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Association between *GABRG2* rs211037 polymorphism and idiopathic generalized epilepsies: a meta-analysis

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Abstract

Background: We performed this meta-analysis to investigate the association between *GABRG2* rs211037polymorphism and the risk for idiopathic generalized epilepsies (IGEs).

Methods: Medline, Embase, Cochrane Library and Chinese National Knowledge Infrastructure (CNKI) databases were searched for eligible studies (until May 5, 2020) on the association between *GABRG2* rs211037 polymorphism and IGE. The odds ratios were calculated using a fixed or random model in STATA 15.0 software. Subgroup analyses for ethnicity, age, source of controls, type of seizure syndrome and therapeutic responses were conducted.

Results: We found no significant associations between *GABRG2* rs211037 polymorphism and the susceptibility to IGEs. In addition, no significant association was detected between *GABRG2* rs211037 polymorphism and drug resistance in IGE patients. The results did not change after stratification by Asian population, healthy controls, children, juvenile myoclonic epilepsy, and childhood absence epilepsy.

Conclusion: The current studies indicated that the *GABRG2* rs211037 polymorphism was not related to susceptibility or drug resistance of IGE. Further well-designed studies are needed to verify the results.

Keywords: GABRG2, rs211037, Idiopathic generalized epilepsies, Polymorphism

Background

Idiopathic generalized epilepsies (IGEs) are featured by recurring generalized seizures without intracranial lesions [1], affecting 0.3% of the general population and accounting for 30% of all epilepsy disorders [1]. Epilepsy with generalized tonic clonic seizures (EGTCS), childhood absence epilepsy (CAE), juvenile myoclonic epilepsy (JME) and juvenile absence epilepsy (JAE) and were common syndromes of IGEs [2]. The causes of IGE are highly heterogeneous and genetic factors seem to be an important one.

Previous studies indicated that disruption of the gamma-amino butyric acid (GABA)-mediated inhibitory neurotransmission results in neuronal hyperexcitability, which is proved to participate in epileptogenesis [3–5]. Genetic alterations can influence channel function, increase neuronal excitability and induce neuronal networks into synchronous activity, and lead to in epileptic seizures [6]. Recent studies have identified *GABRG2* genetic variants in relation with increased risk of epilepsy, of which rs211037 (C588T) is receiving much attention [7]. The *GABRG2* rs211037 variant may alter the transcription and translation efficiency of GABAA receptor subunits, modify the composition of receptor, and influence the sensitivity to extrinsic environmental signals [8].

The association between *GABRG2* rs211037 polymorphism and the risk for IGE have been investigated in several studies. Nevertheless, the results are inconsistent. Haerian BS et.al. conducted a meta-analysis with 4

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studies included and found no significant association between *GABRG2* rs211037 and the susceptibility to IGEs [7]. However, several studies investigating the association between *GABRG2* rs211037 and IGEs since 2003. In the study, we performed an updated meta-analysis to assess the relationship between *GABRG2* rs211037 and IGEs.

Methods

Literature search strategy

Eligible studies were searched in the databases of Medline, Embase, Wanfang, Cochrane Library and Chinese National Knowledge Infrastructure (CNKI) (until May 2020) using the following search keywords: 'epilepsy' OR 'seizure', 'polymorphism' OR 'variant' OR 'mutation', and '*GABARG2*'. In addition, we searched the references of reviews and relevant studies. This meta-analysis was conducted according to Meta-analysis for Observational Studies in Epidemiology guidelines.

Inclusion and exclusion criteria

Two authors (Xiaohui Yang and Hongyun Wei) screened each eligible article independently, and a third author (Xiaosa Chi) would rejudge the article in case of any disagreement. The study inclusion criteria were: (1) assessing the relation between *GABRG2* rs211037 polymorphism and IGEs; (2) case-control or cohort study; (3) providing sufficient data on genotype distributions; and (4) in English or Chinese language. Studies were excluded if they: (1) are reviews and meeting abstracts; (2) did not report sufficient data; and (3) are animal studies or in vitro experiments.

