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## Polymorphism Ala54Thr of *Fatty Acid-Binding Protein 2* Gene is Not Associated with Stroke Risk in Han Population of Hunan China

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Data Interpretation D  
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**Background:** It is still unclear which genetic factors have a role in stroke. Studies have found that Ala54Thr of *Fatty Acid-Binding Protein 2* (*FABP2*) was associated with stroke risk. This study aimed to determine whether polymorphism Ala54Thr of *FABP2* is associated with stroke risk in the Hunan Han population of China.

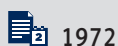
**Material/Methods:** A total of 206 cerebral infarction (CI) patients, 185 cerebral hemorrhage (CH) patients, and 172 controls were enrolled in this study. Ala54Thr genotyping was done by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP).

**Results:** No significant difference was observed in genotypic distribution of *FABP2* Ala54Thr between the stroke group (CI subgroup, CH subgroup included) and control group. In the stroke group, plasma triglycerides (TG) levels of subjects who carried Ala/Thr, Thr/Thr were significantly higher than those carrying Ala/Ala. In the control group, blood lipids were not significantly different among 3 genotypes of Ala54Thr. There was no significant difference in blood pressure and fasting blood sugar between the stroke group and controls.

**Conclusions:** Our study showed that Ala54Thr of *FABP2* may be not associated with stroke risk but may be associated with plasma TG level of stroke patients from a Hunan Han population of China.

**MeSH Keywords:** **Cerebral Hemorrhage • Cerebral Infarction • Fatty Acid-Binding Proteins • Polymorphism, Genetic • Polymorphism, Restriction Fragment Length • Stroke**

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## Background

Stroke is well known as one of the most serious diseases endangering human health. In recent years, with the aging of population and lifestyle changing in China, the incidence and mortality of stroke increased rapidly, causing huge burdens to the economy, families, and society [1,2]. Stroke, as one of complex diseases, is widely considered to be caused by interaction between genetic and environmental factors. For individualized treatment and screening susceptible populations at risk of stroke, it is important to find the key genes involved [3].

*Fatty acid-binding protein 2 (FABP2)* gene is located in 4q26 and contains 4 exons interrupted by 3 introns. *FABP2* gene encodes intestinal fatty acid binding protein, which is secreted by small intestine epithelial cells and participates in uptake, intracellular metabolism, and transport of long chain fatty acids [4]. Many studies have shown that Ala54Thr (rs1799883) polymorphism of *FABP2* is associated with stroke risk factors such as type 2 diabetes mellitus, hyperlipidemia, carotid atherosclerosis, metabolic syndrome, and cardiovascular diseases [5–11]. Martínez-López found that Ala54Thr was associated with cardiovascular disease risk in Mexican obese subjects [12]. Wanby et al. reported that carrying the Thr allele of Ala54Thr was a significant risk factor for internal carotid artery stenosis, together with diabetes [13]. Yamada showed that Ala54Thr may be a risk factor for atherothrombotic cerebral infarction with metabolic syndrome [14]. Carlsson et al. confirmed the association of the *FABP2* Thr54 allele with increased concentrations of cholesterol and triglycerides (TG) and reported that it may increase susceptibility to stroke [15].

To the best of our knowledge, it has not been determined whether Ala54Thr of *FABP2* is associated with stroke risk in a Chinese population. Therefore, we genotyped Ala54Thr to ascertain whether this association exists in a Chinese Han population from Hunan Province.

## Material and Methods

### Subjects

This study was approved by the Medical Ethics Committee of Xiangya Hospital (Changsha, Hunan province, China). All subjects signed an informed consent. We enrolled 391 stroke patients in the Department of Neurology, Xiangya Hospital from May 1, 2008 to February 28, 2009. They were divided into 2 subgroups: Cerebral infarction (CI) subgroup, 206 patients (134 men and 72 women, average age 62.74±9.9 years); and Cerebral hemorrhage (CH) subgroup, 185 patients (117 men and 68 women, average age 58.9±11.7 years). All the stroke patients were diagnosed through CT and/or MRI according

with the Diagnostic Criteria of Fourth National Cerebrovascular Disease Conference of China [16]. Patients with cerebral infarction caused by cardiogenic factors, arteritis, hematological disorders, tumors, or cerebral vascular malformations were excluded. Patients who took oral anticoagulants or contraceptives in the last 3 months, who were pregnant, or who had liver and kidney diseases or autoimmune diseases were excluded.

