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The association of *F11* genetic variants with the risk of incident venous thrombosis among women, by statin use

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Genetic variants in the factor XI structural gene, *F11*, are associated with a greater risk of incident venous thrombosis (VT) (1-3) and statin use may lower the risk of VT (4-6). It has been suggested that VT risk associated with *F11* risk alleles for rs2036914 and rs2289252 is blunted among statin users compared with non-users (7), but replication is needed. In this letter we present results from the Heart and Vascular Health (HVH) study, in which we evaluated the association between these 2 *F11* variants and VT risk, among statin users and non-users, and, assessed the presence of interaction.

Methods

VT cases were female enrollees of Group Health Cooperative (GHC), aged 18-89 years, who had experienced a first deep venous thrombosis (DVT) or pulmonary embolism (PE) between January 1, 1995 and December 31, 2010 (VT case n=2,876). (8) Participants provided written consent and the GHC Human Review Committee approved this study.

All VT cases were identified using International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes and *ICD-10* death record codes; events were validated by review of participants' inpatient and outpatient medical records. Control subjects were a random

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Disclosure of Conflict of Interest

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sample of female GHC members without a prior VT who were frequency-matched to HVH study MI events (largest case group) by design variables: age, hypertension status, and identification year (control n=6,698). For VT cases the index date was the date of the incident VT and for controls was a randomly chosen date within the calendar year from which they were serving as a control. From all VT cases and controls (n=9,574), we excluded women with unmeasured genotypes (n=5,422), cancer diagnosed in the 2 years prior to up to 14 days after the index date (n=274), and of nonwhite race (n=299) (3,579 women eligible).

Using the GHC computerized pharmacy database, we considered women to be current statin users at the index date if the final pre-index date prescription included enough medication to last until the index date, assuming 80% compliance.

For 1,416 participants, candidate single nucleotide polymorphisms (SNPs), including rs2289252, had been measured. For 2,163 women, genotyped markers from 2 different SNP arrays (rs2036914 and rs2289252) were imputed to the 1000 Genomes reference panel.⁽⁹⁾ In analyses, measured genotypes were preferentially selected over imputed. rs2036914 was available for 1,189 controls and 974 cases and rs2289252 for 2,605 controls and 974 cases.

We estimated the main effect association between the additive number of risk alleles (C allele for rs2036914 and T allele for rs2289252) and the risk of VT, adjusting for HVH design variables. Multiple logistic regression models separately estimated the main effect association between current statin use and VT risk, adjusting for design variables and confounders determined *a priori*: BMI, smoking status, and cardiovascular disease history. Logistic regression models stratified by current statin use estimated the additive association between the continuous number of risk alleles for each SNP and incident VT risk. All logistic regression models estimated odds ratios (ORs) and 95% confidence intervals (CIs).

The presence of effect modification on the multiplicative scale was evaluated by using a 2-degree-of-freedom Wald test, with an alpha level of 0.05. The presence of effect modification on the additive scale was evaluated by calculating the relative excess risk due to interaction (RERI) and corresponding 95% CIs (10, 11).

Results

Our eligible population included 974 white women with incident VT and 2,605 matched controls. Cases were slightly younger than controls (62.0 vs. 66.1 years, respectively), had a higher mean BMI than controls (32.3 vs. 28.8 kg/m², respectively), and had a higher prevalence of cardiovascular disease than controls (16.8% vs. 13.7%, respectively) (Supplemental Table 1). A greater proportion of VT cases (15.0%; n=146) were current users of statins than controls (12.9%; n=336). In controls, the risk allele (C) frequency was 0.531 for rs2036914 and, for rs2289252, the risk allele (T) frequency was 0.407.

Each additional risk allele for rs2036914 (C) and for rs2289252 (T) was associated with a greater risk of VT [(OR=1.15; 95%CI: 1.01, 1.32), and (OR=1.22, 95%CI: 1.08, 1.37), respectively] (Supplemental Table 2). Current statin use was associated with a 25% lower risk of VT than no current statin use (OR_{adj}=0.75; 95%CI: 0.57, 0.98).

For SNP rs2036914, statin use-stratified analyses suggested that each additional risk allele was associated with a similar risk of incident VT among non-users (OR=1.13; 95%CI: 0.98, 1.30) and users (OR=1.24; 95%CI: 0.89, 1.74) of statins (Table). We did not detect rs2036914-statin interaction on multiplicative (OR=1.10; 95%CI: 0.78, 1.56; $p=0.61$) or additive (RERI=0.051; 95%CI: -0.23, 0.33; $p=0.72$) scales.

