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Association of Rs2071410 on *Furin* with Transient Ischemic Attack Susceptibility and Prognosis in a Chinese Population

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Background: Because genotype CG/GG of *Furin* rs2071410 can increase susceptibility to hypertension, this study investigated whether *Furin* rs2071410 is correlated with transient ischemic attack (TIA) susceptibility and prognosis.





Material/Methods: The odds ratios (ORs) and their 95% confidence intervals (95% CIs) were evaluated to assess the association of rs2071410 with TIA risk, and logistic regression was used to estimate the effects of various risk factors (e.g., diabetes, hypertension, and hyperlipidemia) on TIA.

Results: Compared with the homozygous genotype CC of rs2071410, the frequency of CG + GG genotype in the case group was significantly higher than in the control group (OR=1.47, 95% CI: 1.05–2.05, $P<0.05$). The CG + GG genotype carriers were observed to have worse 90-day prognosis after TIA treatment than patients carrying CC genotype (OR=12.86, 95% CI: 7.41–22.33, $P<0.05$). Moreover, logistic regression analysis found that age, diabetes, hypertension, and hyperlipidemia were associated with the onset of TIA ($P<0.05$, all). Of note, individuals with CG + GG genotype had 49.3% increased risk of TIA compared with individuals with CC genotype (OR=1.49, 95% CI: 1.05–2.12), and patients with CG + GG genotype had worse 90-day prognosis after TIA treatment than patients with CC genotype (OR=11.39, 95% CI: 6.29–20.62).

Conclusions: *Furin* rs2071410 was significantly correlated with TIA occurrence and prognosis in the Chinese population.

MeSH Keywords: **Disease Susceptibility • Furin • Ischemic Attack, Transient • Prognosis**

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Background

Transient ischemic attack (TIA), commonly known as “small stroke”, is a sudden, transient, and reversible nerve dysfunction caused by focal cerebral ischemia. Moreover, focal cerebral ischemia is triggered by the transient deficiency of blood supply in the carotid and vertebral-basilar artery system [1–3]. TIA is not considered to be a rare disease, with an annual incidence of between 0.31 and 0.64 per 1000 and it is commonly observed in middle-aged and elderly individuals [4–7]. The prevalence of TIA exponentially increases with age, and the annual prevalence is reported to be 2.93 cases per 1000 among individuals, with an average age of 75 [8]. TIA is thought to be a clinical syndrome with sporadic recurrence and it is usually accompanied by brain dysfunction during the interictal period, which seriously affects living and work. The chance of brain infarction within 1 month and 5 years after TIA were about 4–8% and 24.29%, respectively, and the proportion of TIA patients with cerebrovascular disease within the first 5 years is 5.9% [8]. Studies have shown that the risk and prognosis of TIA are closely affected by the degree of hypertension, hyperlipidemia, and heart disease [9].

Judging from the inheritance of TIA, it could be hypothesized that single-nucleotide polymorphisms (SNP) contributing to hypertension might also be a pathogenic factor of TIA, such as Furin polymorphisms [10,11]. Furin, a bacillus subtilis serine protease, is usually used to specifically cleave precursor proteins in eukaryotes [12–14]. In this way, certain hypertension-related proteins can be activated, including epithelial Na⁺ channel (ENaC), endothelin, and transforming growth factor (TGF-β); otherwise, hypertension mainly results from abnormal blood pressure (BP), disordered Na⁺ homeostasis, or vascular growth [15–17]. Thus, Furin, which is expressed in most tissues with a widespread substrate, is critical in prevention of the normal physiological process in people with hypertension and even TIA [9,14]. Because it has been suggested in a Chinese population that rs2071410 on *Furin* was associated with hypertension, and CG + GG genotype might elevate risk of hypertension in comparison to genotype CC [10], we suspected that rs2071410 on *Furin* was probably linked with development of TIA.

No *Furin* variants have been reported to be linked with the onset and prognosis of TIA. Hence, this study aimed to confirm the association of *Furin* rs2071410 with susceptibility to TIA, providing an effective strategy for the early detection of TIA in the Chinese population.

