# Advances in understanding chronic thromboembolic disease and pulmonary hypertension

## S108 GENOME-WIDE ASSOCIATION STUDY IN CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION REVEALS NEW INSIGHTS INTO AETIOLOGY

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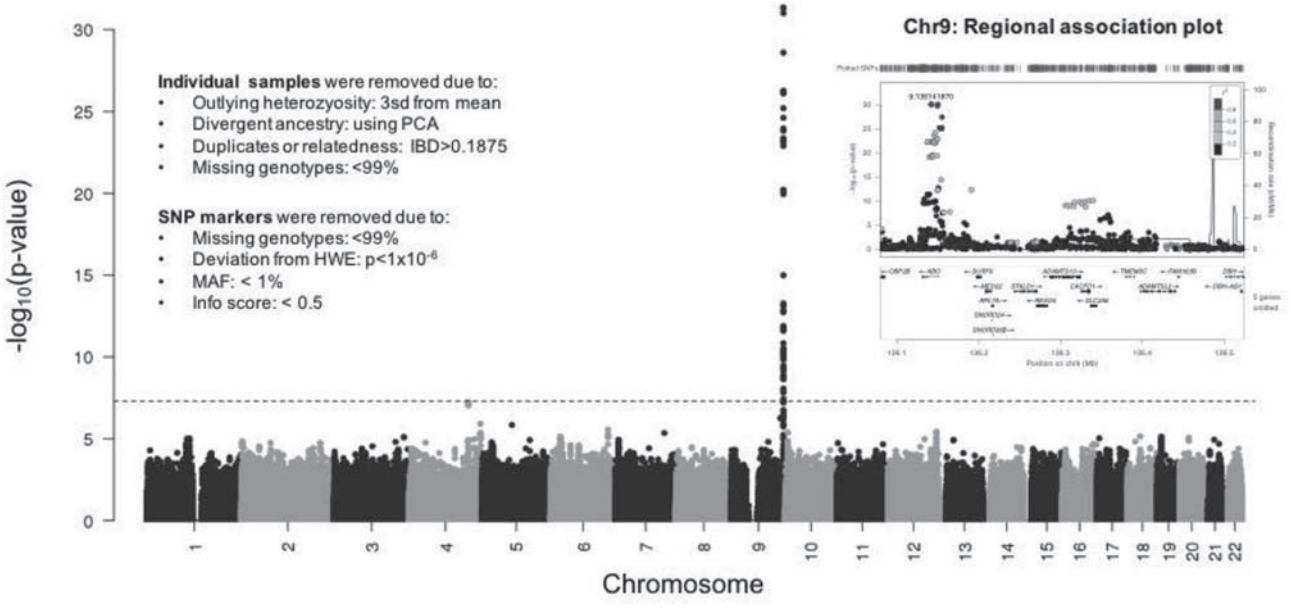
**Introduction** Chronic thromboembolic pulmonary hypertension (CTEPH) is an infrequent but important complication of acute pulmonary embolism (PE). Thrombophilias and non-O blood groups are genetic risk factors for venous thromboembolism (VTE), however they are not independently associated with CTEPH. Identifying genetic risk factors for CTEPH would provide important insights into pathobiology and might allow risk-stratification following PE. We undertook a genome-wide association study (GWAS) in CTEPH to identify novel disease loci.

**Methods** To date, 1457 Caucasian CTEPH patients were enrolled from 10 European and US Centres and compared to 1536 healthy Caucasian controls from the Wellcome Trust Case Control Consortium. Genotyping was performed using the HumanOmniExpressExome-8 array. Quality control criteria and statistical analysis are summarised in figure 1.

**Results** 1250 CTEPH cases, 1492 controls and 7 million single-nucleotide polymorphisms (SNPs) were included after quality control exclusions. Two loci, in chromosomes 4 and 9 were significantly associated with CTEPH (figure 1). The lead SNP in chr9 (rs532436, OR=2.38, $p=4.6x10^{-32}$) is highly correlated with the tagging SNP for the A1 blood group (rs507666, $R^2=0.99$). Reconstructing genetic ABO groups confirmed an over-representation of the A1A1 group in CTEPH compared to controls (7% vs. 2.9%, OR 4.5). Additionally, there were 11 significant SNPs in the chr9 *ADAMTS13* gene locus that is moderately correlated with *ABO* ($R^2=0.33$).

The lead SNP in chr4 (rs13130318, OR=1.4, $p=5.6x10^{-8}$) is highly correlated with a missense variant in *FGG* (rs6050, $R^2=0.89$) associated with decreased fibrinogen protein and increased resistance to fibrinolysis in CTEPH. There were no associations at the *F5* locus, which is highly significant in VTE.

**Conclusions** We report the first GWAS in CTEPH, identifying at least 2 genetic loci associated with the disease. The *ABO* association is driven by the A1 blood group and represents the largest population attributable genetic risk factor for CTEPH, which is higher than previously reported for VTE. The potential *ADAMTS13* association is a plausible biological candidate, and further work will establish whether it is independent from *ABO*. The lack of associations with other loci found in VTE suggests that *ABO* might have a pathobiological role in CTEPH in addition to its contribution to VTE.




**Abstract S108 Figure 1** Manhattan plot of significant loci in chromosome 4 and 9 associated with CTEPH. Quality control exclusion thresholds and chromosome 9 regional association plot shown within figure. Dotted line represents a Genome-wide significance threshold of $p=5x10^{-8}$ (Bonferroni). Imputaton was performed from the Haplotype Reference Consortium (Sanger imputation service). An additive model of association was applied using logistic regression with gender and 1 principal component as covariates. HWE (Hardy-Weinberg equilibrium), IBD (iderity by descent), MAF (minor allele frequency), PCA (principal component analysis), SNP (single nucleotide polymorphism).