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Association between *GABRG2* rs211037 polymorphism and febrile seizures: a meta-analysis

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Abstract

Background: Emerging evidence has implied that the *GABRG2* gene play a role in the mechanism of febrile seizure (FS), however, the relationship between *GABRG2* rs211037 polymorphism and the risk of FS remains controversial. This meta-analysis was conducted to investigate the relationship of *GABRG2* rs211037 polymorphism with the susceptibility to FS.

Methods: MEDLINE, Embase, Cochrane Library and CNKI databases were searched (until April 6, 2019) for eligible studies on the relationship between *GABRG2* rs211037 polymorphism and FS. We calculated the odds ratios (ORs) by a fixed or random model with the STATA 15.0 software. Subgroup analyses for the ethnicity, the source of the control, and age and sex matching of controls were conducted.

Results: A total of 8 studies consisting of 775 FS patients and 5162 controls were included in this study. Based on the overall data, he *GABRG2* rs211037 polymorphism was not significantly associated with the risk of FS (TT + CT vs CC: OR = 0.95, 95%CI 0.64–1.41, $P = 0.80$). Notably, the *GABRG2* rs211037 variant was significantly associated with decreased risk of FS in Asian populations (TT vs CT + CC: OR = 0.63, 95%CI 0.45–0.88, $P = 0.006$), but increased risk in Caucasian populations (CT vs CC: OR = 1.56, 95%CI 1.14–2.15, $P = 0.006$). Significant associations were also detected when healthy controls out of the whole controls were employed for comparison (TT vs CT + CC: OR = 0.59, 95% CI 0.45–0.77, $P < 0.001$) and when data from studies with age- and sex-matched controls were used (TT + CT vs CC: OR = 0.60, 95% CI 0.43–0.86, $P = 0.001$).

Conclusion: The *GABRG2* rs211037 polymorphism may decrease the risk of FS in Asian populations, while increasing the risk in Caucasian populations. Further well-designed studies with large sample sizes are essential to verify the conclusions in other ethnicities.

Keywords: *GABRG2*, rs211037, Febrile seizure, Polymorphism

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Background

Febrile seizure (FS) is a type of seizure related with fever, but the causes and mechanisms of FS remain to be determined. As the most common seizure subtype in children, FS affects 2–5% of children, especially those younger than 5 years [1]. Although the exact pathogenesis of FS remains obscure, genetic factors may act as an important factor [2].

The gamma-aminobutyric acid type A (GABAA) receptor (GABAAR) contains mainly α, β and γ subunits and mediates a great many inhibitory neurotransmission in the brain [3, 4]. The γ2 subunit is vital for postsynaptic clustering and synaptic maintenance of GABAARs by affecting the kinetics of the GABAAR channels [5–7]. Mutations in the *GABRG2* gene could produce a nonfunctioning or clipped γ protein, thereby disturbing subunit assembly, reducing the expression of surface receptor, decreasing the GABAergic inhibitory effect, and finally inducing epileptogenesis [8, 9]. Previous studies have revealed several epilepsy risk variants of *GABRG2*, among which the rs211037 variant has attracted much attention. The *GABRG2* rs211037 variant can disturb the expression levels of the GABAAR subunits by influencing transcription, mRNA stability, and translation efficiency, resulting in varied sensitivity to extrinsic environmental signals [10].

The relation between *GABRG2* rs211037 polymorphism and the risk of FS has been investigated in previous studies. Haerian et al. conducted a meta-analysis to investigate the relationship between the *GABRG2* gene polymorphism and epilepsy, and indicated that rs211037 was associated with FS in Asians. Nevertheless, the number of included articles was relatively small, so it may be underpowered to verify the association. Although several new studies have been published recently [11–14], some important factors, including the type of control, the

