Associations of β-Fibrinogen Polymorphisms with the Risk of Ischemic Stroke: A Meta-analysis

Hailong Luo, MD,*[,1] Xin Li, MD,†[,1] Aiying Jiang, MD,‡ Benzhuo Zhang, MD,§ Pengxiang Bi, MD,§ Yan Dong, MD,§ and Yanqin Guo, MD*

Background: Recently, the roles of β-fibrinogen (*FGβ*) polymorphisms in ischemic stroke (IS) were intensively analyzed, but the results of these studies were inconsistent. Thus, we performed this study to better assess potential relationship between *FGβ* polymorphisms and the risk of IS. *Methods:* Eligible studies were searched in PubMed, Medline, Embase, and CNKI. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate correlations between *FGβ* polymorphisms and IS. *Results:* A total of 49 studies were included for analyses. Significant associations with the risk of IS were detected for *FGβ* −148 C/T and −455 G/A polymorphisms in overall analyses. Further subgroup analyses according to ethnicities of participants revealed that the −148 C/T polymorphism was significantly correlated with the risk of IS in both Asians and Caucasians, while the −455 G/A polymorphism was only significantly correlated with the risk of IS in Asians. When we stratified available data according to types of disease, we found that both *FGβ* −148 C/T and −455 G/A polymorphisms were significantly correlated with the risk of cerebral infarction. *Conclusions:* Our findings indicated that *FGβ* −148 C/T and −455 G/A polymorphisms may serve as potential biological markers for IS in Asians. Moreover, the *FGβ* −148 C/T polymorphism may also serve as a potential biological marker for IS in Caucasians.

Key Words: β-fibrinogen (*FGβ*)—gene polymorphisms—ischemic stroke (IS)—meta-analysis

Introduction

Ischemic stroke (IS), characterized by necrosis of brain tissue resulted from stenosis or even obstruction of cerebral arteries, is the leading cause of death and disability worldwide.[1] To date, the exact cause of IS remains ambiguous despite extensive investigations. Nevertheless, accumulating evidence suggests that genetic factors may play crucial parts in its pathogenesis. First, numerous genetic variants have been found to be associated with an increased risk of IS by previous genetic association studies.[2-4] Second, screening of common causal variants has also been proved to be an efficient way to predict the individual risk of developing IS.[5] Overall, these findings jointly indicated that genetic predisposition is crucial for the occurrence and development of IS.

Fibrinogen, a glycoprotein consists of α, β, and γ chains, functions as a vital clotting factor and plays an important role in regulating thrombosis formation.[6] It is encoded by 3 different genes located at q23-q32 of chromosome 4.[7] Previous experimental studies have demonstrated that −148 C/T and −455 G/A polymorphisms of β-fibrinogen (*FGβ*) could affect plasma fibrinogen levels and these 2 polymorphisms were also associated with an increased risk of thrombotic disorders.[8,9] It is well documented that thrombosis formation plays a central role in

From the *Department of Neurology, Hongqi Hospital of Mudanjiang Medical University, Mudanjiang, China; †Department of Neurology, First Affiliated hospital of Jiamusi University, Jiamusi, China; ‡Department of Respiratory Medicine, Hongqi Hospital of Mudanjiang Medical University, Mudanjiang, China; and §Department of Neurology, Second Affiliated Hospital of Mudanjiang Medical University, Mudanjiang, China.

Received July 22, 2018; revision received August 18, 2018; accepted September 2, 2018.

Funding: This study was supported by Natural Science Foundation of Heilongjiang Province (H2017077).

Address correspondence to Yanqin Guo, MD, Department of Neurology, Hongqi Hospital of Mudanjiang Medical University, No. 5 Tong Xiang Road, Mudanjiang 157011, China. E-mail: yanqinguo9958@aliyun.com

[1]These authors contributed equally to this work.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.09.007

the development of IS. Consequently, *FGβ* −148 C/T and −455 G/A polymorphisms are considered to be ideal candidate genetic biomarkers of IS.

Recently, numerous studies have been conducted to investigate potential associations between *FGβ* polymorphisms and the risk of IS. But the results of these studies were inconsistent and the sample size of individual studies was inadequate to draw a definite conclusion.[10-13] Thus, we conducted this meta-analysis to better analyze the roles of *FGβ* polymorphisms in the development of IS.

