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Significant genetic association of a functional TFPI variant with circulating fibrinogen levels and coronary artery disease

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Abstract

The tissue factor pathway inhibitor (TFPI) gene encodes a protease inhibitor with a critical role in regulation of blood coagulation. Some genomic variants in TFPI were previously associated with plasma TFPI levels, however, it remains to be further determined whether TFPI variants are associated with other coagulation factors. In this study, we carried out a large population-based study with 2313 study subjects for blood coagulation data, including fibrinogen levels, prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT). We identified significant association of TFPI variant rs10931292 (a functional promoter variant with reduced transactivation) with increased plasma fibrinogen levels (P = 0.017 under a recessive model), but not with PT, APTT or TT (P > 0.05). Using a large case–control association study population with 4479 CAD patients and 3628 controls, we identified significant association between rs10931292 and CAD under a recessive model (OR 1.23, P = 0.005). For the first time, we show that a TFPI variant is significantly associated with fibrinogen levels and risk of CAD. Our finding contribute significantly to the elucidation of the genetic basis and biological pathways responsible for fibrinogen levels and development of CAD.

Results

Table 1 Characteristics of the study subjects for the association analysis between TFPI SNP rs10931292 and blood coagulation parameters

Characteristics	*N* or %
Total number, *n*	2313
Male number, *n* (%)	1429 (61.78%)
Age, years (mean ± SD)	64.93 ± 11.97
CAD, *n*	1871 (80.9%)
Fg/FIB (fibrinogen level) (mean ± SEM) (g/L)	4.07 ± 0.08
PT (prothrombin time) (mean ± SEM) (s)	12.83 ± 0.13
APTT (activated partial thromboplastin time) (mean ± SEM) (s)	34.88 ± 1.50
TT (thrombin time) (mean ± SEM) (s)	16.56 ± 0.19

Fig. 1 Analysis of association of TFPI SNP rs10931292 and coagulation indicators.

A. Fibrinogen levels (Fg/FIB). Mean fibrinogen levels for different genotypes: N_{AA} = 980 subjects, 3.99 ± 0.15 g/L; N_{AG} = 790 subjects, 4.18 ± 0.14 g/L; N_{GG} = 305 subjects, 5.21 ± 0.97 g/L.

B. PT. Mean PT for different genotypes: N_{AA} = 1084 subjects, 12.92 ± 0.20 s; N_{AG} = 886 subjects,12.86 ± 0.23 s; N_{GG} = 335 subjects, 12.46 ± 0.10 s.

C.APTT.Mean APTT for different genotypes: N_{AA} = 1079 subjects, 36.52 ± 3.14 s; N_{AG} = 866 subjects, 33.59 ± 0.46 s; N_{GG} = 330 subjects, 32.89 ± 0.49 s.

D. TT. Mean TT for different genotypes: N_{AA} = 992 subjects, 16.58 ± 0.24 s; N_{AG} = 786 subjects, 16.34 ± 0.28 s; N_{GG} = 296 subjects, 17.08 ± 0.76 s.

Prec, P value after adjustment with age and gender under a recessive model

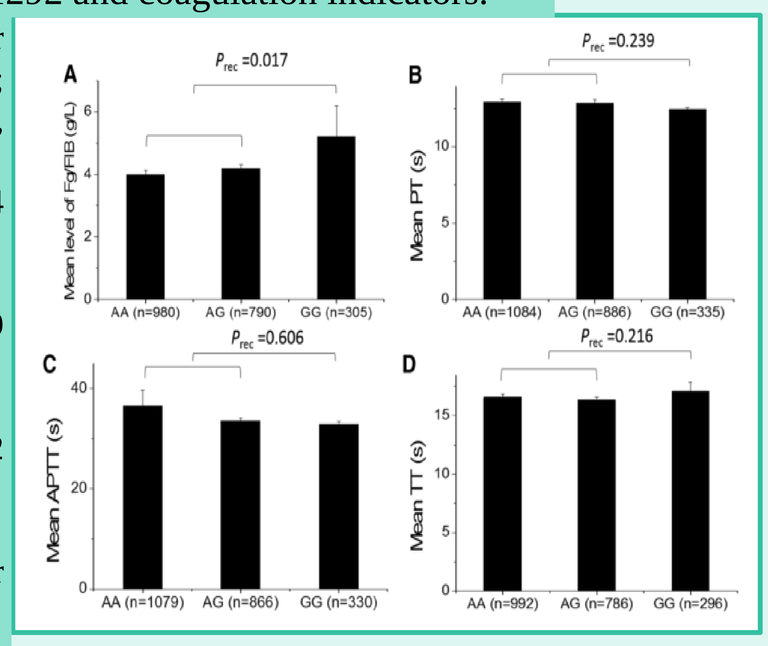

Table 2 Analysis of the association of TFPI SNP rs10931292 with coagulation parameters