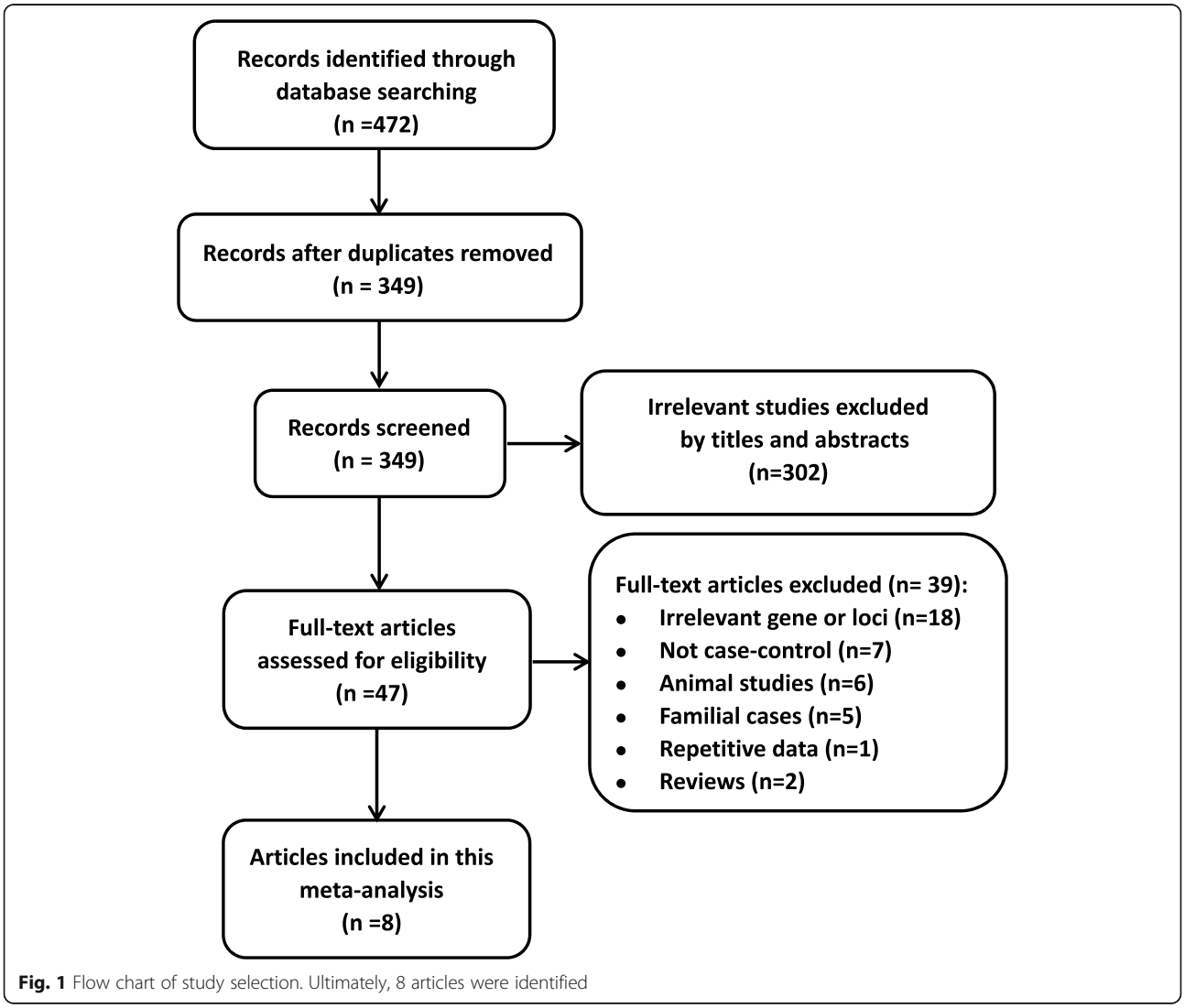

Fig. 1 Flow chart of study selection. Ultimately, 8 articles were identified

Table 1 Baseline characteristics of eligible case-control studies

Author	Year	Country/Region	Ethnicity	Genotyping method	Control	Matched control	HWE	Total	Case	Control
Abdel	2012	Egypt	Mixed	PCR-RFLP	Healthy	Yes	Yes	220	100	120
Balan	2013	India	Mixed	AS-PCR	MTLE-HS without FS	Yes	Yes	203	138	65
Butila	2018	Romania	Caucasian	PCR-RFLP	Patients	No	Yes	207	54	153
Chou	2003	Mainland of China	Asian	PCR-RFLP	Healthy	No	Yes	186	103	83
Haerian	2015	Hong Kong, China	Asian	MassARRAY	Healthy	Yes	Yes	2894	50	2844
Haerian	2015	Malaysia (Chinese)	Asian	MassARRAY	Healthy	Yes	Yes	494	17	477
Haerian	2015	Malaysia (Malay)	Asian	MassARRAY	Healthy	Yes	Yes	370	11	359
Haerian	2015	Malaysia (Indian)	Asian	MassARRAY	Healthy	Yes	Yes	244	2	242
Kinirons A	2006	United Kingdom	Caucasian	tSNP	Healthy	No	Yes	414	84	330
Kinirons B	2006	Ireland	Caucasian	tSNP	Healthy	No	Yes	363	80	283
Nakayama	2003	Japan	Asian	DHPLC	Healthy	No	Yes	200	94	106
Ponnala	2012	India	Mixed	PCR-RFLP	Healthy or patients	No	Yes	186	86	100

AS-PCR Allele-specific polymerase chain reaction, *DHPLC* denaturing high-performance liquid chromatography, *MassARRAY* matrixassisted laser desorption/ionization time of flight mass spectrometry, *MTLE-HS* mesial temporal lobe epilepsy with hippocampal sclerosis, *NA* not available, *PCR-RFLP* polymerase chain reaction-restriction fragment length polymorphism, *RT-PCR* reverse transcription- polymerase chain reaction, *tSNP* a tagging single nucleotide polymorphism

matching criteria of control and the consistency of Hardy-Weinberg equilibrium (HWE) were not considered in subgroup analysis. On account of the important role of the GABRG2 rs211037 polymorphisms in FS, we carried out this meta-analysis to strengthen the statistical power and further identify the association.

Methods

Literature search strategy

Studies related to the relation of *GABRG2* rs211037 polymorphism with FS were searched in the MEDLINE, Embase, Cochrane Library and CNKI databases until April 6, 2019. The following search terms were used: ('febrile seizure'), ('GABRG2') and ('polymorphism' OR 'variant' OR 'mutation'). No language restriction was set on the literature search. Furthermore, we conducted a manual search from the references of reviews and eligible studies.

