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ARTICLE

Analysis of *GABRG2* C588T polymorphism in genetic epilepsy and evaluation of *GABRG2* in drug treatment

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Abstract

Epilepsy is a common disorder with complex inheritance, and its treatment is very unsatisfactory. An association between the *GABRG2* C588T polymorphism and genetic generalized epilepsy has been studied by several genetic association studies. However, these results were inconsistent, and the role of *GABRG2* in epilepsy treatment remains unknown. To evaluate the role of *GABRG2* in epilepsy, we performed meta-analysis, expression quantitative trait loci analysis, protein–protein interaction analysis, and drug–gene interaction analysis. The combined results indicated that the *GABRG2* C588T polymorphism was associated with genetic generalized epilepsy risk under dominant and allelic models (odds ratio [OR] = 1.25, 95% confidence interval [CI] = 1.02–1.54, $p = 0.03$, $I^2 = 0\%$ and OR = 1.21, 95% CI = 1.03–1.42, $p = 0.02$, $I^2 = 20\%$, respectively). In the Asian population, we also found similar results under dominant and allelic models (OR = 1.93, 95% CI = 1.18–3.16, $p = 0.009$, $I^2 = 0\%$ and OR = 1.69, 95% CI = 1.20–2.37, $p = 0.003$, $I^2 = 11\%$, respectively). We first found that the *GABRG2* C588T polymorphism regulates *GABRG2* expression in human brain tissues and that the protein encoded by *GABRG2* interacts with targets of approved antiepileptic drugs (AEDs). Interestingly, we also found that *GABRG2* itself interacts with approved AEDs. Taken together, the results indicate that the C588T polymorphism might alter the $GABA_A$ receptor by modulating *GABRG2* gene expression, resulting in increased risk for epilepsy, and that *GABRG2* may be a potential therapeutic target for epilepsy.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Epilepsy is a common disorder with complex inheritance, and its treatment is largely unsatisfactory. The role of *GABRG2* in epilepsy treatment requires further investigation, as does the role of the C588T polymorphism in epilepsy.

WHAT QUESTION DID THIS STUDY ADDRESS?

Is the *GABRG2* gene related to epilepsy treatment? Is the C588T polymorphism related to epilepsy?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The *GABRG2* C588T polymorphism might alter the $GABA_A$ receptor by modulating *GABRG2* expression, resulting in epilepsy risk. In addition, *GABRG2* might be a potential therapeutic target for epilepsy.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Our study will aid in the translation of genetic findings into clinical therapies, as it provides helpful information for understanding the complex pathogenesis of epilepsy and the association between *GABRG2* and drug treatment.

INTRODUCTION

Epilepsy affects ~ 65 million people worldwide[1] and is a significant global health burden. So far, the pathogenesis of epilepsy has not been well-elucidated. Increasing numbers of studies have shown that genes are involved in the development of epilepsy.[2–5] The contribution of genetic factors in the response to antiepileptic drugs (AEDs) has also been known for a long time.[4–6] However, elucidating how these risk loci influence both epilepsy risk and the response to AEDs remains a daunting task.

An imbalance of neuronal inhibition in the brain may result in epileptic seizures.[7,8] Considering the role of the $GABA_A$ receptor in neuronal inhibition, the role of impaired GABAergic transmission by altered GABA receptors has been extensively studied.[9–11] The $GABA_A$ receptor has multiple binding sites for AEDs in the brain.[12–15] The main $GABA_A$ receptor in the brain is composed of a1, ß2, and γ2 subunits. The γ2 subunit was reported to change the kinetics of $GABA_A$ related to channels and to the synaptic and postsynaptic clustering and maintenance.[16–19] C588T, located in the *GABRG2* gene encoding the γ2 subunit, has previously been shown to cause genetic generalized epilepsy (GGE) risk and response to AEDs[20–22]; however, other results were found to have conflicting results.[23–26]

Here, we aimed to explore whether the *GABRG2* C588T polymorphism predicts susceptibility to GGE and to evaluate the role of *GABRG2* in epilepsy treatment. To this end, we performed meta-analysis, functional characterization of the C588T polymorphism, protein–protein interaction (PPI) analysis, and drug–gene interaction analysis to determine the specific association. To our knowledge, this study is the first study to identify that C588T might alter the $GABA_A$ receptor by modulating *GABRG2* gene expression, resulting in increased risk for epilepsy, and that *GABRG2* might be a potential therapeutic target for epilepsy.

