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Project summary: **GENOMICS STUDIES ON ARTERIAL HYPERTENSION**

Persistently elevated blood pressure (BP) or hypertension (HTN) is the most frequent cardiovascular risk factor and accounts for a large proportion of cardiovascular mortality, the main cause of death worldwide [1, 2]. Population-based data from high-income countries indicate that 20-30% of the adult general population has HTN, other major cardiovascular risk factors being smoking, hypercholesterolemia, and diabetes [3, 4]

A vexing reality in treating hypertensive patients is that the root cause of BP elevation, after accounting for confounding factors such as obesity and age, is unclear for the large majority of patients. Some patients have secondary hypertension, including rare monogenic hypertensive syndromes, but the great majority of patients (~95-99% according to the setting [5]) has primary hypertension, where no cause can be recognized.

Genetics and genomics provide a major opportunity to investigate the root cause of blood pressure because BP is moderately heritable (30-50%) [2, 6, 7]. The importance of genetic influence is perhaps best illustrated by the observation that the presence of a family history of hypertension increases the risk of developing hypertension by ~4 times compared to the general population [8, 9]. The use of genomics in a quest to solve the unknown origins of blood pressure and hypertension is attractive because of the unbiased nature of the experimental approach: Somewhere in the genome reside genetic determinants that influence the BP level of a given individual. The three attached manuscripts (Ehret et al., Liu et al., and Hoffmann et al.) are contemporary attempts to investigate both rare genetic and common genomic causes of BP elevation.

Three different experimental approaches were used: Ehret et al. used targeted genotyping to genotype ~200,000 SNPs in up to 342k individuals and identify 17 novel BP loci. Liu et al. used a genotyping platform targeted et rare genetic variants in up to 317k individuals and identify 31 novel loci. Hoffmann et al. use two large single studies imputed to millions of SNPs (1000G) and one other replication resource and identify 44 novel BP SNPs. These studies bring the number of independent BP loci to ~300 [10-24] (www.bloodpressuregenetics.org – maintained by my laboratory).

The findings have been used for several downstream analyses: Mendelian randomization analyses that discredit a significant role of the kidney in hypertension pathogenesis, pathway analyses and expression analyses that incriminate the large blood vessels.

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