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ORAL ABSTRACTS

332.THROMBOSIS AND ANTICOAGULATION: CLINICAL AND EPIDEMIOLOGICAL

Meta-Analysis of National-Level Genotyping Datasets to Determine the Risk of Thrombosis in Double Heterozygous Carriers of Factor V Leiden and the Prothrombin G20210A Mutation across 876,417 Individuals

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Introduction

Factor V Leiden (FVL) and the prothrombin G20210A mutation (PTGM) are well-known genetic risk factors for venous thrombosis. However, the clinical significance of double heterozygosity (DH) for FVL and PTGM remains poorly understood. Prior studies of the DH genotype have produced varying risk estimates and were limited by small sample size, heterogenous case and control groups, inclusion restricted to patients presenting for medical attention, and a lack of adjustment for potential confounders. Leveraging deeply-phenotyped, population-scale genomic datasets offers a unique opportunity to surmount these shortcomings and arrive at a more robust estimate of the risk experienced by DH individuals.

Methods

We utilized two large-scale population-level registries with paired genetic and phenotypic data: the UK Biobank (UKBB) and the FinnGen project. Our analyses focused on 6 genotypes: FVL heterozygous (FVL het), PTGM heterozygous (PTGM het), FVL homozygous (FVL hom), PTGM homozygous (PTGM hom), double heterozygous (DH), and wild-type for both PTGM and FVL (WT). Four thrombotic phenotypes were evaluated, including stroke (CVA), myocardial infarction (MI), peripheral artery disease (PAD), and venous thromboembolism (VTE). Multivariate Firth's logistic regression models adjusting for age, sex, and principal components of ancestry were used to assess risk of thrombotic events between genotypic groups. Sensitivity analyses included 1) restricting the Firth's regression to unrelated participants, and 2) controlling for additional covariates including body mass index (BMI), blood group, smoking status, platelet count, and C-reactive protein (CRP). An additional interaction term for the FVL and PTGM mutations was examined to evaluate whether the two variants functioned in an additive or multiplicative manner. The results were combined using random-effects meta-analysis. Rates of incident VTE were compared between WT and DH individuals using Cox proportional hazards regression and Kaplan Meier analysis.

Results

In total, we analyzed 485,835 individuals in the UKBB and 390,582 individuals in the FinnGen project. Between the two cohorts, 806,273 individuals were WT, 13,683 were PTGM het, 69 were PTGM hom, 36,600 were FVL het, 402 were FVL hom, and 646 were double heterozygous. As expected, after adjustment for age, sex, and ancestry, an increased risk of VTE was associated with PTGM het (OR = 1.88, 95% CI: 1.56 - 2.26, $p = 2.7 \times 10^{-11}$) and FVL het (OR = 2.27, 95% CI: 2.03 - 2.54, $p = 1.5 \times 10^{-47}$) relative to the WT genotype. By contrast, individuals with the DH genotype demonstrated a markedly higher VTE

risk relative to WT than either singly heterozygous genotype (OR = 5.24, 95% CI: 3.99 - 6.89, p = 1.4 x 10^{-32}) (**Figure 1**). None of the mutant genotypes was associated with a significantly increased risk of CVA, MI, or PAD, except FVL het carriers experienced a marginally increased risk for PAD, as previously described (OR = 1.17, 95% CI: 1.10 - 1.24, p = 5.2 x 10^{-7}) (**Figure 2**). Estimates for VTE risk associated with the DH genotype were not appreciably different after restricting the analysis to unrelated individuals (OR=5.66, 95% CI: 3.65-8.77, P = 9.7 x 10^{-15}) or adjusting for additional risk factors (OR=4.40, 95% CI: 3.33-5.72, P = < 1.0 x 10^{-16}). While VTE risk in individuals with DH genotype appeared additive, we observed a statistically significant interaction term for the two constituent genotypes (OR = 1.3, 95% CI: 1.05 - 1.60, p = 0.017). This finding suggests that although there is a statistically significant multiplicative interaction between the two mutations, they likely behave in an additive manner for the purposes of clinical care. Finally, we found that the rate of incident VTE was significantly higher among PTGM het individuals (P=8.5 x 10^{-15}), FVL het individuals (P <2 x 10^{-16}), and DH individuals (P=7.6 x 10^{-5}) compared to those with the WT genotype.