MATERIALS AND METHODS

Literature search and inclusion criteria

All research articles on the association of *GABRG2* polymorphisms with epilepsy were identified in the MEDLINE, CNKI, and EMBASE databases (up to March 2020). The following keywords were used: GABRG2 AND (polymorphism OR SNP OR allele OR genotype) AND (epilepsy OR seizure OR epileptic). There was no language restriction implemented. The inclusion criteria were: (1) genotype data were reported in all subjects; and (2) the study was on GGE. The exclusion criteria were as follows: (1) data obtained from previous research; (2) reviews and meta-analyses were excluded, but reference lists were checked for additional relevant articles; and (3) genotype data in the control group that did not meet the Hardy–Weinberg equilibrium (HWE).

Data extraction and quality assessment

The distributions of allele and genotype, first author, year of publication, genotyping method, and ethnicity of the population were extracted. Two different researchers reviewed the extracted data independently. If discrepancies arose, a third researcher was recruited to resolve them. The quality of the included studies was scored independently by two researchers and confirmed by a third researcher using the Newcastle–Ottawa quality assessment scale.[27] A score of six points or above indicated high quality.

Sensitivity analysis and publication bias

We conducted a sensitivity analysis by excluding every study. If the result remained significant in all or most of the included studies, the study was considered to be highly replicable.[28] We applied Begg's and Egger's tests to assess the publication bias.

Statistical analysis

We used Review Manager 5.3 and Stata 15.1 software for all analyses. All probability values were two-sided, and p values of < 0.05 were considered significant. The HWE for the C588T was identified by using the χ^2-based goodness-of-fit test. Heterogeneity was examined using the inconsistency index (I^2), with $I^2 > 50\%$ considered statistically heterogeneous.[29] If there was no statistical heterogeneity, the fixed-effects were calculated; otherwise, the random effects were calculated.

Function prediction and expression quantitative trait loci analysis

Functional annotation for the C588T polymorphism was assessed by using the CADD database.[30] We used a large brain tissue database, BRAINEAC (http://www.braineac.org/), to test whether C588T regulates *CABRG2* expression. The BRAINEAC database is an important tool for assessing the relationship between gene expression and single nucleotide polymorphisms, and contains brain tissues from the following regions: the putamen (PUTM), substantia nigra (SNIG), medulla (MEDU), hippocampus (HIPP), frontal cortex (FCTX), thalamus (THAL), cerebellum (CRBL), temporal cortex (TCTX), white matter (WHMT), and occipital cortex (OCTX). Findings in the BRAINEAC database were further confirmed by using BrainCloud (http://eqtl.brainseq.org) and the Genotype-Tissue Expression project (GTEx: http://www.gtexportal.org/home/) databases.

Evaluating the potential of *GABRG2* in drug treatment

To evaluate the potential of *GABRG2* in treatment, we identified approved AED targets using two databases, DrugBank 5.0[31] and the Therapeutic Target Database 2020.[32] PPI analysis was conducted to find the potential interaction between the protein encoded by *GABRG2* and targets of AEDs. We used Cytoscape version .3.7.2.[33] to draw the subsequent PPI network. We also scanned the Drug–Gene Interaction Database[34] to further investigate for the potential of *GABRG2* in epilepsy treatment.

RESULTS

Data acquisition, sensitivity analysis, and publication bias

A flowchart of the included articles and the characteristics of all studies are shown in Figure 1 and Table 1, respectively. Six high-quality studies including 1962 subjects were ultimately included. We applied Begg's and Egger's tests to assess publication bias and found no publication bias in the included studies ($p > 0.3$; Table 2). Sensitivity analysis suggested that our results were credible by excluding every included study.