Table 2 Genotypes of *GABRG2* rs211037 polymorphism

Author	Year	Case				Control			
		n	TT	CT	CC	*n*	TT	CT	CC
Abdel	2012	100	32	42	26	120	62	46	12
Balan	2013	138	3	40	95	65	4	17	44
Butila	2018	54	18	24	12	153	17	57	79
Chou	2003	103	31	55	17	83	42	32	9
Haerian	2015	50	11	29	10	2844	1063	1387	394
Haerian	2015	17	7	5	5	477	184	227	66
Haerian	2015	11	4	5	2	359	105	163	91
Haerian	2015	2	0	0	2	242	21	94	127
Kinirons A	2006	84	3	35	46	330	13	114	203
Kinirons B	2006	80	2	35	43	283	14	99	170
Nakayama	2003	94	20	50	24	106	25	58	23
Ponnala	2012	41	1	8	32	100	1	12	87

n, total number

Inclusion and exclusion criteria

Xiaohui Yang and Jing Chi screened each eligible study independently, and Xiaosa Chi would rejudge the study if any disagreement. The inclusion criteria of publications were as follows: (1) assessing the association between *GABRG2* rs211037 variants and FS; (2) genotype frequency data of both case and control groups were available; (3) having a case-control design; and (4) English or Chinese publications. Accordingly, the exclusion criteria were as follows: (1) providing insufficient genotype information; (2) animal studies or experiments in vitro; (3) family-based or linkage studies; (4) reviews and conference abstracts; and (5) case reports or lacking a control group. Besides, articles including subjects at the same hospital during overlapping times were regarded as duplications, and only the study with the largest sample size was included for analysis.

Data extraction

Two authors (Xiaohui Yang and Xiaomeng Wang) extracted the baseline data from the included studies seperately and repeatedly, and any discrepancies were figured out by discussion. We extracted the following information from each article: first author, year of publication, country, ethnicity of the subjects, source of controls (healthy control or patients), matching criteria of controls (age-, sex-matched or not), HWE of controls, study period, genotyping methods, quality of control, numbers of cases and controls, and frequencies of genotype.