Material and Methods

Subjects characteristics

All the 304 cases were selected from TIA patients admitted in the Affiliated Hospital of Shandong Medical College from July 2013 to May 2015. All cases were confirmed by brain magnetic resonance imaging (MRI), ultrasound, and electrocardiogram following transient ischemic diagnostic criteria [18]. The inclusion criteria were: (1) age ≥40 years; (2) patients diagnosed with acute mild ischemic stroke or TIA and hospitalized within 24 h of symptom onset; (3) all patients were defined as Han Chinese without any family relationships with other patients; and (4) all participants were lucid and able to cooperate with examinations. Exclusion criteria were: (1) previous history of stroke; (2) underwent cerebral infarction or myocardial infarction; (3) history of intracranial hemorrhage, vascular malformations, brain tumor, brain abscess, or other non-ischemic cerebrovascular disease; (4) severe disease that significantly impairs physical ability. A total of 253 healthy individuals undergoing physical examinations during the same period in our hospital were chosen as the control group. All patients included in this study signed the informed consent and the clinical trial passed the examination and was approved by the ethics committee from our hospital prior to its commencement.

Therapies

All patients were treated by antiplatelet and cholesterol-lowering therapy according to the treatment specification of ischemic cerebrovascular disease. Each subject was given 100 mg oral aspirin along with 20 mg statin per day were administered. All the patients were continuously administered statin (20 mg/d) and aspirin (100 mg/d) as the secondary prevention treatment for 1 month after discharge.

The collection of information and specimen

Basic information of patients, including sex, age, blood pressure, blood lipid, blood sugar, and other biochemical data, were collected and recorded in detail. Fasting venous blood (5 ml) was extracted from each subject and serum was separated from blood through centrifugal experiments (Eppendorf, Germany). Lipid detection was performed within a month after the collection of blood serum. Blood cells were stored at –80° for other experimental use. Measurement of blood lipid was performed by scientists from the clinical laboratory. As recommended by the Chinese adult dyslipidemia prevention guide [19], patients with triglyceride (TC) ≥6.19/L or low-density lipoprotein cholesterol (LDL-C) ≥4.14 L were diagnosed as having hyperlipidemia.

The detection of polymorphism inside *Furin*

Genomic DNA was extracted from 20 μ l of fasting venous blood obtained from each patient. Lysis liquid was added into the centrifuge tube with blood cells included for blending and then the supernatant was discarded. After that, 1 ml proteinase K along with anhydrous ethanol was added and centrifuged at 5000 rpm. UNIQ-10 columns with the addition of Elution Buffer were then centrifuged for 1 min to obtain the genomic DNA.

Forty-eight patients aged between 40 and 60 years were randomly selected from the samples to sequence the coding and promoter of *Furin* using the 3100xl gene analyzer (Applied Biosystems, CA). Sequencher 4.7 gene sequence analysis software (Gene Codes, MI) was used to investigate the mutation *loci* and the nature of the variation after comparing sequencing results with the standard *Furin* sequence alignment. Professional genetic analysis software of SNPalyze Ver. 7.0.1 pro (Dynacom, Chiba, Japan) was used to analyze specific SNPs.

Genotypes were identified by means of ABI 7900 ht PCR (Applied Biosystems). The genotyping primers were: positive-sense strand, 5' GGGATGATGGGTGTCGGATGT-3'; anti-sense strand, 3' CCGATGTTGCGGGCGTAAC-5'. The PCR reaction system was: 25 μ l of reactive reagents, including a TaqMan gene polymorphism pre-mixed solution (Applied Biosystems) of 12.5 μ l, single-nucleotide polymorphisms parting probe/l primers pre-mixed solution (Applied Biosystems) as 1.25 μ l, DNA template (20 ng/ μ l) of 2 μ l with 9.25 μ l deionized water; reaction conditions: pre-degeneration (95°C, 10 min, a loop), modified (92°C, 15 s) + annealing (60°C, 1 min) + extension (72°C, 1 min) 43 cycles, and finally with total extension (72°C, 7 min, a loop).

Prognostic evaluation

The modified Rankin scale [20] was used to evaluate the condition of patients 3 months after their treatments. Subjects were divided into 5 levels: (1) asymptomatic – 0 points; (2) some symptoms, but can perform activities of daily living and work – 1 point; (3) mildly disabled and unable to complete all activities but can complete daily routines without help – 2 points; (3) moderately disabled and complete daily routines with some help, but can walk independently – 3 points; (4) more than moderately disabled, unable to walk, and need help for daily tasks – 4 points; (5) severely disabled, cannot get out of bed, and completely rely on others during daily life – 5 points. Patients with a score of 0–1 are able to cope with normal life and they had good prognosis, while patients with a score of higher than 2 were defined as having poor prognosis.

