

Understanding the role of genetics in hypertension

Riyaz S. Patel, MD, FESC¹; Stefano Masi, MD, Ph.D., FESC^{1,2}; Stefano Taddei², MD, FESC

1. Institute of Cardiovascular Science, University College London, UK
2. Department of Clinical and Experimental Medicine, University of Pisa, Italy

This editorial refers to ‘Risk for Hypertension Crosses Generations in the Community: a Multi-Generational Cohort Study’[†], by T. Niiranen *et al.*, on page

Key words: Hypertension, Genetics, Heritability, Precision Medicine

Total number of words: 1339 (references excluded)

Correspondence to:

Riyaz S Patel
Institute of Cardiovascular Science, University College London, 222 Euston Rd, London, NW1 2DA,
UK
Tel: 020 3549 5332
Email: Riyaz.patel@ucl.ac.uk

.....

Hypertension, is a major modifiable risk factor for renal, cardiovascular and cerebrovascular disease and a leading underlying cause of global mortality and morbidity(1). Incremental advances in our understanding of blood pressure have highlighted its complex pathophysiology, whereby genetic and environmental factors combine with a plethora of physiological pathways and mechanisms to ultimately yield the phenotype. While epidemiological studies have improved our understanding of environmental factors in relation to blood pressure, especially with regards to diet and exercise, the exact role of genetics in this setting has been challenging to tease apart from the shared environment often found in families and communities(2).

In this issue of the European Heart Journal, Niiranen et al. provide an intriguing insight into this topic. Using blood pressure data systematically acquired across three generations of the Framingham Heart Study, the authors showed that higher blood pressure, not only in parents, but also in grandparents, is associated with risk of the same condition in the third generation individuals. Specifically, a family history of hypertension developed before 55 years of age represents the strongest risk factor for high blood pressure in the offspring, independently from several measured environmental factors known to influence the risk of hypertension, including levels of physical activity, dietary sodium and alcohol intake. Importantly, the fact that grandparental hypertension confers risk in grandchildren and that only 10% of the grandchildren had last reported living in Framingham, suggests that the impact of shared environment here is likely to be low, making the genetic effect perhaps more apparent. There are of course limitations in the approach which the authors describe, but overall these data support the concept of genetic predisposition to hypertension.

Understanding these genetic factors has been a key challenge facing investigators over time. Twin and family based studies have indicated that as much as 30%-50% of the variance in blood pressure readings may be heritable, while a growing list of rare disorders have led to the identification of clear and causal Mendelian mutations(3). At a population level however, the smooth Gaussian distribution of blood pressure suggests that these mutations are unlikely to play a major role and that, if anything, multiple genetic effects, each of a small size, are likely be contributing or adding susceptibility to high blood pressure levels. With the advent of the genomic era, it is now generally accepted that the most common form of hypertension is a complex trait with a polygenic basis and environmental influences that may also exert effects through epigenetic changes which could even be transmitted across generations(3-5).

The completion of the Human Genome Project and HapMap initiatives yielded a multitude of genome wide association studies (GWAS) that have sought to discover these common genetic

variants. From the early and negative GWAS for hypertension within the Wellcome Trust Case Control Consortium(6) to the more recent reports by Warren et al.(7) and Hoffman et al(8), hundreds of genetic variants have been associated with risk of high blood pressure, as well as other traits such as coronary artery disease, for which hypertension may be on the causal pathway. Although the contribution of each SNP to systolic and diastolic blood pressure values is typically very small(9), when combined together their cumulative impact is more revealing. For example, in the recent report by Warren et al. combination of multiple SNPs into a risk score, accounted for a difference in systolic blood pressure values up to 10mmHg between individuals(7). Despite this, the combined contribution of these multiple genetic variants to heritability estimates remains lower than expected leading to questions about “missing” heritability. This however is not unique to hypertension and is seen in other complex traits such as coronary disease(10). Although it is expected that many more yet undiscovered loci will contribute to explain the missing heritability, it has been postulated that, at least in part, this discordance could be also related to an over-estimation of initial hereditary estimates as well as phenotypic pleiotropy.

Phenotype is of course as critical as genotype in these studies. As with other traits, premature onset of a condition is often considered to be more specific and genetically driven than environment or lifestyle factors. This is also supported by the findings from Niiranen et al, who report that early (onset before 55 years) rather than late onset of hypertension in first and second degree parents is a stronger predictor of the risk of elevated blood pressures values in offspring. From about 50-55 years, values of systolic blood pressure are known to increase while diastolic blood pressure decreases due to a generalised process of vascular ageing which results from poor ventricular coupling and increased arterial stiffness secondary to arteriosclerosis(11). The risk of elevated values of blood pressure and cardiovascular disease observed after 55 years of age, therefore, are likely to reflect not only genetic influences affecting specific pathways involved in the pathogenesis of the disease, but also the contribution of gene variants regulating the evolution of cellular ageing(12). This could explain the persistence of a strong association between early onset of blood pressure in grandparents and risk of hypertension in grandchildren, even when the association was adjusted for the number of parents and grandparents with late-onset hypertension were included in the same model.

