney that manage the handling of sodium and potassium,[11] as well as the oxidative stress and the components of the extracellular matrix. However, as expected for a complex trait, each identified SNP explains only a small proportion of the BP variation (by increasing BP values by 0.5–1 mmHg), making the translation of the genetic information into pathophysiology sometimes difficult. Recently, the presence of certain SNPs in genomic regions associated with the components of the renin–angiotensin system or of the extracellular matrix and inflammation has been also associated with the development of large artery stiffness, as documented by an increase in pulse wave velocity (PWV).[12]

The study by Ceceljaa *et al.*[13] in this issue of the *European Heart Journal* fits very well with this stage of the debate. The authors, in fact, through an elaborate statistical approach applied to genetics, made up of GWAS, structural equation modelling, and Mendelian randomization, demonstrate in two cohorts (Twins UK and UK Biobank cohorts) a high heritability impact for systolic and pulsatile components of BP (>50%) and PWV (65%). Systemic vascular resistance, cardiac index, and heart rate appeared, in contrast, to be related to environmental factors. Furthermore, the authors reported the presence of a high proportion of shared genes (>50%) between the pulsatile components of BP and arterial stiffness, expressed as PWV. The original finding of this work is the first significant evidence of a

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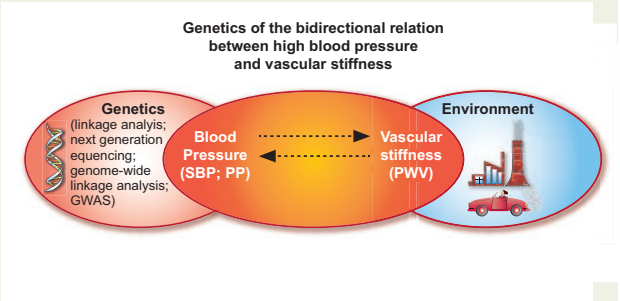

Figure 1 Genetics of the bidirectional relation between high blood pressure and vascular stiffness. GWAS, genome-wide association study; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.

bidirectional relationship between the genetic determinants of BP and of pulsatile components of BP, with mutations that influence the BP level directly and others that act on PWV to increase the BP level (*Figure 1*). This elegant demonstration, obtained in a large cohort including a suitable genetic sample made up of twins, confirms previous hypotheses of a heritable basis of intermediate phenotypes ultimately contributing to the distant phenotype (hypertension). Furthermore, a suggestive pathophysiological link was detected for an SNP in the *FERM2* gene. Nowadays, it is still debated whether the increase in arterial stiffness represents a prerequisite for the development of arterial hypertension or one of the first signs of hypertension-related organ damage.[14] Despite this, whether it is a primary cause or an early consequence, the presence of high PVW, as well as other types of organ damage, represents an important marker in the clinical management of the patient affected by hypertension according to the most recent European guidelines.[15] Indeed, it is recommended to achieve BP targets early in the course of treatment, possibly within 3 months, to prevent the development of organ damage. The 'earlier and faster' BP levels are effectively reduced and normalized, the more likely is the prevention of large artery damage and then a benefit on outcomes.[16]

In this setting, at least two other elements add complexity to the definition of the heritable components of arterial hypertension. First, the wealth of knowledge that we are accumulating on the role of many regulatory mechanisms of genome transcription, better known as epigenetics, cannot continue to be overlooked. In fact, it is well known that a gene, independently of DNA changes, can be expressed differently due to epigenetic modifications, as a result of alterations related to packaging and/or translation of genetic information, mostly under the influence of environmental stimuli. Furthermore, while on the one hand the technological evolution and the diffusion of tools for the collection and management of big data have facilitated the development of genomic analysis, technical innovations have also radically modified the study of arterial hypertension during the recent decades. Therefore, in the field of genomics applied to hypertension new questions and new trenches in which to venture are already taking place. However, it still seems worthwhile to go through these 'minefields', since a correct and complete evaluation of the heritable component of arterial hypertension appears paradoxically easier than the complete assessment of the effect of the fickle environment on individuals. When obtained, this would represent a key achievement for the development of targeted, and therefore effective, therapeutic strategies, with a view on precision medicine.

Conflict of interest: none declared.

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