Statistical analysis

We found no statistical heterogeneity in different genetic models ($I^2 \leq 20\%$; Figure 2a,b). All included studies were in conformance with the HWE with regard to the control population ($p > 0.05$; Table 3). The combined results of all

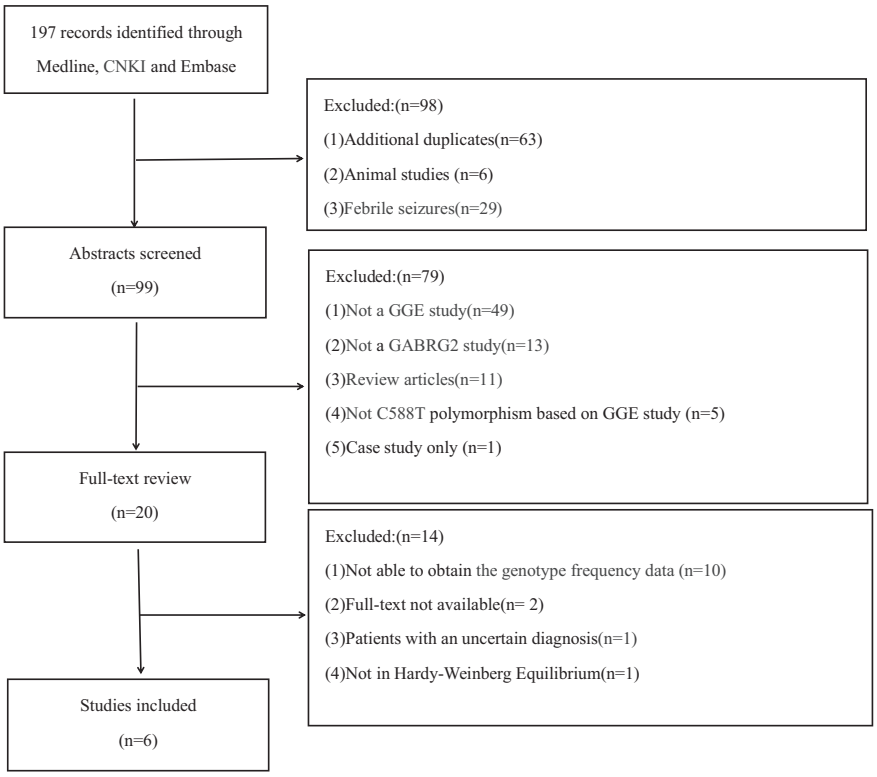

FIGURE 1 Flowchart of included articles. GGE, genetic generalized epilepsy

TABLE 1 Characteristics of all studies on C588T polymorphism and genetic generalized epilepsy

Author	Year	Origin	Definition of GGE	Method of genotyping	NOS score
Kananura et al.	2002	German	ILAE	PCR amplification Direct sequencing	8
Kinirons et al.	2006	British	ILAE	Taqman real time-PCR	9
Kinirons et al.	2006	Irish	ILAE	Taqman real time-PCR	9
Gitai et al.	2012	Brazilian	ILAE	PCR-RFLP	7
Butilă et al.	2018	Romanian	ILAE	PCR-RFLP	7
Abou El Ella et al.	2018	Egyptian	ILAE	PCR-RFLP	7
Kim et al.	2012	Korean	ILAE	PCR amplification Direct sequencing	7

Abbreviations: GGE, genetic generalized epilepsy; ILAE, International League Against Epilepsy; NOS, Newcastle-Ottawa quality assessment scale; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism.

TABLE 2 Test for publication bias

C588T	Begg's test (*p*)	Egger's test(*p*)
T vs. C	0.37	0.38
CT vs. CC	0.37	0.59
TT + CT vs. CC	0.76	0.75

included studies indicated that C588T was associated with GGE risk under dominant and allelic models (CT + TT vs. CC: odds ratio [OR] = 1.25, 95% confidence interval [CI] = 1.02–1.54, $p = 0.03$, $I^2 = 0\%$; T vs. C: OR = 1.21, 95% CI = 1.03–1.42, $p = 0.02$, $I^2 = 20\%$). In the Asian population, we also found similar results under dominant and allelic models (CT + TT vs. CC: OR = 1.93, 95% CI = 1.18–3.16, $p = 0.009$, $I^2 = 0\%$; T vs. C: OR = 1.69, 95% CI = 1.20–2.37, $p = 0.003$, $I^2 = 11\%$). Statistical analyses results are shown in Figure 2a,b.