Data extraction

Baseline information were extracted in duplicates from all of the eligible studies by Xiaohui Yang and Hongyun Wei independently, and any dispute was figured out by discussion. The extracted data included: name of the

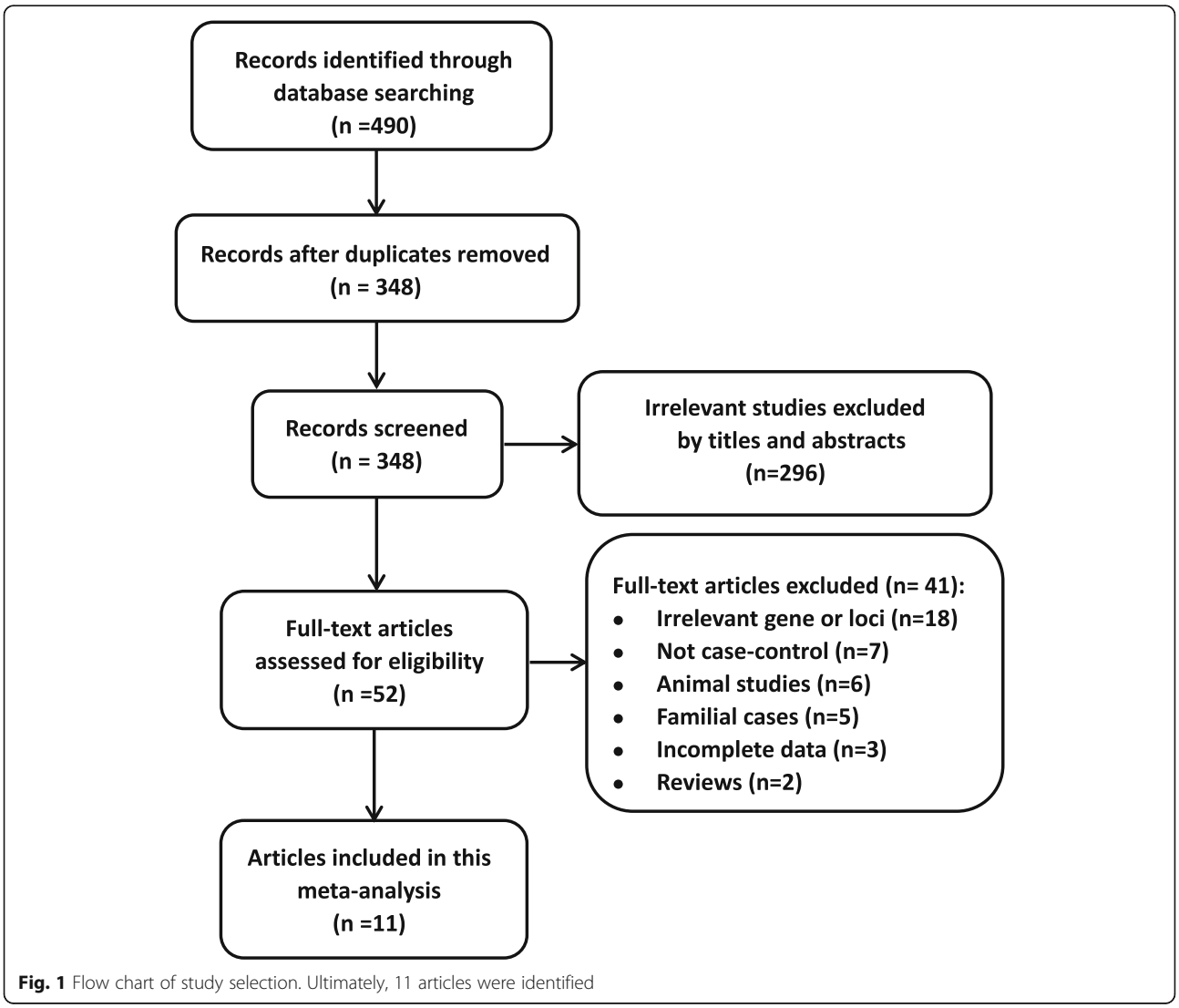

Fig. 1 Flow chart of study selection. Ultimately, 11 articles were identified

Table 1 Baseline characteristic of eligible case-control studies

Author	Year	Country	Ethnity	Type of epilepsy	Genotyping Methods	Control	Total	Case	Control
Abou [9]	2018	Egypt	Asian	IGE	PCR-RFLP	healthy	210	100	110
Balan [10]	2013	India	Asian	JME	AS-PCR	healthy	500	235	265
Bhat [11]	2018	India	Asian	JME	PCR-RFLP	healthy	150	50	100
Butila [12]	2018	Romania	Caucasians	IGE	PCR-RFLP	patients	213	60	153
Chou [13]	2007	China	Asian	IGE	PCR-RFLP	healthy	160	77	83
Gitai [14]	2012	Brazil	Mixed	JME	PCR-RFLP	healthy	228	98	130
Haerian [15]	2015	Malaysia	Asian	IGE	MassARRAY	healthy	1,254	176	1,078
Kananura [16]	2002	Germany	Caucasian	CAE	RT-PCR	healthy	289	135	154
Kim [17]	2012	Korean	Asian	CAE	PCR	healthy	242	35	207
Kinirons A [18]	2006	UK	NA	IGE	tSNP	healthy	408	78	330
Kinirons B [18]	2006	Ireland	NA	IGE	tSNP	healthy	400	117	283
Ponnala [19]	2012	India	Asian	IGE	PCR-RFLP	healthy or patients	186	86	100

AS-PCR Allele-specific polymerase chain reaction, *CAE* childhood absence epilepsy, *IGE* childhood idiopathic generalized epilepsy, *JME* Juvenile myoclonic epilepsy, *MassARRAY* matrixassisted laser desorption/ionization time of flight mass spectrometry, *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

first author, publication year, country of origin, ethnicity, source of cases and controls, study period, genotyping methods, quality control, the numbers of cases and controls, and frequencies of genotype.

Statistical analysis

We calculate the pooled odds ratios (ORs) and corresponding 95%CI to estimate the strength of association between *GABRG2* rs211037 polymorphism and the risk for IGE. The dominant model, recessive model, co-dominant model and allele model were conducted to evaluate the association. In addition, subgroup analyses were conducted for ethnicity, age, source of control (non-IGE or healthy control), JME, CAE, and drug resistance. We calculated Z test to evaluate the significance of pooled ORs, and regarded $P < 0.05$ as statistically significant.

We evaluated the inter-study heterogeneity by Cochran's Q test and I^2 statistic. $I^2 \geq 50\%$ was considered as statistically significant. In this condition, the random-effects model was applied to count 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 was analyzed with STATA (version 15.0; Stata Corp, College Station, TX).