Genetic discoveries from GWAS now awaits further inquiry to ascertain whether new mechanisms and pathways for hypertension exist with possibly novel therapeutic targets. The key question remains whether we can use this genetic information directly to improve our patient’s care. Currently, the majority of interventions for hypertension are initiated later in life when blood pressure values are already elevated, vessels stiffened or end organ damage initiated. We then

follow the general approach of prescribing the same sequence of anti-hypertensive drugs for all patients with the disease, based on specific algorithms endorsed by professional societies. Although this approach has the advantage of simplifying treatment decisions, it does not take into account the variable contribution of different biological pathways involved in the pathogenesis of hypertension in any given individual. Screening the human genome for known variants associated with increased risk of hypertension and combination of this information into genetic risk scores, could provide not only information on an individual's risk of developing hypertension but also perhaps which pathways are primarily responsible. This approach could lead to more effective prevention of cardiovascular disease based on: a) earlier identification of subjects at risk before development of the phenotype, b) implementation of aggressive and perhaps targeted lifestyle interventions and c) a more rational and targeted selection of cardiovascular drugs that are likely to be effective and safe for that individual. These concepts are at the foundation of "precision medicine", which is based on identifying pre-symptomatic, high-risk patients with distinct mechanisms of disease and particular responses to treatments(13). As heart disease and hypertension are highly prevalent and have relatively large effects on life expectancy, precision medicine applied to these diseases might lead much higher to public health and economical benefits than precision medicine initiatives aimed at reducing other common diseases, including diabetes, cancer, stroke and lung diseases(14). Although this is an attractive prospective, the value of DNA sequencing for precision medicine in hypertension or indeed many other complex traits requires additional important steps before its application to a clinical setting can be considered.

The paper by Niiranen et al has leveraged the invaluable information on family structure and rich phenotype data from the Framingham cohort to shed some unique insights into transgenerational blood pressure risk. While it may seem a relatively "low tech" approach, the authors have highlighted that simply asking patients about a family history of early onset hypertension in parents and possibly grandparents could provide the clinician with a simple instrument to identify young patients at potentially higher risk of hypertension due to a shared genetic and environmental background. These individuals, at the very least, should be offered aggressive lifestyle modification and closer monitoring for development of high blood pressure. Perhaps a useful intermediate step while we await the promise of precision medicine.

Conflict of Interest: None

References

1. Poulter NR, Prabhakaran D, Caulfield M. Hypertension. *Lancet* 2015;386:801-812.
2. Kotchen TA, Cowley AW, Jr., Liang M. Ushering Hypertension Into a New Era of Precision Medicine. *Jama* 2016;315:343-344.
3. Ehret GB, Caulfield MJ. Genes for blood pressure: an opportunity to understand hypertension. *European heart journal* 2013;34:951-961.
4. Dominiczak A, Delles C, Padmanabhan S. Genomics and Precision Medicine for Clinicians and Scientists in Hypertension. *Hypertension* 2017;69:e10-e13.
5. Wang J, Gong L, Tan Y, Hui R, Wang Y. Hypertensive epigenetics: from DNA methylation to microRNAs. *Journal of human hypertension* 2015;29:575-582.
6. Consortium WTCC. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007;447:18.
7. Warren HR, Evangelou E, Cabrera CP et al. Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. *Nature genetics* 2017;49:403-415.
8. Hoffmann TJ, Ehret GB, Nandakumar P et al. Genome-wide association analyses using electronic health records identify new loci influencing blood pressure variation. *Nature genetics* 2017;49:54-64.
9. International Consortium for Blood Pressure Genome-Wide Association S, Ehret GB, Munroe PB et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature* 2011;478:103-109.
10. Manolio TA, Collins FS, Cox NJ et al. Finding the missing heritability of complex diseases. *Nature* 2009;461:747-753.
11. Williams B. Vascular ageing and interventions: lessons and learnings. *Therapeutic advances in cardiovascular disease* 2016;10:126-132.
12. Codd V, Nelson CP, Albrecht E et al. Identification of seven loci affecting mean telomere length and their association with disease. *Nature genetics* 2013;45:422-7, 427e1-2.
13. Collins FS, Varmus H. A new initiative on precision medicine. *The New England journal of medicine* 2015;372:793-795.
14. Dzau VJ, Ginsburg GS, Van Nuys K, Agus D, Goldman D. Aligning incentives to fulfil the promise of personalised medicine. *Lancet* 2015;385:2118-2119.