Materials and Methods

Literature Search and Inclusion Criteria

This meta-analysis was adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline.[14] Potentially eligible articles were searched in PubMed, Medline, Embase, and CNKI using the combination of following key words: "β-fibrinogen," "FGβ," "polymorphism," "variant," "mutation," "genotype," "allele," "ischemic stroke," "cerebral infarction," "brain infarction," "transient ischemic attack," and "cerebrovascular disease." The initial literature search was conducted in February 2018 and the latest update was performed in July 2018. The reference lists of all retrieved publications were also screened to identify other potentially relevant articles.

Included studies should met all the following criteria: (1) case-control study on correlations between *FGβ* polymorphisms and the risk of IS; (2) provide adequate data to calculate odds ratios (ORs) and 95% confidence intervals (CIs); (3) full text available. Studies were excluded if one of the following criteria was fulfilled: (1) not relevant to *FGβ* polymorphisms and IS; (2) family-based association studies; (3) case reports or case series; (4) abstracts, reviews, comments, letters, and conference presentations. For duplicate reports, only the study with the largest sample size was included. No language restrictions were imposed in this meta-analysis.

Data Extraction and Quality Assessment

The following data were extracted from included studies: (1) name of the first author; (2) year of publication; (3) country and ethnicity of participants; (4) the number of cases and controls; and (5) genotypic distributions of *FGβ* polymorphisms in cases and controls. In addition, the probability value (*P* value) of Hardy-Weinberg equilibrium (HWE) was also calculated according to genotypic frequency of *FGβ* polymorphisms in the control group.

The Newcastle-Ottawa scale (NOS) was employed to assess the quality of eligible studies from 3 aspects: (1) selection of cases and controls; (2) comparability between cases and controls; and (3) exposure in cases and controls.[15] The NOS has a score range of 0-9, and studies with a score of more than 7 were thought to be of high quality.

Two reviewers (Luo and Li) conducted data extraction and quality assessment independently. When necessary, the reviewers wrote to the corresponding authors for extra information or raw data. Any disagreement between the 2 reviewers was solved by discussion with the third reviewer (Guo) until a consensus was reached.

Statistical Analyses

All statistical analyses were conducted with Review Manager Version 5.3.3 (The Cochrane Collaboration, Software Update, Oxford, United Kingdom). ORs and 95% CIs were calculated to assess potential associations of *FGβ* polymorphisms with the risk of IS in the dominant, recessive, additive, and allele models and a *P* value of .05 or less was considered to be statistically significant. Between-study heterogeneities were evaluated based on Q test and I^2 statistic. If *P* value of Q test was less than .10 or I^2 was greater than 50%, random-effect models would be used for analyses due to the existence of significant heterogeneities. Otherwise, fixed-effect models would be applied for analyses. Subgroup analyses by ethnicities of participants and types of disease were subsequently conducted to obtain more specific results. Sensitivity analyses were carried out to test the stability of synthetic results. Funnel plots were applied to evaluate possible publication bias.

Results

Characteristics of Included Studies

The literature search identified 287 potentially relevant articles. After exclusion of irrelevant and duplicate articles by reading titles and abstracts, 97 articles were retrieved for further evaluation. Another 48 articles were subsequently excluded after reading the full text. Finally, a total of 49 eligible studies were included in this meta-analysis (see Fig 1). Characteristics of included studies were summarized in Table 1.

Overall and Subgroup Analyses

To investigate potential correlations of *FGβ* polymorphisms with the risk of IS, 25 studies about *FGβ* −148 C/T polymorphism (3928 cases and 4505 controls) and 33 studies about *FGβ* −455 G/A polymorphism (5201 cases and 6584 controls) were enrolled for analyses. Significant associations with the risk of IS were detected for *FGβ* −148 C/T (dominant model: *P* = .0008, OR = .72, 95% CI .59-.87; additive model: *P* = .0006, OR = 1.29, 95% CI 1.12-1.50; allele model: *P* = .001, OR = .77, 95% CI .65-.90) and −455 G/A (dominant model: *P* < .0001, OR = .69, 95% CI .58-.82; recessive model: *P* = .001, OR = 1.34, 95% CI 1.12-1.61; additive model: *P* = .0004, OR = 1.38, 95% CI 1.15-1.65; allele model: *P* < .0001, OR = .75, 95% CI .67-.86) polymorphisms in overall analyses.