Statistical analysis

We assessed the strength of the correlation between *GABRG2* rs211037 polymorphism and the risk of FS by

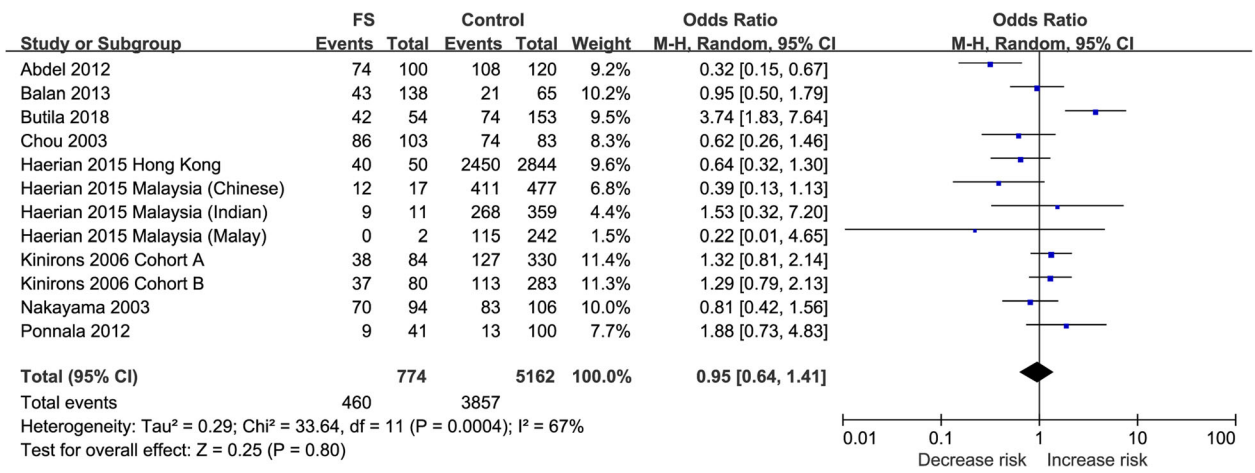

Fig. 2 Forest plot of the relationship between the *GABRG2* rs211037 polymorphism and risk of FS. No significant association was observed

the pooled OR and corresponding 95% CI, using dominant model (TT + CT vs CC), recessive model (TT vs CT + CC), and other genetic models (TT vs CC, CT vs CC, and T vs C). Furthermore, subgroup-analyses were stratified by ethnicity, source of the control (non-FS or healthy control) and the matching criteria in controls (age-, sex-matched or not). We calculated the pooled OR using the Z test, and regarded $P < 0.05$ as statistical significance.

We used Cochran's Q test and the I^2 statistic to estimate the inter-study heterogeneity among the eligible studies, and regarded $I^2 \geq 50\%$ as statistical significance. In this condition, the random-effects model was applied to calculate the pooled OR. Otherwise, the fixed-effects model was applied. Moreover, publication bias was evaluated using visual inspection of Funnel plot which was obtained from Begg's test. All data were calculated and analyzed with the STATA software (version 15.0; Stata Corp, College Station, Texas).

Results

Study selection

Altogether 472 potentially related articles were yielded at the initial database search, and 349 were left after duplicate removal (Fig. 1). After manual screening by titles and abstracts, 302 studies were excluded according to the exclusion criteria. Forty-seven full-text studies were used for further evaluation. Ultimately, 8 eligible studies consisting of 5937 subjects (775 FS patients and 5162 controls) were included in this study [11–18]. The detailed information of all included studies are present in Table 1. The genotype distributions of *GABRG2* rs211037 polymorphism of included studies are shown in Table 2.

