Identification of regulatory variants in vascular genes causing coronary artery disease

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Genome-wide association studies have identified a plethora of coronary artery disease (CAD) susceptibility loci, the majority located in non-coding regions. Gene prioritisation and enrichment analyses have confirmed well-established pathways such as lipid metabolism and inflammation and added vascular-related pathways to those playing a major role in disease pathogenesis. We have examined the landscape of accessible chromatin in human coronary artery endothelial (HCAEC) and smooth muscle (HCASMC) cells, intersecting these potentially regulatory chromosomal regions with 21,461 CAD-associated variants at the 1% FDR level from 181,522 CAD cases (1,156,690 participants). These prioritised variants (*n* = 650) were examined using the STARR-seq massively parallel reporter assay (MPRA) to determine variants with allelic effects on reporter expression in vascular endothelial and smooth muscle cells. We also examined the effect of VEGF on allele-specific reporter expression in endothelial cells, due to its dual pro-atherogenic and protective roles in CAD progression. The MPRA assay identified 41 variants showing significant (logFC > 1, *p*adj < 0.05) allele-specific effects on gene expression (16 HUVEC, 17 HCASMC, 22 VEGF+ HUVEC), with many variants sharing functionality between cell types and ±VEGF stimulation. From the 41 significant variants, 16 were located proximal to genes with a known vascular involvement,
including *PODXL*, *FRS2*, *CXCR4*, *SMAD3*, *PDE5A* and *CD151*, regulating angiogenesis, vascular permeability, vascular remodelling and EC/SMC proliferation and migration. For the 25 variants proximal to genes not related to known vascular processes, ongoing work is involved to establish molecular mechanisms relating to CAD pathogenesis.