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GABRG2 rs211037 polymorphism and epilepsy: A systematic review and meta-analysis

Batoul Sadat Haerian [a,*], Larry Baum [b]

[a] *Department of Pharmacology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia*
[b] *School of Pharmacy, The Chinese University of Hong Kong, Shatin, Hong Kong, China*

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ABSTRACT

Purpose: The gamma-aminobutyric acid A receptor, gamma 2 (*GABRG2*) gene encodes the GABRγ2 protein, which has been implicated in susceptibility to epilepsy. Several studies have examined a possible link between the exonic *GABRG2* rs211037 locus and susceptibility to febrile seizure (FS) and idiopathic generalized epilepsy (IGE), however results have been inconclusive. We therefore performed a systematic review and meta-analysis to examine whether this polymorphism is associated with FS or IGE.

Methods: Eight studies comprising 1871 epilepsy patients and 1387 controls, which evaluated association of the *GABRG2* rs211037 polymorphism with susceptibility to epilepsy, were included in this meta-analysis. Meta-analysis was carried out separately for FS and IGE.

Results: Meta-analysis showed a significant association between this polymorphism and susceptibility to FS in a codominant (TT vs. CC, OR 0.47, 95% CI 0.30–0.73, $p = 0.0008$ and TT vs. CT, OR 0.59, 95% CI 0.42–0.83, $p = 0.003$) and dominant (OR 0.54, 95% CI 0.39–0.75, $p = 0.0002$) genetic models, influenced by two studies with small sample size. Neither allele nor genotype association was observed with IGE.

Conclusion: This study showed significant association of *GABRG2* rs211037 with susceptibility to FS, caused by two studies with small sample sizes, however the possibility of false positive results due to the effect of significant studies for FS cannot be excluded. Future studies with larger sample sizes of these patients are suggested to verify the results.

1. Introduction

Gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the central nervous system. This molecule exerts its function primarily through several receptors, including GABA-A. The GABA-A receptor is part of a ligand-gated ion channel complex which allows chloride ions to enter neurons, resulting in hyperpolarization that reduces the probability of an action potential. The GABA-A receptor is the most common receptor in the mammalian brain and mediates a majority of fast synaptic inhibition.[1] The GABA-A receptor is pentameric and consists of two α, two β, and one γ subunits, with the most common subunit composition being α1, β2, and γ2, encoded by the *GABRA1*, *GABRB2*, and GABRG2 genes, respectively. Various mutations in these genes impair channel gating and/or reduced mRNA stability, aberration in subunit folding and glycosylation which result in abnormal receptor assembly and trafficking.[2–4]

The *GABRG2* gene is located in 5q34 and is highly expressed in the brain.[5] Studies have suggested that mutations such as R43Q, Q40X, K289M, and IVS6+2T in this gene are involved in childhood absence epilepsy (CAE), febrile seizures (FS), generalized epilepsy with febrile seizures plus (GEFS+), and Dravet syndrome.[6,7] Previous studies examined whether the 588C>T Asn196Asn exon 5 polymorphism (rs211037) is related to susceptibility to FS or idiopathic generalized epilepsy (IGE) in different populations, however the results were inconsistent (Table 1 and Fig. 1).[10–18] To shed light on the association between rs211037 and susceptibility to epilepsy, we carried out a systematic review and meta-analysis.

2. Methods

2.1. Search strategy and selection

This meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[19] Articles were sought by using the MeSH terms "epilepsy," "polymorphism," "variant," "*GABRG2*," "rs211037," "rs211037 C>T," "Crs211037T," and "susceptibility,"

* Corresponding author. Tel.: +60 3 7967 4702/4703/5725; fax: +60 3 7967 4791.
E-mail address: batoolsadat@yahoo.com (B.S. Haerian).

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Table 1
Allele and genotype distribution of *GABRG2* rs211037 polymorphism in the included studies.