Statistical analysis

SPSS 19.0 (SPSS Inc., IL) statistical software was used for data processing. Measurement data are expressed as mean \pm standard deviation (SD), while count data and categorical variables are expressed as percentages and frequencies. Comparison of clinical phenotype measurement data was carried out using the *t* test if 2 groups were involved, whereas analysis of variance was performed to compare more than 2 groups. Furthermore, logistic regression adjusting for confounding factors was used to assess the association between multiple risk factors and TIA, while count data was analyzed using the chi-square test. Three genetic models – dominant model (WM+MM vs. WW), allelic model (M vs. W), and homozygous model (MM vs. WW) – were established to analyze the frequency distribution of genotypes and alleles, respectively. Comparisons between the 2 groups were performed with SNPalyze Ver. 7.0.1 pro. software and $P < 0.05$ was considered as statistically significant. The logistic regression not only assessed the effect of various risk factors on TIA, but also removed the insignificant risk factors, and the corresponding odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Results

General characteristics comparison

As shown in Table 1, the case group was composed of 178 men and 185 women with mean age of 54.91 ± 7.25 years (age range 30–80 years old), while the control group included 164 males and 226 females with a mean age of 50.60 ± 8.59 years (age range 30–80 years old). The analysis results revealed that there was no significant difference in sex and high-density lipoprotein cholesterol (HDL-C) between the 2 groups ($P > 0.05$). In the case group there were 265 (73.0%) patients with hypertension, 120 (33.1%) with diabetes, and 178 (49.4%) with hyperlipidemia; however, the corresponding figures in the control group were 211 (54.1%), 70 (17.9%), and 156 (40.0%), respectively. The proportion of people in the case group with high cholesterol, hypertension, and diabetes was significantly higher than that in the control group (all $P < 0.05$). There were significant differences in several other biochemical indexes, including age, total cholesterol (TG), TC, LDL-C, and blood sugar, between the case group and control group (all $P < 0.05$) (Table 1).

Association of rs2071410 with the occurrence of TIA

The genotype distribution of *Furin* rs2071410 in both the case group and control group complied with Hardy-Weinberg equilibrium ($P > 0.05$, both), indicating that the genotype was evenly distributed and representative. The genotype frequency and allele frequency distribution of *Furin* rs2071410 are shown in

Table 1. Basic characteristics of subjects in transient ischemic attack patients and healthy controls.

Clinical characteristics	Cases (n=363)	Controls (n=390)	P-value
Age	54.91±7.25	50.60±8.59	<0.001*
Gender			
Male	178	164	0.054
Female	185	226	
Hypertension			
Yes	265	211	<0.001*
No	98	179	
Diabetes			
Yes	120	70	<0.001*
No	243	320	
Hyperlipidemia			
Yes	178	156	0.013*
No	185	234	
TC (mmol/L)	5.17±1.06	4.90±1.03	<0.001*
TG (mmol/L)	1.25±0.47	1.01±0.37	<0.001*
HDL-C (mmol/L)	1.44±0.39	1.47±0.38	0.286
LDL-C (mmol/L)	3.16±0.86	2.94±0.81	<0.001*
Blood glucose (mmol/L)	5.13±1.33	4.84±0.68	<0.001*

TC – total cholesterol; TG – triglyceride; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol;
* $P < 0.05$.

Table 2. The G allele frequency of rs2071410 in the case group was significantly higher than in the control group ($P < 0.05$), suggesting that G allele carriers may have higher risk of TIA than C allele carriers (OR=1.50, 95% CI: 1.13–2.01). Compared with rs2071410 homozygous genotype CC, the frequency of CG + GG genotype in the case group was obviously higher than in the control group (OR=1.47, 95% CI: 1.05–2.05, $P < 0.05$). Compared to CC genotype as the reference, GG genotype carriers had a higher relative risk of TIA ($P < 0.05$).

Correlation of rs2071410 with 90-day prognosis of TIA

The CG + GG genotype carriers had a significantly worse 90-day prognosis after treatment than CC genotype carriers ($P < 0.05$) (Table 3). Compared to patients with CC genotype, TIA patients with CG + GG genotype had a significantly higher risk of adverse outcomes after therapy (OR=12.86, 95% CI: 7.41–22.33). Moreover, the proportion of G allele carriers with unfavorable 90-day prognosis was 36.6% which was significantly higher than the proportion of G allele carriers with good prognosis (5.7%) (OR=9.58, 95%CI: 6.00–15.29, $P < 0.05$). Therefore, G

allele carriers have significantly higher risk of poor TIA prognosis compared to patients with C allele (Table 3).