Sex- and age-matched controls consisted of 172 healthy volunteers (109 men and 63 women, average age 60.8±10.5 years), recruited over the same time period. Exclusion criteria of the control group were: history of stroke or family history of stroke; liver or kidney diseases; hematological diseases; and autoimmune diseases.

### Blood biochemistry tests and genomic DNA extraction

For each subject, 3 ml of peripheral blood was collected for examination of fasting blood sugar (FBS) and blood lipids. Another 3 ml of the blood sample (EDTA anticoagulant) was used for genomic DNA extraction by the phenol/chloroform method.

### Genotyping by PCR-RFLP

The primers for Ala54Thr genotyping were designed according to the reference [17] and synthesized by Sangon Biotech Co., Ltd., (Shanghai, China). The sequence of the primers was 5'-ACAGGTGTTAATATAGTGAAAAG-3' (forward primer) and 5'-TACCCTGAGTTCAGTTCGGTC-3' (reverse primer). The length of the amplification product was 180 bp. PCR was conducted: pre-denaturation at 94°C for 6 min, 35 cycles of denaturation at 94°C for 35 s, annealing at 53°C for 30 s, then extension at 72°C for 30 s; and final extension at 72°C for 30 s.

An Hha I restriction enzyme cutting sites exists in the PCR amplification product of wild-type homozygotes. Variant of G→A (Ala→Thr) can lead to loss of this enzyme cutting site [17]. We took 5 µl of PCR product for digestion with restriction enzyme Hha I (Biolabs Co., UK). The enzyme cutting reaction was incubated at 37°C for 5 h, and 5 µl of reaction product was taken for electrophoresis (0.5×TBE, 110 V, 45 min) on a 3% agarose gel containing 0.5 g/ml ethidium bromide. Genotype detection: wild-type homozygotes (Ala/Ala), with 2 fragments at 99bp and 81bp; heterozygotes (Ala/Thr), 3 fragments with lengths of 180bp, 99bp, and 81bp respectively; and only 1 fragment for the mutant homozygotes (Thr/Thr) with length of 180 bp.

### Statistical analysis

Genotypic and allelic frequencies were calculated using the direct gene counting method. Statistical analysis was performed using SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). The  $\chi^2$  test was used to determine Hardy-Weinberg

**Table 1.** Demographic data of stroke patients and the control subjects.

Clinic characters	Stroke group (n=391)	CI subgroup (n=206)	CH subgroup (n=185)	Control group (n=172)
Mean age (years)	61.4±10.1	62.7±9.9	58.9±11.7	60.8±10.5
Men/Women	251/140	134/72	117/68	109/63
BMI (kg/ m <sup>2</sup> )	23.1±2.5	23.8±2.3*	22.8±2.7	22.5±2.0
Smoking (N/Y)	176/215	92/114	84/101	76/96
Drinking (N/Y)	104/287	54/152	50/135	45/127
SBP (mmHg)	155±25*	150±24*	165±25*	130±18
DBP (mmHg)	91±16*	88±15*	97±16*	80±10
FBS (mmol/l)	5.90±2.25	5.94±2.47	5.80±1.60	5.51±1.67
TC (mmol/l)	4.38±1.50	4.40±1.34	4.35±1.28	4.25±0.80
TG (mmol/l)	2.23±1.42	2.35±1.53*	2.03±1.22	2.10±1.77
HDL (mmol/l)	2.65±0.88	2.73±0.89*	2.42±0.79	2.45±0.73
LDL (mmol/l)	1.35±0.55*	1.23±0.44*	1.30±0.39*	1.62±0.34

Stroke group and 2 subgroups were compared with control group respectively. \*  $P < 0.05$ . CI – cerebral infarction; CH – cerebral hemorrhage; N – no; Y – yes; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; FBS – fasting blood sugar; TC – total cholesterol; TG – triglycerides; HDL – high-density lipoprotein; LDL – low-density lipoprotein.

equilibrium and to compare genotype and allele frequencies between groups. The odds ratio (OR) and 95% confidence interval (95%CI) were used to indicate relative risk. Data are expressed as  $\bar{x} \pm s$ . Data from the groups were compared using the t test or analysis of variance. The threshold for statistical significance was  $P < 0.05$ .