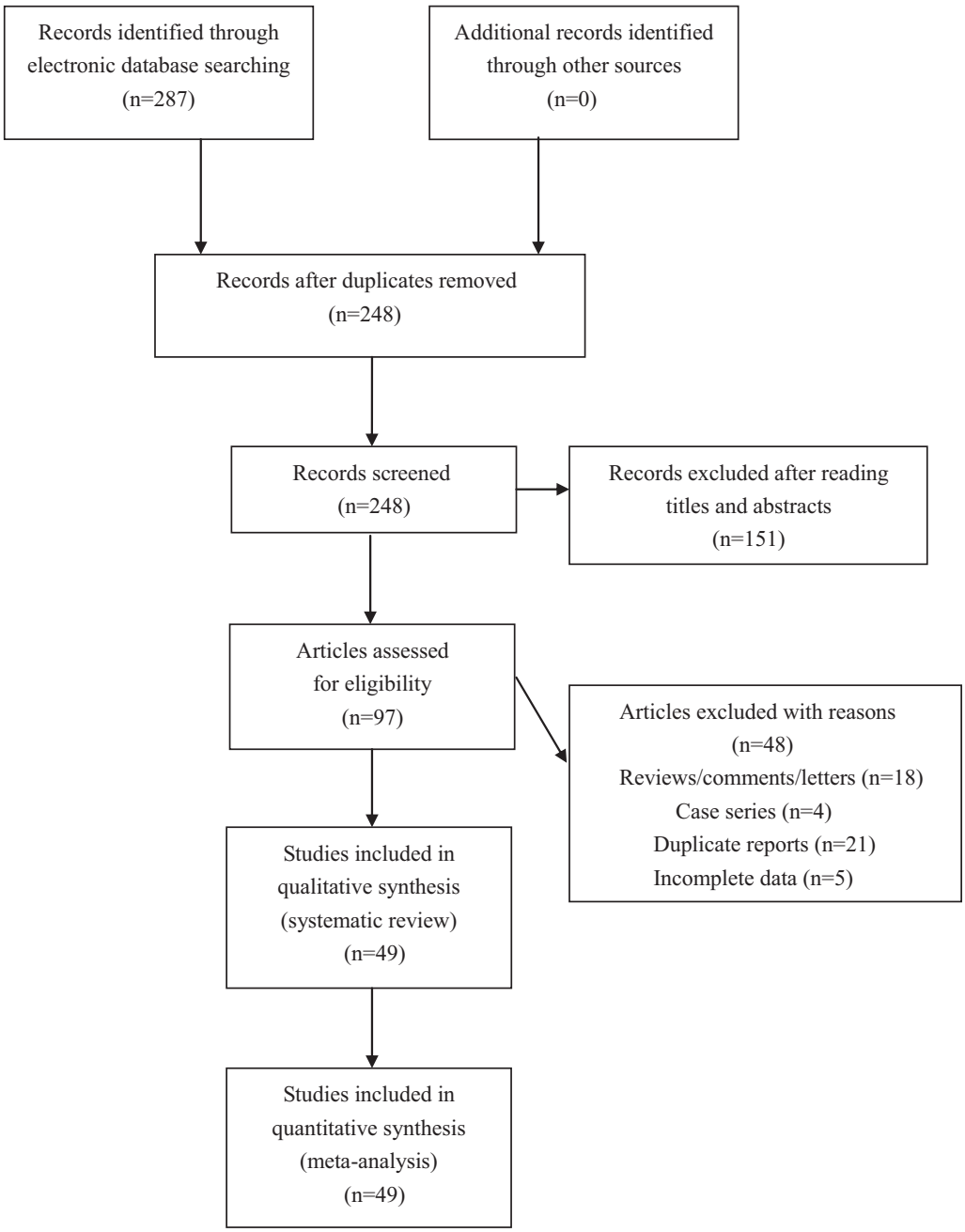

Figure 1. *Flowchart of study selection for the present study.*

Further subgroup analyses based on ethnicities of participants revealed that the −148 C/T polymorphism was significantly correlated with the risk of IS in both Asians (dominant model: $P = .002$, OR = .71, 95% CI .57-.88; recessive model: $P = .05$, OR = 1.43, 95% CI 1.01-2.03; additive model: $P = .002$, OR = 1.29, 95% CI 1.10-1.52; allele model: $P = .002$, OR = .75, 95% CI .63-.90) and Caucasians (dominant model: $P = .001$, OR = .61, 95% CI .46-.83; additive model: $P = .001$, OR = 1.65, 95% CI 1.21-2.24; allele model: $P = .005$, OR = .69, 95% CI .54-.89), while the −455 G/A polymorphism was only significantly correlated with the risk of IS in Asians (dominant model: $P < .0001$, OR = .65, 95% CI .55-.78; recessive model: $P = .002$, OR = 1.35, 95% CI 1.12-1.63; additive model: $P < .0001$, OR = 1.46, 95% CI 1.21-1.76; allele model: $P < .0001$, OR = .73, 95% CI .64-.83).

When we stratified available data according to types of disease, we found that both *FGβ* −148 C/T (dominant model: $P = .001$, OR = .72, 95% CI .59-.88; recessive model: $P = .001$, OR = 1.55, 95% CI 1.19-2.03; additive model: $P = .002$, OR = 1.24, 95% CI 1.08-1.42; allele model: $P = .0004$, OR = .76, 95% CI .66-.88) and −455 G/A

Table 1. *The characteristics of included studies for* FGβ *polymorphisms and IS*

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotype distribution		*P* value for HWE	NOS score
					Cases	Controls		
−148 C/T					CC/CT/TT			
Blake 2001	USA	Mixed	IS	209/751	137/67/5	468/243/40	.255	8
Cai 2003	China	Asian	CI	202/204	98/92/12	122/73/9	.643	7
Cui 2010	China	Asian	CI	92/98	36/48/8	56/37/5	.725	7