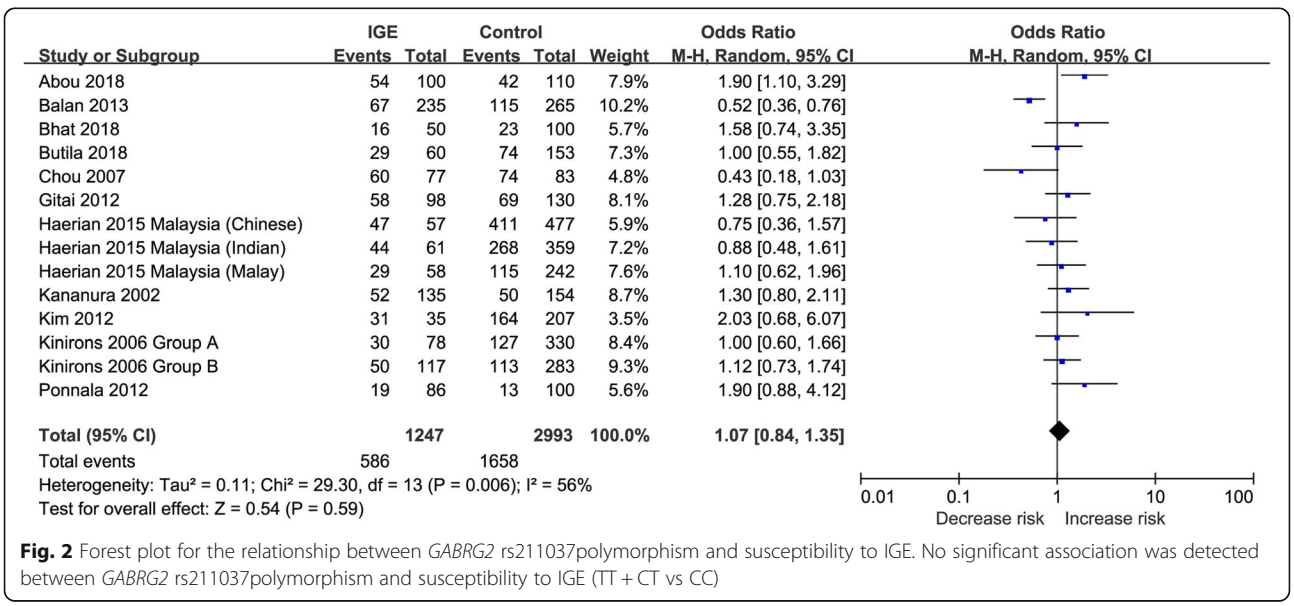

Fig. 2 Forest plot for the relationship between *GABRG2* rs211037polymorphism and susceptibility to IGE. No significant association was detected between *GABRG2* rs211037polymorphism and susceptibility to IGE (TT + CT vs CC)

Table 2 Stratified analysis of *GABRG2* rs211037 polymorphism on IGE

Variables	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	1.07 [0.84, 1.35]	0.006	1.04 [0.72, 1.49]	0.007	1.10 [0.73, 1.67]	0.005	0.99 [0.84, 1.16]	0.070	1.06 [0.87, 1.31]	< 0.001
Ethnicity										
Asian	1.04 [0.70, 1.55]	< 0.001	1.10 [0.69, 1.74]	0.005	1.15 [0.65, 2.02]	0.003	0.95 [0.67, 1.36]	0.030	1.06 [0.77, 1.47]	< 0.001
Healthy control	1.15 [0.97, 1.38]	0.250	1.11 [0.73, 1.68]	0.003	1.16 [0.72, 1.87]	0.004	1.12 [0.93, 1.36]	0.240	1.10 [0.89, 1.35]	0.003
JME	0.97 [0.47, 2.02]	0.004	1.36 [0.86, 2.15]	0.190	1.30 [0.61, 2.75]	0.080	0.72 [0.36, 1.44]	0.060	1.08 [0.57, 2.04]	< 0.001
CAE	1.42 [0.92, 2.20]	0.470	1.05 [0.57, 1.94]	0.400	1.30 [0.59, 2.86]	0.520	1.49 [0.94, 2.37]	0.590	1.23 [0.89, 1.69]	0.630
Children	1.19 [0.76, 1.88]	0.050	0.98 [0.44, 2.20]	0.006	1.14 [0.40, 3.27]	0.002	1.28 [0.96, 1.72]	0.460	1.07 [0.68, 1.69]	< 0.001
Drug resistance	1.64 [0.87, 3.07]	0.002	1.97 [0.57, 6.79]	0.020	2.84 [0.61, 13.25]	0.002	1.41 [0.84, 2.37]	0.040	1.70 [0.93, 3.11]	< 0.001

CAE childhood absence epilepsy, *JME* Juvenile myoclonic epilepsy; P_{het} *P* value of Q-test for heterogeneity

Results

Study selection

Altogether, 490 records were yielded by the initial search, leaving 348 after duplicate removal. After manual screening by titles and abstracts, 52 papers were selected (Fig. 1). Fifty two full-text studies were used for further evaluation, and eventually, 11 articles were included [9–19]. Finally, 1,161 IGE patients and 2,993 controls were included in the meta-analysis. The detailed information of included studies is presented in Table 1.