No.	Author	Year	Origin	Epilepsy	Definition of epilepsy	Category	Samples (*N*)		Genotypes						Alleles (N)				Ass.	Ref.
									C/C		C/T		T/T		C		T			
							P	C	P	C	P	C	P	C	P	C	P	C		
1	Kananura et al.	2002	German	IAE	ILAE	IGE	135	154	83	104	47	42	5	8	213	250	57	58	No	11
2	Madia et al.	2003	Italian	SMEI (FS + AFS)	ILAE	All types	53	96	28	48	21	40	4	8	77	136	29	56	No	12
3	Chou et al.	2003	Taiwanese	FS	ILAE	FS	104	83[a]	17	9	55	32	31	42	89	50	117	116	Yes	13
4	Nakayama et al.	2003	Japanese	FS	Freeman JM, 1980	FS	94	106	24	23	50	58	20	25	98	104	90	108	No	14
5-1	Kinirons et al.	2006	British	All	ILAE	All types	569	330	342	203	187	114	40	13	871	520	267	140	No	15
5-2	Kinirons et al.	2006	British	FS	ILAE	FS	84	330	46	203	35	114	3	13	127	520	41	140	No	15
5-3	Kinirons et al.	2006	British	IGE	ILAE	IGE	78	330	48	203	24	114	6	13	120	520	36	140	No	15
5-4	Kinirons et al.	2006	Irish	All	ILAE	All types	699	283	376	170	262	99	31	14	1014	439	324	127	No	15
5-5	Kinirons et al.	2006	Irish	FS	Other	FS	80	283	43	170	35	99	2	14	121	439	39	127	No	15
5-6	Kinirons et al.	2006	Irish	IGE	ILAE	IGE	117	283	67	170	48	99	2	14	182	439	52	127	No	15
6	Ma et al.	2006	American	Focal epilepsy with FS	Not identified	FS	74	118	73	113	1	5	0	0	147	231	1	5	No	16
7	Chou et al.	2007	Taiwanese	IGE	ILAE	IGE	77	83[a]	17	9	38	32	22	42	72	50	82	116	No	17
8	Salam et al.	2011	Egyptian	Generalized epilepsy with FS	ILAE	FS	100	120	26	12	42	46	32	62	94	70	106	170	Yes	18

Abbreviations: IAE, idiopathic absence epilepsy; SMEI, severe myoclonic epilepsy of infancy; FS, febrile seizure; GS, generalized seizure; IGE, idiopathic generalized epilepsy; AFS, afebrile seizure; P, patient; C, control; ILAE, International League Against Epilepsy.
[a] Samples were the same.

in MEDLINE, Embase, and the *Cochrane Database of Systematic Reviews* without language limitation, the last search being updated in July 2012. The reference lists were hand searched for other relevant publications. Studies that determined the distribution of the *GABRG2* rs211037 genotype in unrelated epilepsy patients and healthy controls were eligible for inclusion in the meta-analysis.

2.2. Data extraction

Publications were eligible for meta-analysis if they met the following inclusion criteria: (a) study had been done in epilepsy patients and controls; (b) genotype frequency data were available for both case and control groups; and (c) genotype distribution complied with Hardy–Weinberg equilibrium (after retesting in this meta-analysis). Major exclusion criteria were as follows: (a) controls were related to patients; (b) data duplicated those of previous publications. The following characteristics were collected from each study: first author's surname, year of publication, ethnicity of patients, numbers of epilepsy patients and of controls with each genotype, and type of epilepsy.

2.3. Statistical analysis

The per-allele odds ratios (OR) of the rare allele (T) as well as the corresponding 95% confidence intervals (CI) and *p* values were calculated to compare epilepsy patients and controls. Codominant (C/C vs. T/T and C/T vs. T/T), dominant (C/C + C/T vs. T/T), and recessive (C/C vs. C/T + T/T) models were also tested. Subsidiary meta-analyses were performed to evaluate the above models on FS, IGE, or all studies. To measure the strength of genetic