Conclusion and Relevance

We have conducted the largest study to date of double heterozygosity for FVL and PTGM. After adjustment for common confounders, DH individuals demonstrate an increased risk of VTE relative to singly heterozygous individuals. By contrast, we found no evidence that DH individuals are at significantly increased risk for arterial thrombosis. Our work may help resolve longstanding uncertainty around the clinical impact of the DH genotype on thrombotic risk.

Disclosures Niiranen: *AstraZeneca:* Honoraria; *Servier Finland:* Honoraria. **Ellinor:** *Novartis:* Consultancy; *Bayer AG:* Consultancy, Research Funding. **Bauer:** *Abbott:* Consultancy, Other: Member of Data and Safety Monitoring Board; *Sanofi:* Other: Member of an ad hoc Advisory Board. **Bendapudi:** *Takeda Pharmaceuticals:* Consultancy; *Alexion Pharmaceuticals:* Consultancy.

Genotypes	Carriers/total N (%)	Carriers/Non-carriers Cases	Controls	OR [95% CI]	*P* value
PTGM het	13,683/876,417 (1.5)	1,048/37,761	7,635/806,273	1.88 [1.56 - 2.26]	$2.7x10^{-11}$
PTGM hom	69/876,417 (<0.01)	7/37,761	62/806,273	3.05 [1.26 - 7.43]	0.014
FVL het	36,600/876,417 (4.2)	3,447/37,761	33,153/806,273	2.27 [2.03 - 2.54]	$1.5x10^{-47}$
FVL hom	402/876,417 (0.05)	83/37,761	319/806,273	6.19 [4.83 - 7.92]	$1.6x10^{-47}$
DH	646/876,417 (0.07)	120/37,761	526/806,273	5.24 [3.99 - 6.89]	$1.4x10^{-32}$

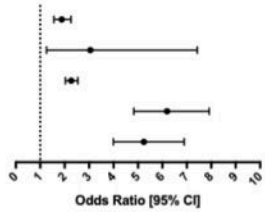

Figure 1: Risk of VTE according to genotype in 876,417 individuals. A random-effects meta-analysis was used to estimate the risks of VTE associated with five genotypes. Non-carriers (WT) were considered the reference value (OR=1.0).

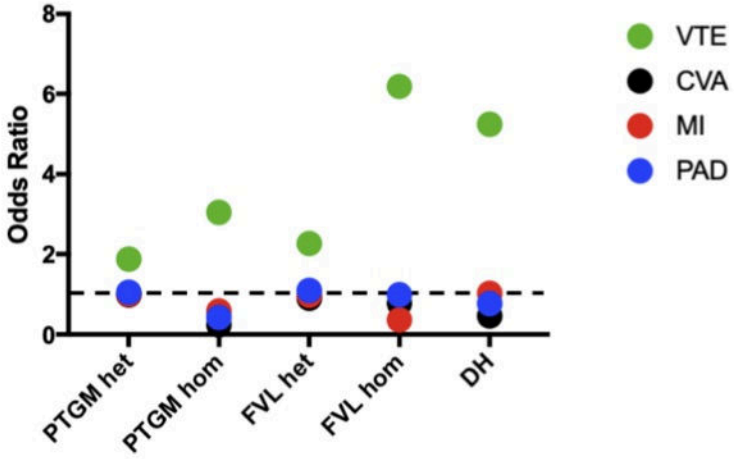

Figure 2: Risk of thrombosis according to genotype and phenotype. A random-effects meta-analysis was used to estimate the risks of four types of thrombotic disease across five genotypes. Non-carriers (WT) were considered the reference value (OR=1.0, dotted line). VTE = Venous thromboembolism; CVA = cerebral vascular accident; MI = myocardial infarction; PAD = peripheral artery disease.

Figure 1

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