Quantitative data analysis

Overall, we found no significant relationship between the *GABRG2* rs211037 polymorphism (TT + CT vs CC) and the risk of FS (dominant model, OR = 0.95, 95%CI 0.64–1.41, $P = 0.80$, Fig. 2). Nevertheless, when stratifying the subjects by ethnicity, the *GABRG2* rs211037 polymorphism (TT vs CT + CC) was significantly related to decreased risk of FS in Asian patients (recessive model, OR = 0.63, 95%CI 0.45–0.88, $P = 0.006$, Fig. 3). As to the Caucasian patients, the *GABRG2* rs211037 polymorphism (CT vs CC) was significantly related to

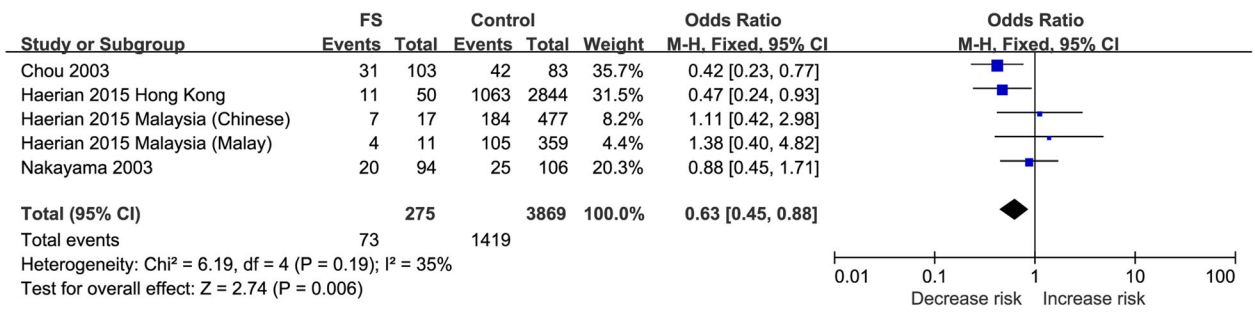

Fig. 3 Forest plot of subgroup analysis in Asian populations. The *GABRG2* rs211037 polymorphism was significantly related to decreased risk of FS in Asian populations

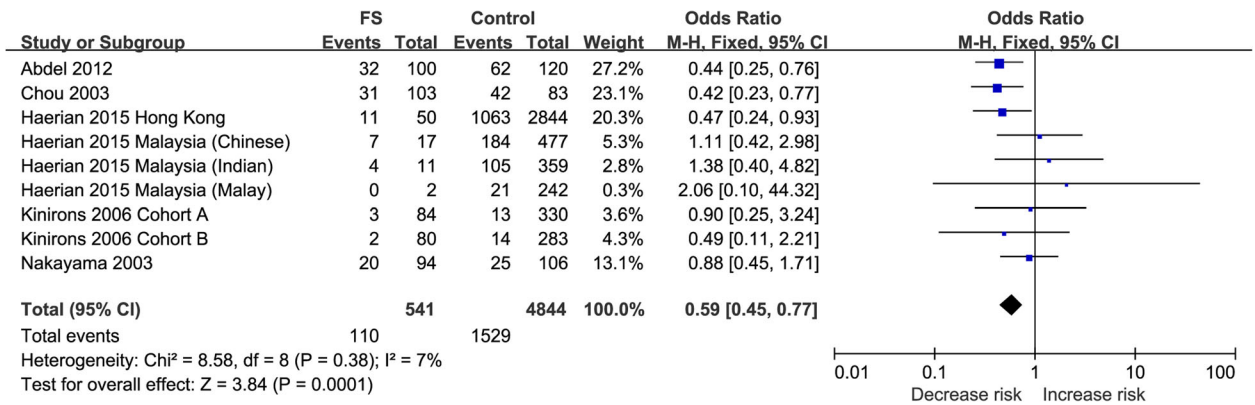

Fig. 4 Forest plot of subgroup analysis in healthy controls. The *GABRG2* rs211037 polymorphism was significantly related to the risk of FS in healthy controls

increased risk of FS (OR = 1.56, 95%CI 1.14–2.15, P = 0.006, Table 3).

To eliminate the potential confounding factors in the control group, we conducted stratified analyses for healthy control subjects and age-, sex-matched controls. We found a significant relation between *GABRG2* rs211037 polymorphism and the susceptibility to FS when healthy controls were employed for comparison (recessive model, OR = 0.59, 95% CI 0.45–0.77, $P < 0.001$, Fig. 4). When analysis was performed using data from studies with age and sex matched controls, significant association was detected between the *GABRG2* rs211037 variant (CT + TT vs CC) and the susceptibility to FS (dominant model, OR = 0.60, 95% CI 0.43–0.86, P = 0.005, Table 3).

