Cardiovascular Genetics: A News Round-Up

Common Genetic Variation of Blood Pressure Traits and Their Relation to End-Organ Damage

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Study Hypothesis

Initial genome-wide association studies (GWAS) for hypertension, a common cardiovascular risk factor, have delivered unexpectedly few and modest associations. The authors of the International Consortium for Blood Pressure Genome-Wide Association Studies set out to identify novel genetic variants in relation to blood pressure, intermediate phenotypes, and cardiovascular disease risk. A joint effort combining data on 200 000 individuals of European descent increased the power to detect DNA variants with small effect sizes.

How Was the Hypothesis Tested?

The authors used a staged approach for discovery, replication, and biological translation of their findings. At the identification stage, they performed a meta-analysis on genome-wide single nucleotide polymorphism (SNP) associations and off-treatment systolic and diastolic blood pressure measurements, as well as the dichotomous variable of hypertension, based on 29 studies (n=70 000 individuals). In 3 resource-efficient sequential follow-up steps of de novo genotyping and SNP look-up in existing GWAS datasets, top hits were validated in >133 000 independent individuals of European descent. Sex and body mass index interaction analyses were performed for the top GWAS findings to understand potential effect modification.

To identify possible causal mechanisms, top GWAS loci were looked up in diverse existing expression SNP data sets for cis-acting gene expression. In addition, neighboring non-synonymous coding SNPs (linkage disequilibrium $r^2 > 0.8$) were searched because amino acid sequence alterations harbor high potential to provide mechanistic insights. Furthermore, genetic loci were investigated in relation to ~300 serum metabolites in >10 000 individuals of metabolomic and lipidomic studies. More than 6000 copy number variation-tagging SNPs were available for the correlation of structural genomic variation and blood pressure traits. A gene set enrichment framework was queried to assess GWAS results in biological pathway analysis.

In addition, a weighted genetic risk score, combining the average effects on blood pressure of the top variants, was created to understand their relation to intermediate phenotypes of cardiac structure and function and cardiovascular disease. Finally, the relevance of GWAS results from European ancestry individuals in other ethnicities (East Asians, South Asians, and Africans) was tested for the top SNPs separately and, to enhance power in the smaller samples, a genetic score was used.

Principal Findings

The authors identified 29 independent signals at 28 genetic loci associated with systolic blood pressure and/or diastolic blood pressure, meeting the genome-wide significance threshold of $P<2.5 \times 10^{-8}$, including 16 novel variants that explained 0.9% of phenotype variance. Some were located in or close to regions of prior blood pressure candidate genes (FURIN, GOSR2) or gene pathways (NPR3, GUCY1A3 to GUCY1B3 gene region, ADM, GNAS to EDN3 gene region, NPPA to NPPB gene region, and CYP17A1) and offer plausible pathobiological candidates. The index SNP close to the NPPA to NPPB gene locus was related to plasma natriuretic peptide concentrations and the NPR3 gene codes for a natriuretic peptide clearance receptor. Other genes in the neighborhood of GWAS hits code for adrenomedullin (ADM) that has a regulatory effect on blood pressure, subunits of soluble guanylate cyclase (GUCY1A3 and GUCY1B3), a renal ion transporter (SLC4A7), and a protein essential for podocyte development (PLCE1). One locus had previously been described in the context of a rare variant (CYP17A1), but the majority of the loci had not been strongly related to blood pressure biology before (MOV10, SLC4A7, MECOM, SLC39A8, EBF1, HFE, BAT2 to BAT5 gene region, CACNB2, PLCE1, FLJ32810 to TMEM133 gene region, JAG1). Prior GWAS findings were largely replicated.

The power of the study allowed the detection of DNA variants with small effect sizes that hardly exceeded a change of 1.0 mm Hg per allele. No interactions for sex or body mass index were observed. Less than one third of the top SNPs that reached genome-wide significance were non-synonymous SNPs or had a nonsynonymous proxy that could help to explain the association at the protein level. Less than half of...
the 29 SNPs revealed corresponding genome-wide expression quantitative trait loci for the index SNP (in 5 cases) or a proxy. Many associations were observed for blood samples and monocytes. None of the look-ups for metabolomic associations reached the predefined significance threshold, most likely because of small sample size. The search for associations with structural genomic variation or gene set-enriched pathways using existing data sets did not result in statistically significant findings that would have provided substantial mechanistic insights.

The genetic risk score was significantly related to blood pressure variables, intermediate phenotypes, and cardiovascular disease outcomes. In the discovery sample, individuals in the upper score quintiles revealed a 4.6 mm Hg higher systolic blood pressure and a 3.0 mm Hg higher diastolic blood pressure compared with the bottom quintile, numbers that imply substantial public health impact when projected for the total population.

In the non-European samples, a small proportion of associations could be replicated. Only approximately half of the SNPs showed the same direction of association across ethnicities. The authors acknowledge comparatively small sample size but also cite inherent differences in allele frequency and linkage disequilibrium as a potential reason for nonreplication, since the gene score showed significant results across ethnicities.

The authors also examined the well-known problem of subthreshold SNPs that were not carried forward for replication. In analyses using cohort-wise partitions to create different discovery and validation datasets of the GWAS sample and empirical negative controls, they estimated that 4 times as many variants with comparable effect size exist.

**Implications**

The current meta-analysis is one of the largest consortium efforts combining data from independent studies into a single GWAS to date. The authors identified 16 novel genomic loci not previously connected with blood pressure that, through intensive future functional studies, may help to find novel pathways and better understand the pathophysiology of blood pressure. The large sample size increased the statistical power and permitted the detection of variants with small effect sizes. Accordingly, the magnitude of association for each of the novel variants, though highly significant, was modest. Even with the addition of another estimated 116 subthreshold variants of similar effect size, the total phenotype variance explained would be \(\approx 2.2\%\). This number appears to be small with regard to overall blood pressure variation in the general population. Information on a large part of the substantial heritability of the trait is still missing. The combination of SNPs into a genetic score underlined the potential public health impact of the study results; the difference of a few millimeters of mercury in blood pressure, determined by common genetic polymorphisms, may be highly relevant at the population level.

The relevance of some GWAS findings to non-European-descended individuals suggests a common biology of blood pressure across ethnicities. Nonreplication for other SNPs may indicate a distinct genetic architecture that could help to explain differences in prevalence and disease associations in different ethnicities, but these initial results also demonstrate that much work needs to be done to provide large enough samples and more detailed genetic maps on allele frequencies and linkage structure for future investigations in non-European-descended populations.

Beyond identifying associations of common polymorphisms with blood pressure, the authors attempted to understand the pathophysiological implications of their findings. The observed associations with intermediate phenotypes and hard cardiovascular disease outcomes may help to highlight novel molecular pathways. Furthermore, the consortium has paved the way for follow-up investigations to establish potential causality of their findings by assessing associations with cis-acting gene expression, metabolomic look-ups, and examination of SNPs in relation to structural genomic variation. More detailed analyses and larger datasets will be necessary in the future to fully exploit existing and emerging data in the field to better understand the pathophysiological underpinnings of genetic variation of blood pressure traits and their clinical implications.

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