## Results

### Characteristics of subjects

The main clinical data of the stroke group and control group are listed in Table 1. There was not significant difference in sex, age, smoking history, or drinking history between the stroke group (2 subgroups respectively) and control group ( $P < 0.05$ ), but systolic blood pressures (SBP) and diastolic blood pressures (DBP) were significantly different ( $P < 0.05$ ). Body mass index (BMI) of the CI subgroup was significantly higher than in controls ( $P < 0.05$ ). High-density lipoprotein (HDL) level of the stroke group (subgroups respectively) was significantly lower than in the control group ( $P < 0.05$ ). TG and low-density lipoprotein (LDL) levels of the CI subgroup were significantly higher than in controls ( $P < 0.05$ ).

### Distribution of genotypes and alleles

We enrolled 563 subjects in this study. Frequencies of genotypes and alleles in both groups were compatible with the Hardy-Weinberg equilibrium. Frequencies of 3 genotypes (Ala/Ala, Ala/Thr, and Thr/Thr) in the stroke group were 45.0%, 43.0%, and 12.0%, respectively, which were not significantly different from the control group. Frequencies of 3 genotypes (Ala/Ala, Ala/Thr, and Thr/Thr) in the CI and CH subgroups were 44.2%, 42.7%, 13.1% and 45.9%, 43.2%, 10.8%, respectively. Frequencies of allele Thr 54/Ala 54 in CI and CH were 0.655/0.345 and 0.676/0.324, respectively. There was no significant difference between the 2 subgroups and the control group ( $P > 0.05$ ) (Table 2).

### Ala54Thr and traditional stroke risk factors

As shown in Table 3, in the stroke group and in the control group there was no significant difference in levels of FBS, BP, TC, LDL, and HDL among the 3 genotypes ( $P > 0.05$ ). In the stroke group, TG levels of subjects carrying Ala/Thr and Thr/Thr genotypes were higher than who carrying Ala/Ala genotype ( $P < 0.05$ ). In the control group, this difference did not exist among the 3 genotypes ( $P > 0.05$ ).

In Table 4 we merged genotypes Ala/Thr and Thr/Thr into Thr (+) alleles and compared them with Thr (–) alleles (Ala/Ala). All

**Table 2.** Genotypic and allelic frequencies of Ala54Thr in patients and controls.

Groups	Genotypic frequencies, n (%)			Allelic frequencies,%	
	Ala/Ala	Ala/Thr	Thr/Thr	Thr54	Ala54
Stroke group (n=391)	176 (45.0)	168 (43.0)	47 (12.0)	66.5	33.5
CI subgroup (n=206)	91 (44.2)	88 (42.7)	27 (13.1)	65.5	34.5
CH subgroup (n=185)	85 (45.9)	80 (43.2)	20 (10.8)	67.6	32.4
Control group (n=172)	78 (45.3)	83 (48.3)	11 (6.4)	69.5	30.5

Genotypic and allelic frequencies of stroke group and its 2 subgroups were compared with control group respectively. All *P* values were >0.05. CI – cerebral infarction; CH – cerebral hemorrhage;

**Table 3.** The relationship between genotypes of Ala54Thr and risk factors of stroke.

Groups	Stroke group			CI subgroup		
	Ala/Ala (176)	Ala/Thr (168)	Thr/Thr (47)	Ala/Ala (91)	Ala/Thr (88)	Thr/Thr (27)
SBP (mmHg)	154±26	153±25	155±27	147±21	149±25	154±26
DBP (mmHg)	92±16	89±15	91±12	87±14	87±17	91±14
FBS (mmol/l)	5.85±1.98	5.97±2.30	5.65±0.94	5.85±2.25	5.98±2.47	5.75±1.11
TC (mmol/l)	4.44±1.29	4.34±1.42	4.15±0.92	4.35±1.28	4.49±1.45	4.51±0.93
TG (mmol/l)	2.08±1.48	2.50±1.40*	2.32±1.70*	2.11±1.53	2.56±1.59*	2.40±1.86*
LDL (mmol/l)	2.32±0.85	2.58±0.87	2.67±0.73	2.45±0.84	2.79±0.90	2.60±0.82
HDL (mmol/l)	1.27±0.36	1.47±0.44	1.35±0.32	1.23±0.33	1.15±0.48	1.25±0.19