Publication bias

The symmetrical Begg's funnel plot indicated that there was no publication bias among included studies (Fig. 5). Quantitative evaluation by Egger's test also demonstrated no publication bias ($t = 0.70$, $P = 0.497$).

Discussion

Evidence is emerging that the *GABRG2* gene is implicated in the mechanisms of FS, however, the relationship between *GABRG2* rs211037 polymorphism and the risk of FS is still controversial. Previous meta-analysis studies have demonstrated that the *GABRG2* rs211037 polymorphisms is significantly relative to the risk of FS, but they are limited by small sample sizes. Thus, we conducted this meta-analysis to further explore the relationship.

Different from the previous meta-analyses, we found that *GABRG2* rs211037 polymorphism was not significantly related to the risk of FS using data combining all ethnicities. However, the *GABRG2* rs211037 polymorphism was significantly related to decreased risk of FS in Asian populations, but increased risk of FS in Caucasian populations. This suggested that ethnicity could modify

Table 3 Stratified analysis of the association between *GABRG2* rs211037 polymorphism and FS

Variable	n^a	TT + CT vs CC		TT vs CT + CC		TT vs CC		CT vs CC		T vs C	
		OR (95%CI)	P_{het}	OR (95%CI)	P_{het}	OR (95%CI)	P_{het}	OR (95%CI)	P_{het}	OR (95%CI)	P_{het}
Total	12	0.95 (0.64, 1.41)	< 0.001	0.82 (0.50, 1.32)	< 0.001	0.76 (0.39,1.46)	< 0.001	1.05 (0.76,1.44)	0.04	0.95 (0.69, 1.32)	< 0.001
Ethnicity											
Asian	5	0.70 (0.48, 1.02)	0.65	0.63 (0.45, 0.88)	0.19	0.56 (0.36,0.87)	0.5	0.79 (0.53, 1.18)	0.57	0.73 (0.59, 0.90)	0.34
Caucasian	3	1.76 (0.97, 3.17)	0.03	1.36 (0.35, 5.27)	0.02	1.73 (0.34,8.78)	< 0.001	1.56 (1.14, 2.15)	0.27	1.57 (0.87, 2.83)	0.003
Healthy control											
Yes	9	0.76 (0.51, 1.12)	0.03	0.59 (0.45, 0.77)	0.38	0.50 (0.35,0.71)	0.41	0.96 (0.75, 1.24)	0.13	0.79 (0.61, 1.02)	0.01
No	3	1.86 (0.78, 4.43)	0.02	1.52 (0.25, 9.11)	0.02	1.92 (0.22,16.68)	0.004	1.67 (1.07, 2.61)	0.2	1.66 (0.71, 3.88)	0.002
Matched controls											
Yes	6	0.60 (0.43, 0.86)	0.2	0.56 (0.39, 0.80)	0.31	0.40 (0.25, 0.63)	0.41	0.71 (0.49, 1.04)	0.28	0.64 (0.52, 0.80)	0.23
No	6	1.35 (0.86, 2.11)	0.02	1.01 (0.43, 2.36)	< 0.001	1.16 (0.41, 3.22)	< 0.001	1.37 (1.05,1.78)	0.27	1.21 (0.77, 1.91)	< 0.001

CI confidence interval, *OR* odds ratio, *Phet* *P* value of Q test for heterogeneity test
[a]Number of datasets included in the meta-analysis

