

### 1625 Genome-Wide Association Analysis and Replication In 810,625 Individuals Identifies Novel Therapeutic Targets for Varicose Veins

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**Aim:** To elucidate the genetic architecture of varicose veins (VVs) and identify genes and biological pathways central to their pathobiology.

**Method:** We performed hitherto the largest two-stage genome-wide association study of VVs in 401,656 subjects from UK Biobank, and replication in 408,969 subjects from 23andMe, Inc (total 135,514 VVs cases and 675,111 controls). Genes and biological pathways were prioritised using several bioinformatic approaches, and potential therapeutic targets were identified in the Open Targets Platform. A weighted genetic risk score (wGRS) for VVs was constructed to compare genetic susceptibility in surgical vs non-surgical VVs patients.

**Results:** 109 genome-wide significant ( $P \leq 5 \times 10^{-8}$ ) loci were identified in UK Biobank, 46 of which successfully replicated in the 23andMe cohort. Twenty-eight loci have not been previously reported. We mapped 237 genes to these loci, many of which are biologically relevant and tractable to therapeutic targeting or repurposing (notably VEGFA, COL27A1, EFEMP1, PPP3R1 and NFATC2). Tissue enrichment analyses implicated vascular tissue, and several genes were enriched in biological pathways relating to extracellular matrix biology, inflammation, angiogenesis, lymphangiogenesis, vascular smooth muscle cell migration, and apoptosis. The wGRS analysis demonstrated that VVs patients requiring surgery have a higher inherent genetic susceptibility than those managed non-surgically ( $P = 2.46 \times 10^{-13}$ ).

**Conclusions:** This study has advanced our understanding of VVs pathobiology with the identification of several biologically plausible genes and pathways, many of which demonstrate strong therapeutic potential. The wGRS correlated with disease severity, representing a first step in personalised medicine approaches to VVs.