Function prediction and expression quantitative trait loci analysis

C588T is predicted to have functional consequences, given that it obtained a CADD score of 10.92. To explore whether C588T is associated with *GABRG2* gene expression in human brain tissues, we performed expression quantitative trait loci (eQTL) analysis using the BRAINEAC database. The *p* values were used to evaluate the association between C588T genotype and *GABRG2* gene expression. Our results showed that C588T was associated with *GABRG2* expression levels in the FCTX ($p = 0.022$) and OCTX ($p = 0.0082$; Figure 3). Furthermore, we found that C588T regulated *GABRG2* expression as assessed by the BrainCloud and the GTEx project databases (Table S1), thus providing further evidence that C588T regulates the expression of *GABRG2* in human brain tissues.

Evaluating the potential of *GABRG2* in drug treatment

We obtained 115 genes (Table S2) targeted by approved AEDs from 2 drug target databases. PPI analysis showed that the protein encoded by *GABRG2* gene interacted with 40 AED targets (Figure 4). After searching the Drug–Gene Interaction Database, we further found that *GABRG2* interacts with 61 drugs (Table S3), some of which are currently approved AEDs, and others that have not yet been approved for epilepsy treatment but may have antiseizure potential. Therefore, more investigation is necessary to gain further insight from genetic findings regarding the above interactions.

DISCUSSION

Previous studies indicated that most disease-associated polymorphisms confer risk for the disease by acting as an eQTL to regulate gene expression.[35–38] Although previous studies have tested for the association between *GABRG2* polymorphisms and GGE risk, our study is the first to identify an association by combining results from a meta-analysis with an eQTL analysis. We also conducted evaluation of *GABRG2* in drug treatment, in order to determine the potential of the gene as a therapeutic target in GGE.

Our findings indicated that the C588T polymorphism is associated with GGE risk in general, and similar results were also observed in the Asian population. However, our study in the White population failed to replicate the polymorphism as a risk for GGE. We believe that this contradiction can be explained as follows. First, ethnic differences in the distribution of C588T in populations need to be taken into account. In several countries,[2,6,25,39] a lower frequency of the C588T polymorphism was observed for TT genotypes, whereas the frequency of TT carriers was higher in other countries.[23,40] The frequency of the TT genotype varies widely across