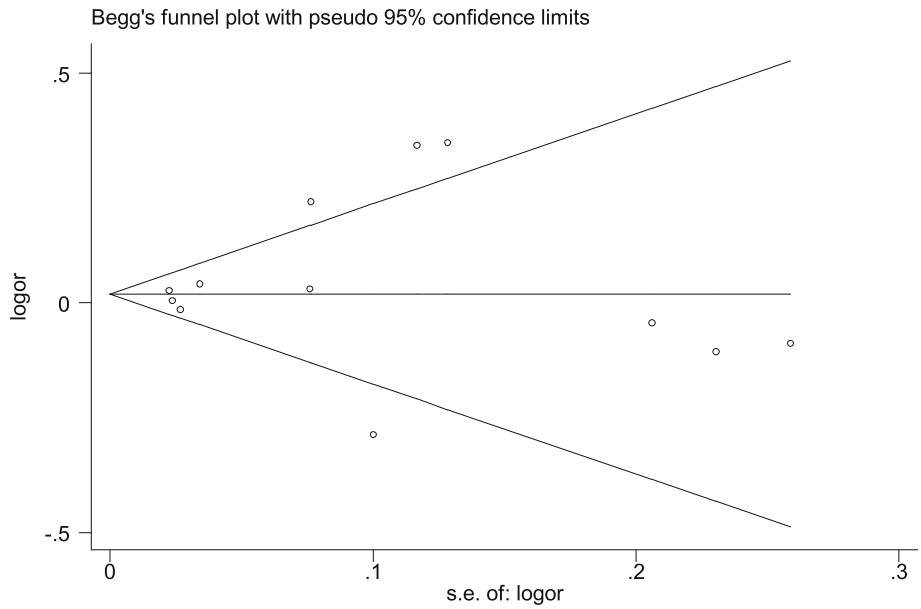

Fig. 5 Begg's funnel plot. The funnel plot suggested absent of publication bias among the eligible studies

the impact of the *GABRG2* gene on the risk of FS. In addition, the *GABRG2* rs211037 polymorphism was associated with decreased risk of FS when healthy controls out of the whole controls were used for comparison.

The γ2 subunit is the major component of GABAAR, and its decrease is reported to affect the phasic or synaptic transmission [19–22]. Studies about cultured hippocampal neurons indicated that the relation of γ2 subunit mutations with FS may be due to the decreased expression of mutant GABAAR on the synaptic surface [23]. In a family with febrile seizures and a *GABRG2* variant R43Q, resting-state fMRI revealed increased functional connectivity within the somatosensory cortex, as compared to the age-matched controls [24]. Besides, *GABRG2* variants may affect the function and expression of several epilepsy-related genes [25]. Thus, mutations in *GABRG2* have been proposed as candidates of FS susceptibility genes. The *GABRG2* rs211037 polymorphism may affect the expression of GABAAR subunits, modify the receptor composition, influence the reaction to extrinsic environmental signals, and eventually alter the neuroinflammatory pathway in FS [10, 26, 27]. In our study, the *GABRG2* rs211037 polymorphism may be a protective factor for FS and play a role in the mechanisms of FS.

However, the results should be explained with caution due to the following limitations. First, relevant studies in other databases may be missed out. Second, stratified studies were not performed in Africans due to limited data. Therefore, our results need to be further verified in Africans. Third, the analysis of gene-gene and loci-loci interactions was not conducted on account of the insufficient data.

Conclusions

In conclusion, the current study indicated that the *GABRG2* rs211037 polymorphism is significantly related to decreased risk of FS compared to healthy control. The *GABRG2* rs211037 polymorphism might diversely contribute to the risk of FS in different ethnicities. Further studies are essential to verify the conclusions and reveal the underlying mechanisms.

Abbreviations

AS-PCR: Allele-specific polymerase chain reaction; CI: Confidence interval; FS: Febrile seizure; DHPLC: Denaturing high-performance liquid chromatography; HWE: Hardy-Weinberg equilibrium; MassARRAY: Matrixassisted laser desorption/ionization time of flight mass spectrometry; MTLE-HS: Mesial temporal lobe epilepsy with hippocampal sclerosis; OR: Odds ratio; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; RT-PCR: Reverse transcription- polymerase chain reaction; tSNP: a tagging single nucleotide polymorphism

Acknowledgements

None.

Authors' contributions

MYJ and CXS designed the study, interpreted the data and revised the study. YXH and CJ conducted the systematic search and extracted the eligible studies. YXH and WXM extracted and analyzed the data. WHY and ZXP analyzed the data. YXH, HY and HS interpreted the data. YXH drafted the manuscript. All the authors approved the final manuscript.

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Availability of data and materials
The datasets in this study are present in Tables.

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors consented to publish this study.

Competing interests
The authors declare no conflicts of interest.

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