Fu 2006	China	Asian	CI	132/171	75/50/7	102/58/11	.483	7
Gao 2006	China	Asian	IS	100/100	54/32/14	68/25/7	.042	7
Huo 2016	China	Asian	CI	55/55	30/15/10	23/17/15	.006	7
Kumar 2017	India	Caucasian	IS	250/250	153/90/7	188/56/6	.459	8
Liang 2006	China	Asian	IS	160/130	55/90/15	71/52/7	.524	7
Liu 2002	China	Asian	CI	96/273	NA	NA	NA	7
Liu 2004	China	Asian	CI	90/102	NA	NA	NA	7
Liu 2008	China	Asian	CI	220/140	105/85/30	84/49/7	.966	8
Liu 2013	China	Asian	CI	135/65	64/59/12	42/19/4	.367	8
Luo 2015	China	Asian	IS	685/774	413/243/29	396/301/77	.079	8
Lv 2007	China	Asian	CI	147/130	71/63/13	79/45/6	.899	8
Ma 2006	China	Asian	CI	151/101	85/63/3	70/30/1	.252	8
Ou 2017	China	Asian	CI	225/221	116/90/19	114/98/9	.031	8
Pan 2005	China	Asian	CI	69/60	41/26/2	41/18/1	.535	7
Qian 2014	China	Asian	CI	102/90	66/30/6	43/39/8	.841	8
Rubattu 2005	Italy	Caucasian	IS	115/180	66/41/8	113/55/12	.147	7
Song 2005	China	Asian	CI	88/80	38/42/8	47/27/6	.449	8
Wang 2005	China	Asian	CI	160/162	101/47/12	112/42/8	.133	7
Xu 2005	China	Asian	IS	90/60	52/32/6	41/17/2	.884	8
Zhang 2003	China	Asian	CI	48/52	25/18/5	39/11/2	.302	7
Zhang 2012	China	Asian	IS	156/143	84/64/8	101/38/4	.852	8
Zhao 2006	China	Asian	CI	151/113	70/65/16	62/47/4	.169	8
-455 G/A					GG/GA/AA			
Bi 2004	China	Asian	IS	134/166	93/37/4	112/46/8	.259	7
Cai 2003	China	Asian	CI	202/204	98/92/12	122/73/9	.643	7
Chen 2006	China	Asian	CI	40/40	21/17/2	32/7/1	.434	7
Coen Herak 2017	Croatia	Caucasian	IS	73/100	36/33/4	42/51/7	.104	8
Cui 2010	China	Asian	CI	92/98	42/44/6	67/27/4	.547	7
Dong 2004	China	Asian	IS	86/90	54/27/5	74/12/4	.002	7
Fu 2005	China	Asian	IS	160/130	54/94/12	72/50/8	.861	7
Fu 2006	China	Asian	CI	132/171	79/50/3	94/68/9	.461	7
Gao 2009	China	Asian	CI	154/83	79/62/13	60/18/5	.039	8