GABRG2 rs211037polymorphism and susceptibility to IGE

No significant association was detected between *GABRG2* rs211037 polymorphism and the risk of IGE (TT + CT vs CC: OR = 1.07, 95%CI = 0.84–1.35, *P* = 0.006, Fig. 2). Further subgroup analysis also showed no significant associations after considering factors of source of control (inclusion of healthy controls in the control group) (TT + CT vs CC: OR = 1.15, 95%CI = 0.97–1.38, *P* = 0.250, Table 2), ethnicity (Asian patients) (TT + CT vs CC: OR = 1.04, 95%CI = 0.70–1.55, *P* < 0.001, Fig. 3), and age (children with IGE) (TT + CT vs CC: OR = 1.19, 95%CI = 0.76–1.88, *P* = 0.050, Table 2).

When stratified by seizure syndrome, we found no significant relationship in patients with CAE. Besides, the *GABRG2* rs211037 polymorphism was not significantly related to the risk of JME.

We further performed a subgroup meta-analysis to explore the relationship between *GABRG2* rs211037 polymorphism and drug resistance in patients with IGE, and no significant association was detected (TT + CT vs CC: OR = 1.64, 95%CI = 0.87–3.07, *P* = 0.002, Fig. 4).

Publication bias

The symmetrical Begg's funnel plot suggested no publication bias (Fig. 5). No publication bias was detected by Egger's test (*t* = 1.50, *P* = 0.159).

Discussion

Previous studies concerning the role of *GABRG2* in IGEs have come to controversial results, so in this study, we performed the meta-analysis to investigate the association of *GABRG2* rs211037 polymorphism with the risk for IGE. The results showed no relationship between *GABRG2* rs211037 polymorphism and IGE. Also no significant associations were found in subgroups of healthy

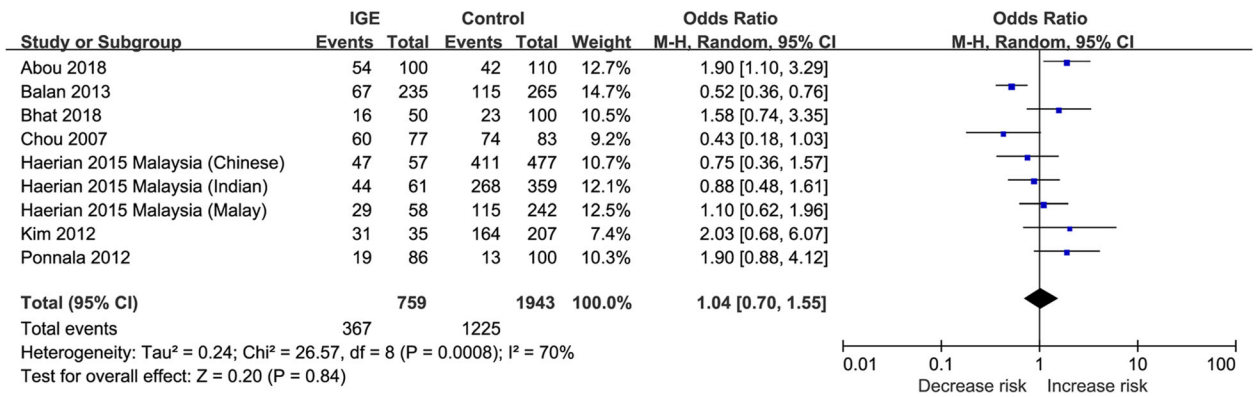

Fig. 3 Forest plot for subgroup analysis of Asian participants. No significant relationship was found between the *GABRG2* rs211037polymorphism and susceptibility to IGE in Asian participants