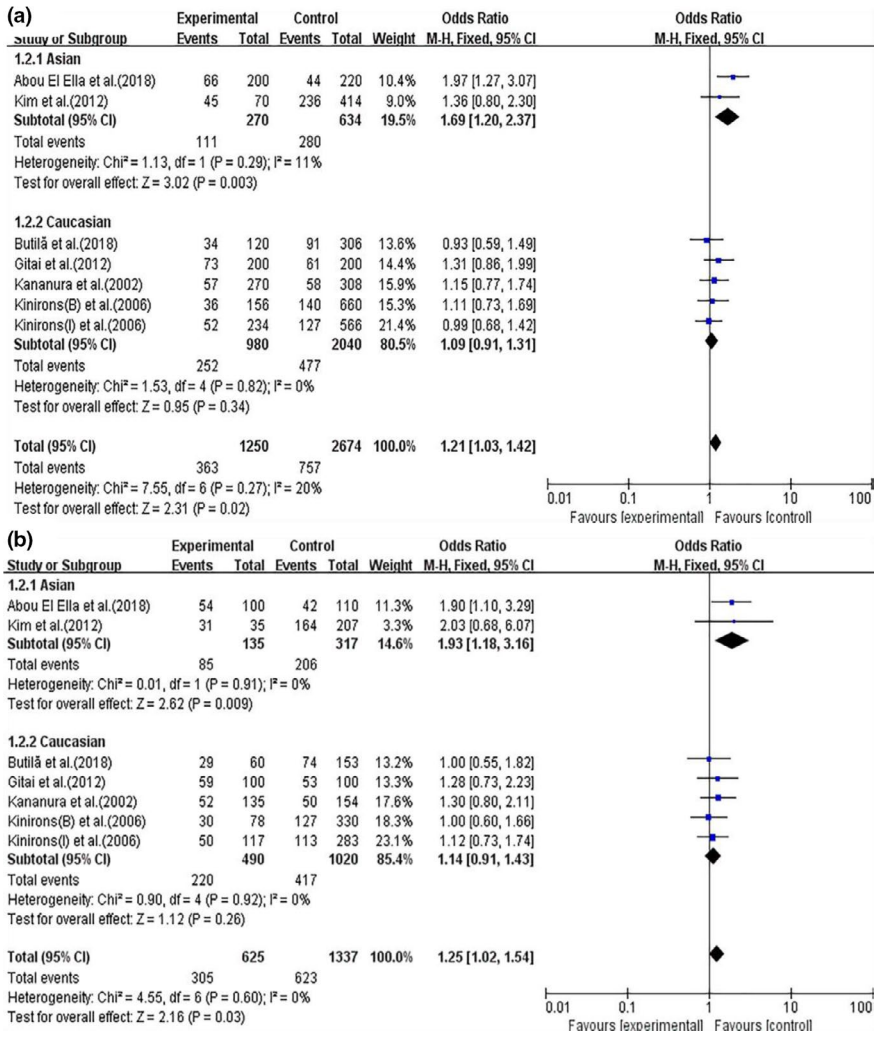

FIGURE 2 Forest plots showing association between the C588T polymorphism and genetic generalized epilepsy: based on the (a) T vs. C model and (b) TT + CT vs. CC model. CI, confidence interval

TABLE 3 Test for HWE

		Distribution of genotype						Distribution of allele				HWE test
		Case			Control			case		Control		
Author	Origin	CC	CT	TT	CC	CT	TT	C	T	C	T	*p* value
Kananura	German	83	47	5	104	42	8	213	57	250	58	0.60
Kinirons	British	48	24	6	203	114	13	120	36	520	140	0.98
Kinirons	Irish	67	48	2	170	99	14	182	52	439	127	1.00
Gitai	Brazilian	41	45	14	47	45	8	127	73	139	61	0.92
Butilă	Romanian	31	24	5	79	57	17	86	34	215	91	0.61
Abou El Ella	Egyptian	46	42	12	68	40	2	134	66	176	44	0.60
Kim	Korean	4	17	14	43	92	72	25	45	178	236	0.64

*Note: The: p*values were calculated based on χ^2 test.

Abbreviation: HWE, Hardy-Weinberg Equilibrium.

different populations worldwide, suggesting that the association of the polymorphism is population specific. Second, the small cohort size may have also distorted the results. Third, rigorous quality control of genotyping results is crucial for genetic association studies. However, we are unaware whether the previously mentioned studies carried out these rigorous quality controls. Finally, adjustment for confounding factors in association studies is also crucial; however,

