Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Gut

Visual Abstract

Hemorrhoids disease (HEM)

ICD10 I84, ICD9 455, self-reported

GWAS meta-analysis

23andMe
UK Biobank
EGCUT
MGI
GERA

5 study cohorts: **218,920 cases**, **725,213 controls**

Results

102 novel genome-wide significant loci with 819 candidate genes

100 prioritized genes > based on tissue and pathway enrichment, as well as gene expression, analyses

Two missense variants; functional effects observed *in vitro* for F608S (rs2186797) in ANO1 protein

Phe > Ser
Ser > Phe

Polygenic risk score analysis

(Genetic) correlation analyses with other diseases/traits

Background

Hemorrhoidal disease affects a large and silently suffering fraction of the population but its etiology, including suspected genetic predisposition, is poorly understood.
No genome-wide significant association has been described until today.

Conclusion:

Hemorrhoids disease has a genetic component that compares to that of other complex diseases and that predisposes to smooth muscle, epithelial and connective tissue dysfunction. Patients with a very high polygenic risk score have an increased risk for recurrent invasive procedures and a younger age of onset.