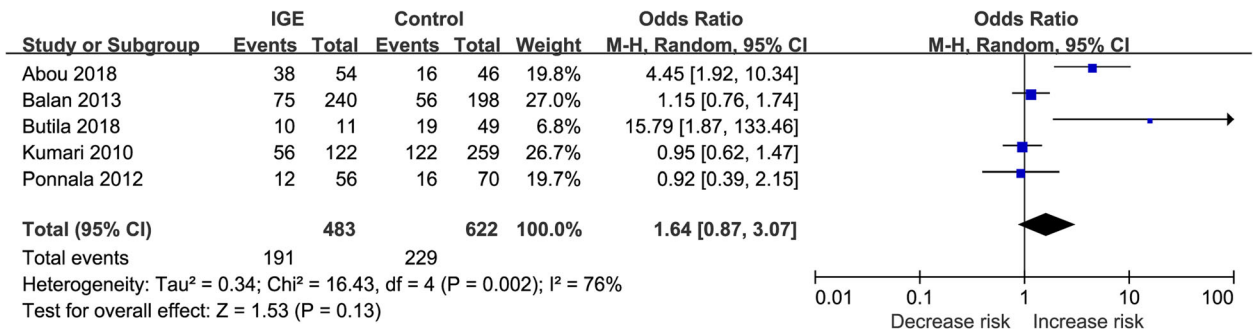

Fig. 4 Forest plot for subgroup analysis of drug resistance. No significant association was found between *GABRG2* rs211037polymorphism and drug resistance

control, Asian ethnicity, JME, CAE or children. Furthermore, the *GABRG2* rs211037 polymorphism was not significantly related to drug resistance.

As a major inhibitory neurotransmitter, GABA affects neuronal excitability and network interactions in the brain [20]. Its binding to receptors leads to the influx of chloride ions through ion channels, resulting in fast postsynaptic inhibition in the brain [21]. Expression and conformation modification of GABAA receptors may be involved in epileptogenesis, such as mRNA lability, irregular subunit folding, distortions of the GABA channel, and glycosylation defects [22, 23]. Mutations in *GABRG2* affect the expression and trafficking of GABAA receptors to the cell membrane [4, 24], and are reported to be associated with IGEs [25]. In addition, the γ2 subunit has been proved to influence the kinetics, synaptic and postsynaptic clustering and maintenance of GABAA-associated channels [26–28]. All these may contribute to epilepsy development. Moreover, lower amplitude of GABA-activated currents was detected in HEK293 cells which expresses the mutant GABAA receptor, suggesting that dysfunction of this receptor may lead to seizures [29]. Further studies are needed to explore the effect of GABAA in idiopathic epilepsy. In addition, we performed a subgroup analysis in Asian people, but failed to detect any association, which is inconsistent with previous studies showing that *GABRG2* rs211037 polymorphism is associated with susceptibility to IGE in Asian people. More studies are needed to clarify this discrepancy. In addition, there are relevant few studies performed in Caucasian populations. Therefore, future studies should be performed with more ethnicities.

Moreover, no association was detected when stratified by subtype of epilepsy syndrome including CAE and JME. Seizure syndromes in IGE have common genetic

