Multivariable Mendelian randomization reveals potential causal genes that contribute to blood pressure traits in diverse populations

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High blood pressure (BP) is a major risk factor for cardiovascular disease. Identifying genes that cause BP variation is crucial for uncovering molecular mechanisms and discovering drug targets. Popular non-experimental methods to investigate causality – such as colocalization, TWAS, and univariable Mendelian randomization (UVMR) – leverage summary-level gene expression data but are not robust because of high correlations among gene expressions in a locus. It is also unclear whether causal genes discovered in European (EUR) populations are transferrable to non-EUR populations. To address these issues, we performed multivariable Mendelian randomization (MVMR) to robustly identify causal genes influencing systolic and diastolic BP (S/DBP) across diverse populations.

We implemented MVMR using MR Joint Outliers-aNd-Exposures Selection (Mr.Jones), which we recently developed to prioritize causal genes and identify horizontal pleiotropy using variable selection penalties. We used summary-level GWAS data for eQTLs in blood tissue from the eQTLGen consortium (n=30K) and for BP traits from Surendran et al. (n=800K), BioBank Japan (n=150K), and Liang et al. (n=30K) for EUR, E. Asian (EAS), and African (AFR) populations, respectively. We targeted the top 10 most significant loci in the European SBP GWAS and searched for causal genes in these loci across populations. Each locus was defined as a 2Mb window centered around the lead SNP.

In EUR, we examined 295 genes and dis identified 28 and 27 genes with P<5E-8 for SBP and DBP, respectively. In EAS and AFR, we analyzed 279 and 232 genes, respectively, resulting in the discovery of 6 and 3 genes for SBP, and 6 and 2 genes for DBP. Additionally, our analysis helped clarify some contradictions found in the existing literature. For instance, we identified *TRAFD* as a significant risk gene for SBP with Z-scores > 20, whereas its effect directions were inconsistent in the TWAS hub across the current six studies.

By leveraging eQTL and GWAS data, our MVMR analysis holds promise for discovering novel genes causally associated with BP traits. In subsequent analyses, we plan to scan the entire genome in search causing BP variation and to examine their functional enrichment.