A Large Scale Genome Wide Association Study of Varicose Veins in the 23andMe Cohort

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Introduction
Varicose veins are a common chronic condition in which veins, usually in the legs, become enlarged and twisted due to deficient functioning of one-way valves that normally return blood to the heart.

While varicose veins are most commonly considered to be a cosmetic problem, in some cases they can lead to, or signal, more serious circulatory problems under the general classification of chronic venous incompetence (CVI). Other symptoms of CVI include pain, edema, swelling, hypopigmentation and ulceration.

Estimates of prevalence of varicose veins range from approximately 5% to 30% in adults with prevalence in females about three times as high as males, although at least one study reports slightly elevated risk in males rather than females.1,2

Methods
Phenotype Data Collection
Participants were drawn from the customer base of 23andMe, Inc., a consumer genetics company. Participants provided informed consent and participated in the research online. Participants answered the question: “Do you have varicose veins on your legs? Yes/No/I’m not sure.” The 47,340 women were roughly three times higher than the 23,565 (25.4%) responded “yes” and 69,101 (74.6%) responded “no”. The 2R44HG006981-02 study was supported in part by the National Human Genome Research Institute of the National Institutes of Health to understand the genetic and environmental factors that contribute to the development of varicose veins.

Statistical Analysis
We conducted a genome wide association study using approximately 905K genotyped SNPs and 13.7M imputed SNPs. We performed logistic regression assuming an additive model for allelic effects, and controlling for age, sex, and population structure (first five principal components) using the model:

\[ \text{logit} \left( \frac{\text{P}(\text{yes})}{\text{P}(\text{no})} \right) = \beta_0 + \beta_1 \text{age} + \beta_2 \text{sex} + \beta_3 \text{population structure} \]

where \( \text{P}(\text{yes}) \) is the probability of a response of “yes” and \( \text{P}(\text{no}) \) is the probability of a response of “no”, and \( \beta_0, \beta_1, \beta_2, \beta_3 \) are the regression coefficients for the corresponding factors. We adjusted for a genomic control inflation factor \( \lambda = 1.074 \) to control for positive dependence of the SNPs.

Acknowledgments
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Results
We found twelve significant novel associations of SNPs with varicose veins (p < 5 x 10^-8). Figure 3 and Table 4 summarize our findings.

Our strongest association was with SNP rs507666 (p=5.2e-20), found in ABO on chromosome, which encodes a protein that belong the AB blood group. SNP rs7111987 (p=2.2e-10) near ADM which is a potent, long-lasting vasodilator peptide, and also inhibits apoptosis and promotes angiogenesis. SNP rs145218303 is in ARHGAP6 which encodes protein that up regulates PLC-delta1, which shows increased activity in hypertension.

The GWAS of varicose veins also points to a role of genes involved in circulatory development. In addition CAS2 to ADAM mentioned above: SNP rs1433198 (p=5.2e-11) is found in ANGPT1 that encodes a type of angiopoietin, a group of proteins with important roles in vascular development; SNP rs869562 (mentioned above) near ANGPT2, that encodes an antagonist for ANGPT1; and SNP rs8605288 (p=1.5e-8) near VEGFA which encodes a protein whose effects include angiogenesis, vasculogenesis and endothelial cell growth. Finally, rs4562181 is in PIEZO1 which encodes a channel protein that plays a role in adult cardiovascular function and disease.

Discussion
This is the first GWAS examining varicose veins. The results of this study provide some interesting insights into the nature and causes of varicose veins. The association with the ABO gene and Kell blood group suggest an inherited susceptibility.

Associations with function of the circulatory system may indicate either a role in causing symptoms, or in the ability of the body to compensate for, or repair vascular incompetence.

Finally associations with genes involved in angiogenesis may provide some indications of the mechanisms underlying the defective valves that cause varicose veins, either through the inability to produce properly formed valves or to repair defects during construction.

References
3. Cornu-Therand et al. Relationship between blood groups (ABO) and varicose veins of the lower limbs. A case-control study. Phlebology 1989; 4, 37-40