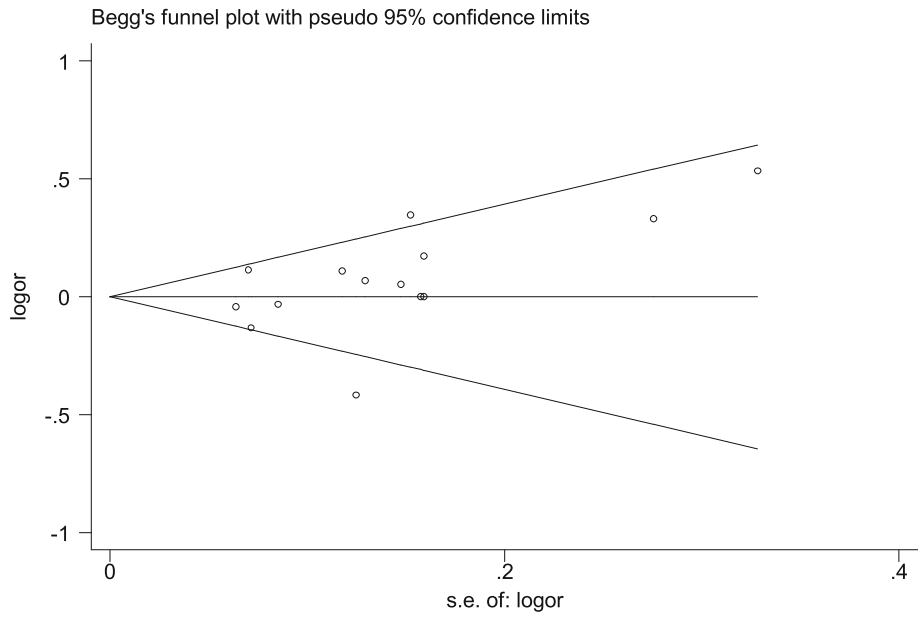

Fig. 5 Begg's funnel plot. The funnel plot suggested no publication bias among the eligible studies

predisposition but various clinical manifestations. The age at onset of the various subgroups included in IGEs differed. The reasons for the discrepancy between previous studies and ours in the associations of *GABRG2* rs211037 polymorphism with IGE may be the lack of specific subtype analysis in previous studies. Meanwhile, a great many genes participated in the mechanisms of IGEs, and the effect of *GABRG2* on IGEs may be little [13]. Therefore, genome-wide association studies are essential to explore the association between *GABRG2* and IGEs.

In this meta-analysis, we also found no relation between *GABRG2* rs211037 polymorphism and drug resistance. It has been reported that the expression of GABAA receptor subunit in drug-resistant rats differs from that in the drug-responsive rats of temporal lobe epilepsy [30]. Abou et al. showed that the *GABRG2* rs211037 polymorphism may contribute to the resistance to antiepileptic drugs (AEDs) among Egyptian children [9]. Several AEDs such as topiramate, gabapentin, and phenobarbital target the GABAA receptor and alter the concentrations of GABA [31]. Nevertheless, relevant studies are still limited, and further research is needed to clarify the relationship and the underlying pathogenesis, which may contribute to identifying therapeutic targets for the development of novel AEDs.

Our study has some limitations. First, our searches were made in limited databases, thus other relevant paper might be missed out. Second, relatively few cases and controls were available in some subgroups, which may influence the power of the test. Third, in most studies Asian participants were employed, so our results may not be suitable for other ethnicities. Finally, further analysis of gene-gene and loci-loci interactions was not conducted on account of insufficient data.

In conclusion, we found no associations between the *GABRG2* rs211037 polymorphism and the risk for IGE. Subgroup analysis stratified by ethnicity, age, healthy control and drug resistance provided similar results. Further well-designed case-control studies with larger sample sizes are needed.

Abbreviations

AEDs: Antiepileptic drugs; CAE: Childhood absence epilepsy; CNKI: Chinese National Knowledge Infrastructure; EGTCS: Epilepsy with generalized tonic clonic seizures; GABA: Gamma-amino butyric acid; IGEs: Idiopathic generalized epilepsies; JAE: Juvenile absence epilepsy; JME: Juvenile myoclonic epilepsy; OR: Odds ratio

Acknowledgements

Not applicable.

Authors' contributions

XSC designed the study, interpreted the data and revised the study. HYD and XHY conducted the systematic search and extracted the eligible studies. XHY and HYW extracted and analyzed the data. HYD and JL analyzed the data. PPL, YZZ and XMW interpreted the data. XHY drafted the study. All the authors read and approved the final manuscript.

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Availability of data and materials

The data in this study are available on reasonable request.

Declarations

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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