Analysis of multiple risk factors for TIA

As suggested by the results from logistic regression, sex was not significantly related to the occurrence of TIA ($P > 0.05$), but age, diabetes, hypertension, and hyperlipidemia were associated with the onset of TIA ($P < 0.05$, all). After adjusting for confounding factors, including hypertension, diabetes, hyperlipidemia, and age, GG genotype of rs2071410 was observed to be associated with TIA ($P < 0.05$). Furthermore, CG + GG genotype carriers had 49.3% higher risk of TIA compared to CC genotype carriers (OR=1.49, 95% CI: 1.05–2.12) (Table 4), revealing that G allele could be an independent risk factor for TIA.

Analysis of TIA prognosis by multiple risk factors

Results from logistic regression also provided evidence that age, hypertension, diabetes, and hyperlipidemia did not have significant effects on TIA prognosis ($P > 0.05$, all). The mutant of

Table 2. Genotype and allele distribution of *Furin* rs2071410 among transient ischemic attack (TIA) patients and healthy controls.

Allele/genotype	Cases (n=363)	Controls (n=390)	Odd ratio	95% (CI)	P-value
C	602 (82.92%)	686 (87.95%)	Ref.	Ref.	Ref.
G	124 (17.08%)	94 (12.05%)	1.50	1.13–2.01	0.006*
CC	261 (71.90%)	308 (78.97%)	Ref.	Ref.	Ref.
CG	80 (22.04%)	70 (17.95%)	1.35	0.94–1.94	0.103
GG	22 (6.06%)	12 (3.08%)	2.16	1.05–4.46	0.035*
CC	261 (71.90%)	308 (78.97%)	Ref.	Ref.	Ref.
CG+GG	102 (28.10%)	82 (21.03%)	1.47	1.05–2.05	0.024*

CI – confidence interval; * P<0.05.

Table 3. Association of genotypes for *Furin* rs2071410 with 90 days' prognosis of transient ischemic attack patients.

Allele/genotype	Score of 90 days prognosis (n=363)		P-value	Odds ratio	95% CI
	Good (≤1) (n=229)	Bad (≥2) (n=134)			
C	432 (94.32%)	170 (63.43%)	Ref.	Ref.	Ref.
G	26 (5.68%)	98 (36.57%)	<0.001	9.58	6.00–15.30
CC	206 (89.96%)	55 (41.04%)	Ref.	Ref.	Ref.
CG	20 (8.73%)	60 (44.78%)	<0.001	11.24	6.25–20.21
GG	3 (1.31%)	19 (14.18%)	<0.001	23.72	6.77–83.11
CC	206 (89.96%)	55 (41.04%)	Ref.	Ref.	Ref.
CG+GG	23 (10.04%)	79 (58.96%)	<0.001	12.86	7.41–22.33
GG	3 (1.31%)	19 (14.18%)	Ref.	Ref.	Ref.
CC+CG	226 (98.69%)	115 (85.82%)	<0.001	12.45	3.61–42.94

CI – confidence interval.

rs2071410 was linked with a poor prognosis of TIA (P<0.05), and the CG + GG genotype of rs2071410 was significantly associated with an increased risk of poor 90-day prognosis of TIA compared to patients with CC genotype (OR=11.39, 95% CI: 6.29–20.62, P<0.05) (Table 5).

Discussion

The present study is the first to examine the association between genetic variations of *Furin* and TIA in human beings. We found that rs2071410 was strongly associated with the occurrence and prognosis of TIA in the Chinese population, and homozygote GG of *Furin* rs2071410 had a negative impact on the development and treatment outcome of TIA under the logistic regression model. These findings indicate that the *Furin* could be considered as a candidate gene that participates in

TIA progression, and G allele of rs2071410 might be a significant risk factor for TIA.

As is previously indicated, *Furin* is a key enzyme involved in processing the (pro) renin receptor ([P] RR), which is a specific receptor for renin and prorenin. Recently, Nguyen et al. demonstrated that *Furin* could degrade endogenous (P) RR [21]. Zachigna et al. discovered that Emilin1 knockout animals were associated with a rise in blood pressure and hence concluded that Emilin1 could suppress the signal of TGF-β via its binding to the proTGF-β precursor and avoiding its maturity by *Furin* [17]. Another study has hypothesized that *Furin* is a candidate gene related to the development of hypertension in humans and the G allele of rs2071410 could be an important risk factor for the onset of hypertension in Chinese populations [10]. As hypertension is one of the most significant risk factors for TIA [22–26] and changes in blood pressure were

Table 4. Association of the risk factors with the risk of transient ischemic attack (TIA).