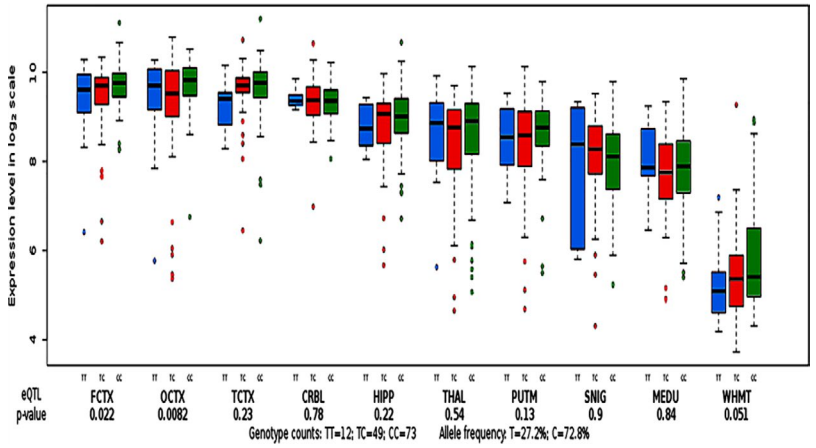

FIGURE 3 C588T was an expression quantitative trait locus (eQTL) and affected GABRG2 gene expression in human brain tissues. *p* values were used to evaluate the association between C588T genotype and *GABRG2* gene expression. Data were retrieved from the BRAINEAC database: CRBL, cerebellum; FCTX, frontal cortex; HIPP, hippocampus; MEDU, medulla; PUTM, putamen; OCTX, occipital cortex; SNIG, substantia nigra; TCTX, temporal cortex; THAL, thalamus; WHMT, white matter

