
Common variation in fibrinogen genes is associated with plasma fibrinogen levels, but not future cardiovascular events: The Cardiovascular Health Study

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Background: While elevated plasma fibrinogen is an independent risk factor for cardiovascular disease (CVD), associations between fibrinogen single nucleotide polymorphisms (SNPs) and disease risk have been less consistent. We investigated whether common variation in the three fibrinogen genes (FGA, FGB, FGG) is associated with fibrinogen concentration, carotid intima-medial thickness (IMT) and risk of incident MI and ischemic stroke in older (>65 years at baseline) Caucasian- (CA) and African-descent (AA) adults from the Cardiovascular Health Study.

Methods: Baseline fibrinogen was measured using a functional assay. Common (frequency \geq 5%) tagSNPs (n=16) in FGA, FGB and FGG were genotyped in CA (n=3969) and AA (n=719) free of MI or stroke at baseline. Haplotypes were estimated across the entire 3-gene locus using *Phase 2.0*. Race-specific linear regression and Cox proportional hazards models included haplotype probability-weighting, adjustment for sex, age and clinic and correction for multiple testing of SNPs.

Results: Fibrinogen tagSNPs and haplotypes were significantly associated with levels in CA. FGA3807, FGB1437 and FGG902 were associated with higher levels; FGA251, FGA2224, FGA6534 and FGG10034 were associated with lower levels, $p < 0.004$ for each. Results for AA followed similar trends (not significant). Haplotypes were not associated with CVD events in CA (Table). Adjusted for traditional risk factors, fibrinogen level (upper vs. lower tertiles) was significantly associated with carotid IMT and risk of MI (HR=1.3, 95%CI: 1.1-1.6), but not ischemic stroke (HR=1.2, 95%CI: 1.0-1.4) in CA.

Conclusion: Although associated with fibrinogen level, variation in fibrinogen genes was not associated with carotid IMT or risk of CVD events in older adults. If fibrinogen is in the CVD causal pathway, it is possible that the modest differences in fibrinogen level associated with haplotypes were not large enough to influence risk of CVD in our study population.

(See table on the next page)

Table: Associations between Fibrinogen Haplotypes and Levels and Risk ¹ of Incident CVD Events							
		% Frequency		Fibrinogen in mg/dL (95% CI)		MI HR (95% CI)	Ischemic Stroke HR (95% CI)
Haplotype	tagSNPs	CA	AA	CA	AA	CA	CA
A	FGB9952 FGG902	20.6	5.9	7.5 (3.0, 12.0)	4.5 (-11.7, 20.7)	0.9 (0.8, 1.2)	0.9 (0.7, 1.2)
B	FGA6534 FGA2224 FGA251 FGG10034	15.5	6.4	referent	referent	referent	referent
C	FGB1038 FGA9205 FGG9340	13.5	8.5	8.4 (3.4, 13.4)	12.0 (-4.1, 28.4)	1.1 (0.9, 1.4)	1.1 (0.9, 1.5)
D	FGB1437 FGA3807 FGG902	12.4	<5	20.3 (15.2, 25.4)	not tested	1.1 (0.9, 1.4)	1.0 (0.8, 1.3)
E	FGA5498 FGA2224 FGA251 FGG9340	9.4	<5	10.0 (4.6, 15.5)	not tested	1.0 (0.7, 1.2)	1.0 (0.8, 1.3)
global test p-value				<0.0001	0.5574	0.6378	0.5925

¹ Association between haplotypes and incident events tested only in CA.