(*continued on next page*)

Table 1 (*Continued*)

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotype distribution		*P* value for HWE	NOS score
					Cases	Controls		
Hu 2017	China	Asian	IS	479/580	271/172/36	382/177/21	.929	8
Kessler 1997	Germany	Caucasian	IS	219/218	129/79/11	109/102/7	.003	8
Kopyta 2015	Poland	Caucasian	IS	83/159	45/32/6	96/55/8	.973	7
Li 2001	China	Asian	IS	104/156	NA	NA	NA	7
Li 2007	China	Asian	CI	78/62	52/23/3	45/15/2	.594	8
Li 2008	China	Asian	IS	101/96	61/36/4	70/24/2	.973	8
Li 2009	China	Asian	CI	274/162	NA	NA	NA	7
Li 2009	China	Asian	CI	156/143	83/66/7	105/35/3	.967	8
Liu 2000	China	Asian	CI	91/74	60/30/1	60/13/1	.759	7
Liu 2002	China	Asian	CI	96/273	NA	NA	NA	7
Liu 2013	China	Asian	CI	135/65	79/45/11	45/16/4	.141	8
Luo 2015	China	Asian	IS	712/744	421/245/46	410/302/62	.542	8
Ma 2001	China	Asian	IS	294/279	185/96/13	175/92/12	.983	8
Nishiuma 1998	Japan	Asian	IS	85/84	NA	NA	NA	8
Ou 2017	China	Asian	CI	189/207	86/67/36	104/95/8	.015	8
Qian 2014	China	Asian	CI	90/102	46/36/8	70/26/6	.108	8
Tang 2010	China	Asian	CI	59/103	35/23/1	53/46/4	.117	7
Yang 2006	China	Asian	CI	108/123	55/43/10	76/42/5	.789	8
Yuan 2009	China	Asian	CI	114/1277	70/43/1	805/428/44	.158	7
Zhang 2012	China	Asian	IS	156/143	83/66/7	105/35/3	.967	8
Zhao 2005	China	Asian	CI	111/123	55/43/13	76/42/5	.789	8
Zhou 2004	China	Asian	CI	72/136	42/29/1	72/59/5	.089	7
Zhou 2010	China	Asian	CI	220/140	92/123/5	95/42/3	.507	8
Zhu 2008	China	Asian	CI	102/53	52/44/6	36/16/1	.607	7

Abbreviations: CI, Cerebral infarction; FGβ, β-fibrinogen; HWE, Hardy-Weinberg equilibrium; IS, Ischemic stroke; NA, Not available; NOS, Newcastle-Ottawa scale.

Table 2. *Overall and subgroup analyses for* FGβ *polymorphisms and IS*

Polymorphisms	Population	Sample size	Dominant comparison	Recessive comparison	Additive comparison	Allele comparison
			P value OR (95%CI)	*P* value OR (95%CI)	*P* value OR (95%CI)	*P* value OR (95%CI)
−148 C/T	Overall	3928/4505	**.0008** **.72 (.59-.87)**	.09 1.31 (.96-1.80)	**.0006** **1.29 (1.12-1.50)**	**.001** **.77 (.65-.90)**
	Asian	3354/3324	**.002** **.71 (.57-.88)**	**.05** **1.43 (1.01-2.03)**	**.002** **1.29 (1.10-1.52)**	**.002** **.75 (.63-.90)**
	Caucasian	365/430	**.001** **.61 (.46-.83)**	.80 1.10 (.54-2.23)	**.001** **1.65 (1.21-2.24)**	**.005** **.69 (.54-.89)**
	CI	2163/2117	**.001** **.72 (.59-.88)**	**.001** **1.55 (1.19-2.03)**	**.002** **1.24 (1.08-1.42)**	**.0004** **.76 (.66-.88)**
−455 G/A	Overall	5201/6584	**<.0001** **.69 (.58-.82)**	**.001** **1.34 (1.12-1.61)**	**.0004** **1.38 (1.15-1.65)**	**<.0001** **.75 (.67-.86)**
	Asian	4826/6107	**<.0001** **.65 (.55-.78)**	**.002** **1.35 (1.12-1.63)**	**<.0001** **1.46 (1.21-1.76)**	**<.0001** **.73 (.64-.83)**
	Caucasian	375/477	.19 1.20 (.91-1.58)	.42 1.29 (.69-2.41)	.09 .79 (.60-1.04)	.44 1.09 (.88-1.36)
	CI	2619/3795	**<.0001** **.65 (.55-.81)**	**.0003** **1.68 (1.27-2.23)**	**.0005** **1.49 (1.19-1.87)**	**<.0001** **.72 (.61-.85)**