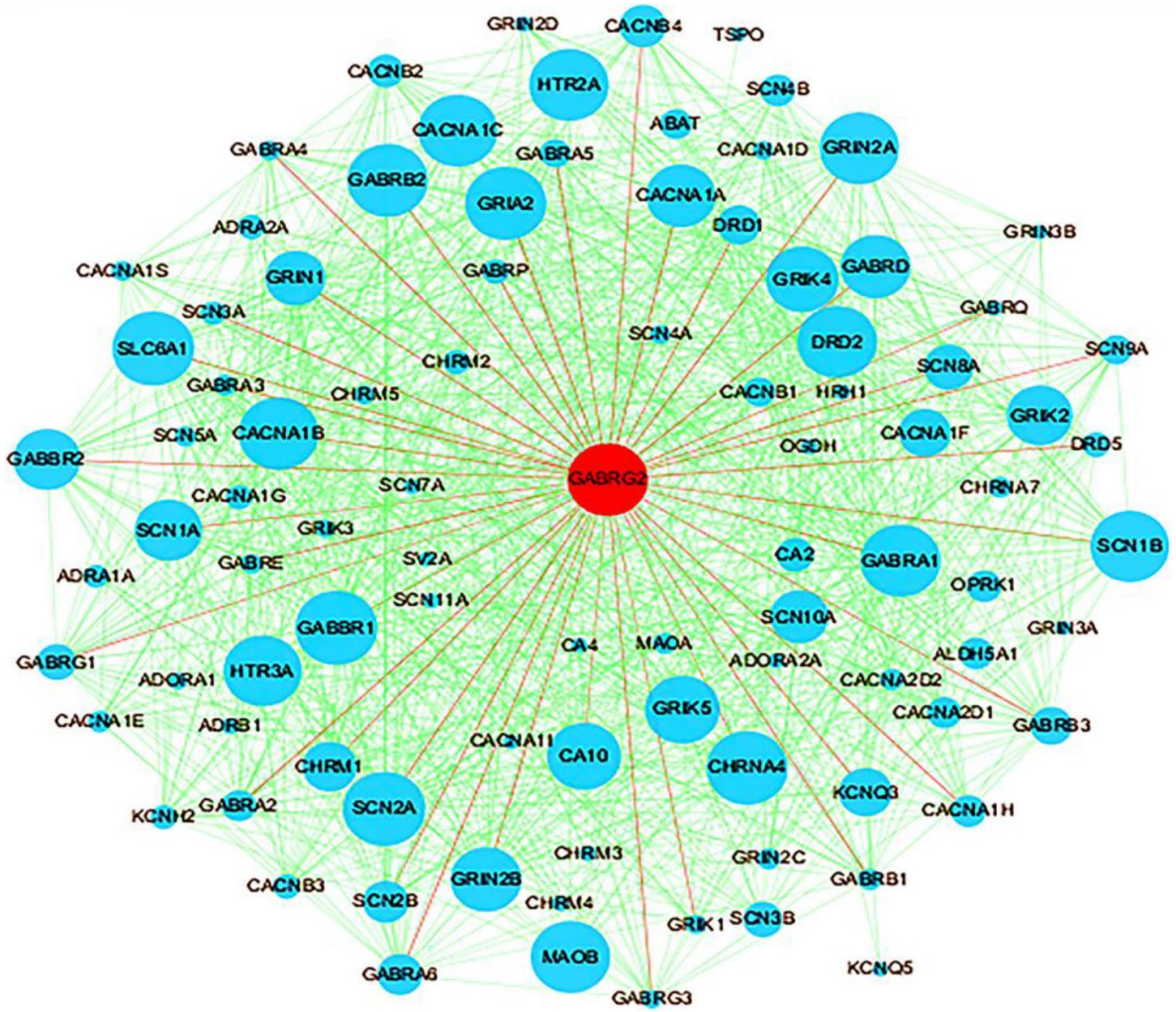

FIGURE 4 Protein-protein interaction (PPI) network of GABRG2 gene and genes targeted by antiepileptic drugs (AEDs). Red node and blue nodes represent GABRG2 gene and genes targeted by AEDs, respectively. The proteins connected by the red line mean that these proteins have direct interaction

relevant analysis was not performed in the current study as we did not have detailed information on all subjects.

To find a functional association between the C588T polymorphism and GGE, we assessed whether C588T regulates *GABRG2* expression in human brain tissues. By integrating the data from three brain tissue databases, we concluded that C588T is an eQTL. These findings provided helpful information for understanding the complex pathogenesis of epilepsy. Importantly, findings that C588T regulates *GABRG2* expression in the FCTX and OCTX provided further support for the involvement of this polymorphism in increased risk for epilepsy. It is known that occipital lobe and temporal lobe epilepsy are common types of epilepsy, and a decreased *GABRG2* expression level in the FCTX and OCTX may lead to impaired GABAergic transmission,[9–11] resulting in epileptic seizures.[41] However, the above results were not replicated in TCTX, PUTM, SNIG, MEDU, HIPP, THAL, CRBL, or WHMT, and this may be due to the fact that C588T regulates the expression of *GABRG*2 in specific areas of the brain. Further research is required to verify our inference.

Although no significant heterogeneity or publication bias was found, there are also some limitations to the current study. First, the unadjusted OR estimates were performed because detailed information regarding subjects in some studies could not be found. Second, the number of subjects in the study was relatively small. Future studies will look to overcome this limitation.

It is interesting to note that the influence of SCN1A on susceptibility to sodium channel blocking AEDs has been indicated by many studies.[42–44] This led to investigations of the potential relationships between AED responses and genes encoding for other drug targets.[45,46] Among 61 drugs that interact with *GABRG2*, it is well known that thiopental sodium, diazepam, and topiramate are common AEDs. Furthermore, it was found that the proteins encoded by SCN2A and SCN3A interact directly with the protein encoded by GABRG2 in our study, and that SCN2A and SCN3A are related to epilepsy.[47] The results of PPI analysis indicated that *GABRG2* may be a target in epilepsy treatment, a result that was confirmed by findings from the drug–gene interaction analysis. However, the antiseizure potential of other drugs not currently approved but that interact with *GABRG2* remains unclear. Taken together, these results may contribute to the discovery of new targets for epilepsy treatment. However, more investigation is needed to gain further insight from the current genetic findings.

CONCLUSION

This study suggested that the *GABRG2* C588T polymorphism might alter the $GABA_A$ receptor by modulating *GABRG2* gene expression, resulting in epilepsy risk, and that *GABRG2* might be a potential therapeutic target for epilepsy. However, further verification of our results in large samples and functional characterization are necessary. Our results will aide in the translation of genetic findings to clinical therapies, as these findings provide helpful information for understanding the complex pathogenesis of epilepsy and the association between *GABRG2* and drug treatment.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

S.W., Y.H., and X.Z. wrote the manuscript. S.W. and Y.H. designed the research. S.W., Y.H., and Q.W. performed the research. Y.H., Q.W., X.Z., and L.Z. analyzed the data. S.W. and L.Z. contributed analytical tools.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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