Risk factor	B	S.E.	Wals	df	Sig	OR	95% CI	
							Lower limit	Upper limit
Age	0.068	0.010	48.458	1	<0.001*	1.07	1.05	1.09
Gender	0.285	0.147	3.749	1	0.053	1.33	0.99	1.78
Hypertension	0.828	0.160	26.710	1	<0.001*	2.28	1.67	3.13
Diabetes	0.865	0.179	23.316	1	<0.001*	1.48	1.67	3.37
Hyperlipidemia	0.391	0.154	6.443	1	0.011*	1.48	1.09	2.00
Dominant model (CG+GG vs. CC)	0.401	0.178	5.064	1	0.024*	1.49	1.05	2.12

* $P < 0.05$. B – partial regression coefficient; S.E – standard error; Wals – wald statistics; df – degree freedom; Sig – significance; OR – odds ratio; CI – confidence intervals.

Table 5. The analysis on the risk factors related to the 90 days prognosis of transient ischemic attack.

Risk factor	B	S.E.	Wals	df	Sig	OR	95% CI	
							Lower limit	Upper limit
Age	-0.008	0.018	0.201	1	0.654	0.99	0.96	1.03
Gender	0.349	0.260	1.794	1	0.180	1.42	0.85	2.36
Hypertension	-0.311	0.297	1.097	1	0.295	0.73	0.41	1.31
Diabetes	-0.167	0.274	0.375	1	0.540	0.85	0.50	1.45
Hyperlipidemia	-0.086	0.260	0.109	1	0.741	0.92	0.55	1.53
Dominant model (CG+GG vs. CC)	2.433	0.303	64.452	1	<0.001*	11.39	6.29	20.62
Recessive model (GG vs. CG+CC)	-0.698	0.677	1.063	1	0.303	0.50	0.13	1.88

* $P < 0.05$. B – partial regression coefficient; S.E – standard error; Wals – wald statistics; df – degree of freedom; Sig – significance; OR – odds ratio; CI – confidence intervals.

found in TIA patients [27], *Furin* rs2071410 might be the key treatment target of TIA.

Hyperlipidemia was reported to be a major risk factor for TIA, and a reduction in hyperlipidemia by primary and secondary prevention was found to decrease the morbidity and mortality of TIA patients [28]. Moreover a series of studies have verified that diabetes is another significant risk factor for acute ischemic stroke [29], because the presence of TIA is mainly attributed to the formation of atherosclerosis, while accumulation of atherosclerotic plaques is possibly the consequence of diabetes [30,31]. Furthermore, decreased HDL-C and increased LDL-C have been revealed to be correlated with the development of acute ischemic stroke, particularly for the elderly, although this is disputed by other studies [32–34]. Altered HDL-C and LDL-C concentrations are tightly related with abnormally elevated BP

(hypertension), contributed to by diabetes; therefore, diabetes is believed to have substantial effects on TIA [33,35]. Reduced *Furin* expression was observed in the diabetic rats when compared with controls, suggesting that *Furin* might act as a hereditary predictor of diabetes-causing TIA [36].

Limitation

The present study has several limitations. Firstly, only part of data in the case group was used in the analysis since data in the case group were only available in the middle of the fiscal year between 2013 and 2015. The missing data contained in the case group may have biased risk estimation. Moreover, this was a single-center observational study which did not provide the strongest evidence and may not be generalizable to other Chinese populations. Secondly, logistic regression only

provided us with limited information since the database only incorporated several variables with respect to the case and control group. Moreover, some key information, such as life-style factors, was not available, so it is essential to carry out future case-control studies that adjust for a wide range of factors to confirm our conclusions. Finally, our study was unable to reveal the exact mechanism of *Furin* with respect to TIA progression and prognosis.

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Conclusions

Our study shows that *Furin* rs2071410 is significantly correlated with the occurrence and prognosis of TIA. Age, hypertension, diabetes, and hyperlipidemia also displayed significant influences on risk of TIA when effects of other confounding factors were excluded. Our results suggest the utility of genetic markers in early prevention of TIA.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.