Abbreviations: CI, Cerebral infarction; CI, Confidence interval; FGβ, β-fibrinogen; IS, Ischemic stroke; NA, Not available; OR, Odds ratio.
The values in bold represent that there are statistically significant differences between cases and controls.

(dominant model: $P < .0001$, OR = .65, 95% CI .55-.81; recessive model: $P = .0003$, OR = 1.68, 95% CI 1.27-2.23; additive model: $P = .0005$, OR = 1.49, 95% CI 1.19-1.87; allele model: $P < .0001$, OR = .72, 95% CI .61-.85) polymorphisms were significantly correlated with the risk of cerebral infarction (CI) (see Table 2).

Sensitivity Analyses

Sensitivity analyses were carried out to examine the stability of synthetic results by eliminating studies that deviated from HWE. No changes of results were observed in any comparisons, which indicated that our findings were statistically reliable.

Publication Biases

Potential publication biases were evaluated with funnel plots. No obvious asymmetry of funnel plots was observed in any comparisons, which suggested that our findings were unlikely to be influenced by severe publication biases.

Discussion

To the best of our knowledge, this is so far the most comprehensive meta-analysis on correlations between *FGβ* polymorphisms and IS. Significant associations with the risk of IS were detected for *FGβ* −148 C/T and −455 G/A polymorphisms in overall analyses. Further subgroup analyses according to ethnicities of participants revealed that the −148 C/T polymorphism was significantly correlated with the risk of IS in both Asians and Caucasians, while the −455 G/A polymorphism was only significantly correlated with the risk of IS in Asians. When we stratified available data according to types of disease, we found that both *FGβ* −148 C/T and −455 G/A polymorphisms were significantly correlated with the risk of CI. No any other positive results were found for investigated polymorphisms in overall and subgroup analyses. The stability of the synthetic results was subsequently evaluated in sensitivity analyses, and no changes of results were observed in any comparisons, which indicated that our findings were quite stable and reliable. As for evaluation of heterogeneities, obvious between-study heterogeneities were detected for *FGβ* −148 C/T and −455 G/A polymorphisms in certain comparisons (data not shown). But in further stratified analyses, a great reduction of heterogeneity was found in the Asian and CI subgroups, which suggested that differences in ethnic background and type of disease could partially explain observed heterogeneities between studies.

There are several points that need to be addressed about the current study. First, previous experimental studies have shown that mutant alleles of *FGβ* −148 C/T and −455 G/A polymorphisms were correlated with higher plasma fibrinogen levels, and this may explain positive findings in current meta-analysis.[8,9] Second, the pathogenic mechanism of IS is highly complex, and hence it is unlikely that a single *FGβ* gene polymorphism can significantly contribute to its development. The significant correlations detected between *FGβ* gene polymorphisms and the risk of IS in our meta-analysis may be attributed to a higher plasma fibrinogen level. However, it is also possible that investigated polymorphisms could modify the individual susceptibility to well-established risk factors of IS, such as hypertension, hyperlipidemia, and diabetes. Therefore, to better illustrate potential correlations of certain gene polymorphisms with IS, we strongly recommend further studies to perform haplotype analyses and explore potential gene-gene interactions.

As with all meta-analysis, this study certainly has some limitations. First, our results were based on unadjusted estimations due to lack of raw data, and failure to perform further adjusted analyses for age, gender, and co-morbidity conditions may impact the reliability of our findings.[16] Second, obvious heterogeneities were detected in certain subgroup comparisons, which indicated that the inconsistent results of included studies could not be fully explained by differences in ethnic background or type of disease, and other unmeasured characteristics of participants may also partially attribute to between-study heterogeneities.[17] Third, associations between *FGβ* polymorphisms and IS may also be influenced by gene-gene and gene-environmental interactions.[18] However, the majority of studies did not consider these potential interactions, which impeded us to perform relevant analyses accordingly. Taken these limitations into consideration, the results of the current study should be interpreted with caution.