For SNP rs2289252, statin use-stratified analyses suggested that each additional risk allele was associated with a similar risk of VT among non-users (OR=1.24; 95%CI: 1.09, 1.41) and users (OR=1.10; 95%CI: 0.80, 1.51) of statins (Table). We did not detect rs2289252-statin interactions on multiplicative (OR=0.88; 95%CI: 0.63, 1.24; $p=0.47$) or additive (RERI=-0.14; 95%CI: -0.50, 0.22; $p=0.44$) scales. Analyses that considered the risk alleles jointly for SNPs rs2036914 and rs2289252 did not provide evidence of a statin interaction.

Discussion

In this case-control study of the association between *FII* variants and VT risk among statin users and non-users, we found risks to be similar between statin strata and there was no statistical evidence of a *FII*-statin interaction. Investigators of the Multiple Environmental and Genetic Assessment of risk factors for VT (MEGA) study previously suggested that in their study, incident VT risk associated with 2 copies of the risk alleles for rs2036914 and rs2289252 was blunted among statin users (rs2036914 OR=1.03; 95%CI: 0.53-1.99, and, rs2289252 OR=1.06; 95%CI: 0.66, 1.71) compared with statin non-users (rs2036914 OR=1.75; 95%CI: 1.54-1.98, and, rs2289252 OR=1.83; 95%CI: 1.60, 2.08).(7) Confidence intervals surrounding effect estimates were wide, particularly among statin users, and no formal tests of interaction were conducted.

In the HVH study, there was little evidence of the hypothesized effect modification. Modification of adverse genetic effects on VT by medications may be of public health importance. However, point estimates from our population-based study suggest only minor differences in relative risk estimates for the risk alleles in users and non-users of statins and confidence intervals around the statin-by-risk allele interaction exclude large effect modification that would warrant a public health response, such as differential prescription of statins by genotype.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table

The risk of incident venous thrombosis associated with SNPs rs2036914 and rs2289252 and statin use among women.

rs2036914							
Minor Allele = T; C = Risk Allele							
	Model with Combined Genotype and Statin Use Exposure Indicator Variable						Additive Model
	TT		TC		CC		Risk for Each Additional Copy of C Allele within Strata of Statin Use
	n with/without VT	Adj. OR (95% CI) * ; p-value	n with/without VT	Adj. OR (95% CI) * ; p-value	n with/without VT	Adj. OR (95% CI) * ; p-value	Adj. OR (95% CI) * ; p-value
No Use of Statins	156/179	1.0 (ref)	400/518	0.87 (0.67, 1.14); p=0.32	272/271	1.21 (0.90, 1.62); p=0.21	1.13 (0.98, 1.30); p=0.10
Statin Use	25/47	0.68 (0.39, 1.20); p=0.18	73/115	0.78 (0.52, 1.16); p=0.21	48/59	1.03 (0.64, 1.67); p=0.90	1.24 (0.89, 1.74); p=0.20

rs2289252							
Minor Allele = T; T = Risk Allele							
	Model with Combined Genotype and Statin Use Exposure Indicator Variable						Additive Model
	CC		TC		TT		Risk for Each Additional Copy of T Allele within Strata of Statin Use
	n with/without VT	Adj. OR (95% CI) * ; p-value	n with/without VT	Adj. OR (95% CI) * ; p-value	n with/without VT	Adj. OR (95% CI) * ; p-value	Adj. OR (95% CI) * ; p-value
No Use of Statins	233/771	1.0 (ref)	421/1,150	1.10 (0.90, 1.34); p=0.37	174/348	1.59 (1.23, 2.05); p<0.001	1.24 (1.09, 1.41); p=0.001
Statin Use	49/113	1.05 (0.70, 1.58); p=0.82	68/173	0.96 (0.67, 1.36); p=0.80	29/50	1.37 (0.79, 2.35); p=0.26	1.10 (0.80, 1.51); p=0.56

CI = confidence interval; OR = odds ratio; SNP = single nucleotide polymorphism; VT = venous thrombosis.

* ORs are adjusted for categorical index year, age (in decade and continuous), and hypertension.