Coagulation indicator	Sample size (AA/AG/GG)	P_{adj}			Effect [*B* (95% CI)]		
		Additive	Dominant	Recessive	Additive	Dominant	Recessive
Fibrinogen	980/790/305	0.026[a]	0.131	0.017	0.53 (0.06 to 1.00)	0.51 (−0.15 to 1.17)	1.14 (0.21 to 2.08)
		0.027[b]	0.136	0.018	0.52 (0.06 to 0.98)	0.51 (−0.16 to 1.17)	1.13 (0.20 to 2.07)
Prothrombin time	1084/886/335	0.289	0.492	0.239	−0.19 (−0.55 to 0.17)	−0.18 (−0.69 to 0.33)	−0.44 (−1.17 to 0.29)
		0.283	0.487	0.232	−0.20 (−0.56 to 0.16)	−0.18 (−0.69 to 0.33)	−0.45 (−1.17 to 0.29)
Activated partial thromboplastin time	1079/866/330	0.308	0.274	0.606	−2.16 (−6.32 to 2.00)	−3.32 (−9.27 to 2.63)	−2.23 (−10.68 to 6.23)
		0.353	0.300	0.679	−1.97 (−6.13 to 2.19)	−3.15 (−9.10 to 2.80)	−1.78 (−10.24 to 6.68)
Thrombin time	992/786/296	0.595	0.915	0.216	0.14 (−0.38 to 0.67)	−0.04 (−0.79 to 0.71)	0.67 (−0.40 to 1.74)
		0.595	0.915	0.216	0.14 (−0.38 to 0.67)	−0.04 (−0.79 to 0.71)	0.68 (−0.40 to 1.75)

Table 3 Clinical and demographical characteristics of the case–control study population for testing association between TFPI SNP rs10931292 and CAD

Characteristics	CAD group	Control group	*P*
Number (*n*)	4479	3628	–
MI, *n* (%)	1083 (24.18%)	0	<0.001
Male, *n* (%)	2707 (60.44%)	2242 (61.80%)	0.22
Age, years (mean ± SD)	65.27 ± 12.55	58.79 ± 11.28	<0.001
Hypertension, *n* (%)	1982 (44.25%)	N/A	–
DM, *n* (%)	631 (14.09%)	N/A	–
Smoker, *n* (%)	1115 (24.89%)	N/A	–
Drinker, *n* (%)	773 (17.26%)	N/A	–
Total cholesterol (mmol/L)[a]	5.97 ± 1.33	N/A	–
LDL cholesterol (mmol/L)[a]	2.76 ± 0.15	N/A	–
HDL cholesterol (mmol/L)[a]	1.55 ± 0.28	N/A	–
Triglyceride (mmol/L)[a]	1.74 ± 0.12	N/A	–

Table 4 Analysis of allelic association between TFPI SNP rs10931292 and CAD

Population (*n*, case/control)	P_{hwe}	Risk allele	Frequency (case/control)	Before adjustment		After adjustment	
				P^{a}_{obs}	OR (95% CI)	P^{b}_{adj}	OR (95% CI)
Overall CAD (4479/3628)	0.08	G	0.34/0.33	0.08	1.06 (0.99–1.14)	0.08	1.07 (0.99–1.15)
Early-onset CAD (1541/3628)	0.08	G	0.33/0.33	0.94	1.00 (0.89–1.14)	0.64	1.04 (0.89–1.20)
Female CAD (1698/1329)	0.33	G	0.35/0.33	0.51	1.04 (0.93–1.16)	0.62	1.03 (0.91–1.16)
Male CAD (2707/2242)	0.20	G	0.33/0.32	0.05	1.09 (1.00–1.19)	0.07	1.09 (0.99–1.19)

Table 5 Analysis of genotypic association between TFPI SNP rs10931292 and CAD under three different genetic models

Population (*n*, case/control)	Genetic model	Before adjustment		After adjustment	
		P^{a}_{obs}	OR (95% CI)	P^{b}_{adj}	OR (95% CI)
Overall CAD (4479/3628)	Additive	0.089	1.06 (0.99–1.13)	0.088	1.06 (0.99–1.14)
	Dominant	0.826	1.01 (0.92–1.11)	0.618	1.03 (0.93–1.13)
	Recessive	0.001	1.25 (1.09–1.44)	0.005	1.23 (1.06–1.42)
Early-onset CAD (700/3628)	Additive	0.944	1.00 (0.89–1.14)	0.644	1.04 (0.90–1.20)
	Dominant	0.428	1.07 (0.91–1.26)	0.061	1.21 (0.99–1.46)
	Recessive	0.167	1.19 (0.93–1.53)	0.049	1.35 (1.00–1.81)
Female CAD (1698/1329)	Additive	0.524	1.04 (0.93–1.15)	0.634	1.03 (0.92–1.16)
	Dominant	0.625	1.04 (0.89–1.21)	0.804	1.02 (0.87–1.20)
	Recessive	0.038	1.27 (1.01–1.60)	0.169	1.19 (0.93–1.52)
Male CAD (2707/2242)	Additive	0.058	1.09 (1.00–1.18)	0.079	1.08 (0.99–1.18)
	Dominant	0.424	1.05 (0.93–1.18)	0.409	1.05 (0.93–1.19)
	Recessive	0.006	1.28 (1.07–1.53)	0.016	1.25 (1.04–1.50)

Conclusion

In summary, we have identified a significant association between TFPI SNP rs10931292 and increased fibrinogen levels and risk of CAD. Our study, for the first time, implicates the TFPI genetic variation in the regulation of plasma fibrinogen levels and developmental of CAD.

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