Overall, our meta-analysis suggested that *FGβ* −148 C/T and −455 G/A polymorphisms may serve as potential biological markers for IS in Asians. Moreover, the *FGβ* −148 C/T polymorphism may also serve as a potential biological marker for IS in Caucasians. However, further well-designed studies, especially in Caucasians, are still warranted to confirm our findings. Additionally, future investigations are needed to explore potential roles of other *FGβ* polymorphisms in the development of IS.

Authors' Contributions

Hailong Luo, Xin Li, and Yanqin Guo conceived of the study, participated in its design. Hailong Luo and Xin Li conducted the systematic literature review. Aiying Jiang, Benzhuo Zhang, Pengxiang Bi, and Yan Dong performed data analyses. Hailong Luo, Xin Li, and Yanqin Guo drafted the manuscript. All authors have read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

Compliance with Ethical Standards

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent

For this type of study, formal consent is not required.

Acknowledgments: None.

References

1. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386:743-800.
2. Markus HS, Bevan S. Mechanisms and treatment of ischaemic stroke—insights from genetic associations. Nat Rev Neurol 2014;10:723-730.
3. Kopyta I, Sarecka-Hujar B, Sordyl J, et al. The role of genetic risk factors in arterial ischemic stroke in pediatric and adult patients: a critical review. Mol Biol Rep 2014;41:4241-4251.
4. Meschia JF, Worrall BB, Rich SS. Genetic susceptibility to ischemic stroke. Nat Rev Neurol 2011;7:369-378.
5. Chauhan G, Debette S. Genetic risk factors for ischemic and hemorrhagic stroke. Curr Cardiol Rep 2016;18:124.
6. Aleman MM, Walton BL, Byrnes JR, et al. Fibrinogen and red blood cells in venous thrombosis. Thromb Res 2014;133(Suppl 1):S38-S40.
7. Fish RJ, Neerman-Arbez M. Fibrinogen gene regulation. Thromb Haemost 2012;108:419-426.
8. Cook DG, Cappuccio FP, Atkinson RW, et al. Ethnic differences in fibrinogen levels: the role of environmental factors and the beta-fibrinogen gene. Am J Epidemiol 2001;153:799-806.
9. Yuan XD, Wang SJ, Xu YR, et al. Relationship between multi-locus fibrinogen polymorphisms and fibrinogen concentration, molecular reactivity and cerebral infarction. Zhonghua Xue Ye Xue Za Zhi 2009;30:582-587.
10. Blake GJ, Schmitz C, Lindpaintner K, et al. Mutation in the promoter region of the beta-fibrinogen gene and the risk of future myocardial infarction, stroke and venous thrombosis. Eur Heart J 2001;22:2262-2266.
11. Coen Herak D, Lenicek Krleza J, Radic Antolic M, et al. Association of polymorphisms in coagulation factor genes and enzymes of homocysteine metabolism with arterial ischemic stroke in children. Clin Appl Thromb Hemost 2017;23:1042-1051.
12. Kopyta I, Niemiec P, Balcerzyk A, et al. Fibrinogen alpha and beta gene polymorphisms in pediatric stroke—case-control and family based study. Eur J Paediatr Neurol 2015;19:176-180.
13. Kumar A, Misra S, Kumar P, et al. Association between beta-fibrinogen C148T gene polymorphism and risk of ischemic stroke in a north Indian population: a case-control study. Pulse 2017;4:165-171.
14. Moher D, Liberati A, Tetzlaff J, et al. PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264-269.
15. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-605.
16. Xie X, Shi X, Liu M. The roles of TLR gene polymorphisms in atherosclerosis: a systematic review and meta-analysis of 35,317 subjects. Scand J Immunol 2017;86:50-58.
17. Xie X, Shi X, Xun X, et al. Endothelial nitric oxide synthase gene single nucleotide polymorphisms and the risk of hypertension: a meta-analysis involving 63,258 subjects. Clin Exp Hypertens 2017;39:175-182.
18. Shi X, Xie X, Jia Y, et al. Associations of insulin receptor and insulin receptor substrates genetic polymorphisms with polycystic ovary syndrome: a systematic review and meta-analysis. J Obstet Gynaecol Res 2016;42:844-854.