Groups	CH subgroup			Control group		
	Ala/Ala (85)	Ala/Thr (80)	Thr/Thr (20)	Ala/Ala (78)	Ala/Thr (83)	Thr/Thr (11)
SBP (mmHg)	166±27	164±22	157±24	131±17	132±19	128±14
DBP (mmHg)	100±17	96±14	88±10	81±10	80±11	75±12
FBS (mmol/l)	5.83±1.38	5.86±1.96	5.70±0.84	5.43±1.73	5.63±1.68	5.35±0.31
TC (mmol/l)	4.39±1.30	4.17±1.32	4.25±0.84	4.23±0.88	4.29±0.78	4.27±1.06
TG (mmol/l)	1.97±1.39	2.15±0.93*	2.20±1.42*	2.11±1.99	2.16±1.63	2.03±2.32
LDL (mmol/l)	2.41±0.82	2.51±0.79	2.35±0.63	2.20±0.72	2.67±0.76	2.38±0.82
HDL (mmol/l)	1.36±0.42	1.22±0.33	1.25±0.59	1.76±0.38	1.68±0.29	1.60±0.28

Clinical data who carrying Ala/Thr, Thr/Thr were compared with those who carrying Ala/Ala in every group/subgroup respectively.

\* *P*<0.05. CI – cerebral infarction; CH – cerebral hemorrhage; SBP – systolic blood pressure; DBP – diastolic blood pressure; FBS – fasting blood sugar; TC – total cholesterol; TG – triglycerides; HDL – high-density lipoprotein; LDL – low-density lipoprotein.

stroke patients were first stratified according to sex and then stratified according to whether they were carrying Thr allele. No significant difference between Thr (+) and Thr (-) (*P* > 0.05) was found in sex, blood pressure, FBS, TC, or LDL levels. For male stroke patients, TG level of Thr (+) was higher than Thr (-) and HDL level of Thr (+) was lower than Thr (-) (*P*<0.05). For female stroke patients, TG level of Thr (+) was significant higher than Thr (-) (*P* <0.05).

**Multiple logistic regression model**

Candidate variables such as sex, body mass index, smoking history, drinking history, hypertension history, diabetes history, SBP, DBP, TC, TG, LDL, HDL, and *FABP2* Ala54Thr genotypes were imported into multivariate logistic regression models. Stepwise regression method was used to filter out the risk factors. Stroke diagnosis was used as the

**Table 4.** Stratified analysis of stroke group.

Clinical data	Male stroke patients		Female stroke patients	
	Thr54(+)	Thr54(-)	Thr54(+)	Thr54(-)
Mean ages (years)	62.2±11.6	60.7±10.9	60.9±11.1	61.3±12.3
BMI (kg/m <sup>2</sup> )	23.2±2.5	23.5±2.7	22.8±2.5	23.1±2.3
SBP (mmHg)	152±25	148±26	158±26	161±26
DBP (mmHg)	93±17	88±16	90±14	91±16
FBS (mmol/l)	5.97±1.69	5.85±1.87	5.81±2.43	5.75±2.68
TC (mmol/l)	4.18±1.21	4.19±1.44	4.66±1.31	4.54±1.58
TG (mmol/l)	2.04±1.64	2.30±1.34*	2.22±2.01	2.45±1.58*
LDL (mmol/l)	2.37±0.73	2.51±0.83	2.46±0.95	2.62±0.90
HDL (mmol/l)	1.44±0.26	1.11±0.41*	1.35±0.25	1.40±0.29

Stratified analysis was made according to different gender, carrying Thr54 allele or not in stroke groups. Comparisons were made between the same genders. \*  $P < 0.05$ . BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; FBS – fasting blood sugar; TC – total cholesterol; TG – triglycerides; HDL – high-density lipoprotein; LDL – low-density lipoprotein.

**Table 5.** The logistic regression model of main stroke risk factors.

Variables	Coefficient	P values	OR	95% CI
Gender	0.244	0.308	0.838	0.621–1.143
BMI (kg/m <sup>2</sup> )	0.448	0.252	1.565	0.727–3.371
Smoking history	0.811	0.557	2.574	1.373–4.824
Drinking history	0.546	0.184	2.191	0.727–3.371
Hypertension history	2.971	0.000*	19.517	10.836–35.154
Diabetes history	0.266	0.487	1.305	0.616–2.763
SBP	0.546	0.175	1.702	0.790–3.667
DBP	0.936	0.003*	2.551	1.366–4.764
TC	-0.438	0.142	0.645	0.359–1.158
TG	0.923	0.000*	2.517	1.823–3.475
LDL	-0.115	0.716	0.892	0.480–1.655
HDL	-1.303	0.001*	0.272	0.126–0.589
Genotypes of Ala54Thr	0.153	0.596	1.858	0.487–1.512

