Overlap between common genetic polymorphisms underpinning kidney traits and cardiovascular disease phenotypes: the CKDGen consortium.

Abstract:
Chronic kidney disease is associated with cardiovascular disease. We tested for evidence of a shared genetic basis to these traits. We conducted 2 targeted analyses. First, we examined whether known single-nucleotide polymorphisms (SNPs) underpinning kidney traits were associated with a series of vascular phenotypes. Additionally, we tested whether vascular SNPs were associated with markers of kidney damage. Significance was set to $1.5 \times 10^{-4}$ (0.05/325 tests). Vascular outcomes were analyzed in participants from the AortaGen (20,634), CARDioGRAM (86,995), CHARGE Eye (15,358), CHARGE IMT (31,181), ICBP (69,395), and NeuroCHARGE (12,385) consortia. Tests for kidney outcomes were conducted in up to 67,093 participants from the CKDGen consortium. We used 19 kidney SNPs and 64 vascular...
SNPs. Vascular outcomes tested were blood pressure, coronary artery disease, carotid intima-media thickness, pulse wave velocity, retinal venular caliber, and brain white matter lesions. Kidney outcomes were estimated glomerular filtration rate and albuminuria. In general, we found that kidney disease variants were not associated with vascular phenotypes (127 of 133 tests were nonsignificant). The one exception was rs653178 near SH2B3 (SH2B adaptor protein 3), which showed direction-consistent association with systolic ($P = 9.3 \times 10^{-10}$) and diastolic ($P = 1.6 \times 10^{-14}$) blood pressure and coronary artery disease ($P = 2.2 \times 10^{-6}$), all previously reported. Similarly, the 64 SNPs associated with vascular phenotypes were not associated with kidney phenotypes (187 of 192 tests were nonsignificant), with the exception of 2 high-correlated SNPs at the SH2B3 locus ($P = 1.06 \times 10^{-07}$ and $P = 7.05 \times 10^{-08}$). The combined effect size of the SNPs for kidney and vascular outcomes may be too low to detect shared genetic associations. Overall, although we confirmed one locus (SH2B3) as associated with both kidney and cardiovascular disease, our primary findings suggest that there is little overlap between kidney and cardiovascular disease risk variants in the overall population. The reciprocal risks of kidney and cardiovascular disease may not be genetically mediated, but rather a function of the disease milieu itself.