Supplementary Material

Using the NetWAS framework: Greene et al. applied NetWAS to identify genes associated with hypertension phenotypes based on the connectivity patterns in a kidney-specific network of genes with marginally significant GWAS hits.[S1] This method not only recovered known hypertension-associated genes, but was also able to identify several other candidate genes, including targets of known anti-hypertensive medications not identified by GWAS alone. To apply NetWAS to a dataset of interest to the user, go to: hb.flatironinstitute.org/netwas. The method requires as an input file a GWAS file summarized by gene, which can be produced, for example, using the VEGAS algorithm.[S2] The webserver provides a sample GWAS file in VEGAS format summarizing a body mass index GWAS study.[S3] Given the input GWAS file, a p-value cutoff for which sub-significant GWAS hits to consider as positives, and a selected tissue-specific network context, NetWAS identifies which genes are most likely to be related to the phenotype under study.

Querying ExPecto predictions: Tissue-specific, genome-wide ExPecto predictions are available through an interactive webserver interface at: hb.flatironinstitute.org/expecto. The user can search for a SNP of interest using the interface either by chromosomal location or by rsid or see all significant predictions around a specified gene. If there are high-confidence predictions for the position of interest, they can then view the predicted tissue-specific effects of all possible mutations at that position. For example, the SNP rs5050 has been shown to be associated with hypertension.[S4] Searching for the SNP in the ExPecto interface indicates that a T to G (A to C on the negative strand) mutation at this position, which is 20 base pairs upstream of the transcription start site, is predicted to increase expression of angiotensinogen. This prediction is supported by an experimental study examining the effect of the change on the expression of the gene.[S5]

Supplementary References

S1. Greene CS, Krishnan A, Wong AK *et al.* Understanding multicellular function and disease with human tissue-specific networks. *Nat. Genet.* 2015; **47**: 569–576.

S2. Mishra A, Macgregor S. VEGAS2: Software for More Flexible Gene-Based Testing. *Twin Res. Hum. Genet.* 2015; **18**: 86–91.

S3. Randall JC, Winkler TW, Kutalik Z *et al.* Sex-stratified genome-wide association studies including 270,000 individuals show sexual dimorphism in genetic loci for anthropometric traits. *PLoS Genet.* 2013; **9**: e1003500.

S4. Purkait P, Halder K, Thakur S *et al.* Association of angiotensinogen gene SNPs and haplotypes with risk of hypertension in eastern Indian population. *Clin. Hypertens.* 2017; **23**: 12.

S5. Park S, Lu K-T, Liu X *et al.* Allele-specific expression of angiotensinogen in human subcutaneous adipose tissue. *Hypertension* 2013; **62**: 41–47.