Stepwise regression method was used. Variable inclusion and exclusion criteria were  $\alpha_{in} = 0.10$  and  $\alpha_{out} = 0.15$ . \*  $P < 0.05$ . 95% CI – 95% confidence interval; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; FBS – fasting blood sugar; TC – total cholesterol; TG – triglycerides; HDL – high-density lipoprotein; LDL – low-density lipoprotein.

dependent variable. Variable inclusion and exclusion criteria were  $\alpha_{in} = 0.10$  and  $\alpha_{out} = 0.15$ . Our results showed that hypertension history, TG, and DBP were risk factors; HDL presented as a protective factor; other candidate variables (including Ala54Thr genotypes) did not enter into the model. The results are shown in Table 5.

## Discussion

In recent years, many studies have found that polymorphisms of *FABP2* gene were associated with several diseases. Polymorphism Ala54Thr of *FABP2* was found to be relevant to insulin resistance by Baier et al. in 1995 [5]. This variant was

reported to be associated with insulin resistance and type 2 diabetes mellitus in white populations in the USA and in Canada, but this association was not confirmed in Finland or Chile [18–25]. Other studies showed that Ala54Thr is related with lipid metabolism disorders. Several studies found Thr54 allele was significantly associated with higher levels of TC and LDL and lower level of HDL [26,27]. Other studies found that genetic variation in *FABP2* may thus lead to individual variation in the response of plasma lipids to different dietary habits [28,29], thus dietary patterns may interact with *FABP2* variants to affect metabolic differences and susceptibility to disease.

In the present study, PCR-RFLP method was used to genotype Ala54Thr in the stroke group and control group. There was no significant difference in frequencies of genotypes and alleles between the 2 groups, suggesting that the Ala54Thr polymorphism of *FABP2* gene may not be associated with increased risk of stroke in a Han population in Hunan China. However, this conclusion is in contrast to that of the study by Yamada [14]. We speculate that the reasons for this are: Firstly, difference in ethnicity and diet habits probably influence the effect of Ala54Thr polymorphism of *FABP2* on stroke susceptibility. Secondly, we also built a multiple logistic regression model of stroke, which showed that hypertension history, DBP, TG were risk factors for stroke; HDL was a protective factor for stroke; and Ala/Thr, Thr/Thr genotype did not enter the stroke risk factors logistic regression model. These findings suggest that Ala54Thr of *FABP2* may be unrelated to the pathogenesis of stroke and that Ala54 allele may not be an independent risk factor of stroke for the Han Chinese population in Hunan. Thirdly, this may be attributable to the small sample sizes. Larger samples are needed to confirm the association between Ala54Thr genotypes and stroke risk.

Accumulating evidence shows that Ala54Thr is closely associated with dyslipidemia. In the Framingham population, Galluzzi

found that Thr54 allele of *FABP2* was related with high serum levels of TC and LDL among women and was associated with high serum levels of LDL and ApoB in men [8]. In our study, in the stroke group, TC level of those carrying Ala/Thr, Thr/Thr genotypes of *FABP2* was significantly higher than in those carrying Ala/Ala. There was no significant difference in TC, LDL, and HDL levels among the 3 genotypes (Ala/Ala, Ala/Thr, and Ala/Thr). In the control group, those 3 genotypes did not affect the fasting blood lipid levels. Stratified analysis was conducted based on sex and genotype. Male stroke patients with Thr (+) alleles had a higher TG level and lower LDL level than those with Thr (–) alleles, but for female stroke patients, only TG level of those with Thr (+) alleles was significantly higher than in those with Thr (–) alleles.

These results indicate that polymorphism Ala54Thr of *FABP2* gene is really related with dyslipidemia of stroke patients. The mechanisms of this association are probably that Ala/Thr and Thr/Thr enhance the affinity of long chain fatty acids, promote the synthesis of fatty acid uptake and oxidation and triglyceride of the small intestine, thus increasing the fasting and postprandial plasma TG levels of [5]. Further studies are needed to understand the underlying mechanisms.

## Conclusions

Although our study found an effect of Ala54Thr on plasma TG level of stroke patients, this variant had nothing to do with stroke risk. Further research with larger sample is warranted to determine if Ala54Thr of *FABP2* is associated with stroke risk.

## Conflict of interest

The authors declare that they have no conflict of interest.

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