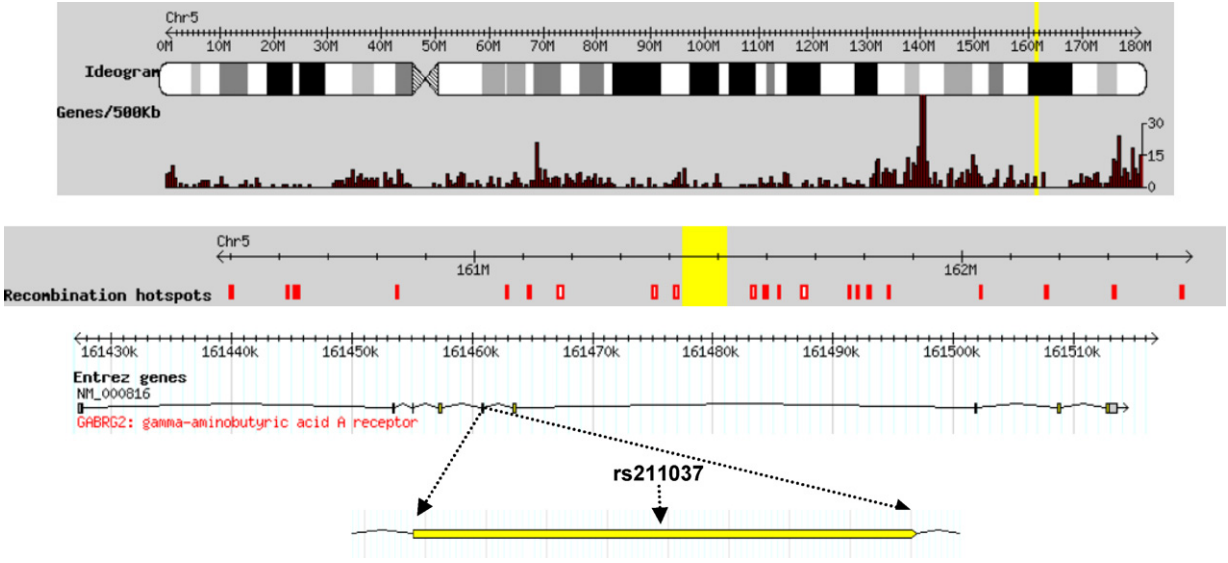

Fig. 1. The rs211037 polymorphism is located within exon 5 of the *GABRG2* gene.

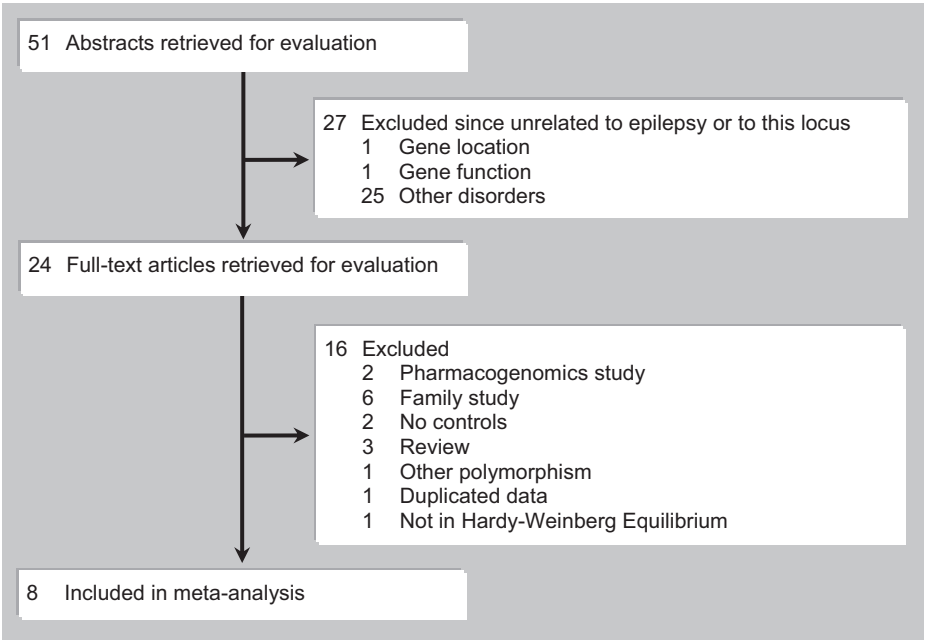

Fig. 2. Selection of studies of the *GABRG2* rs211037 polymorphism.

association, the I^2 test was used for assessing the proportion of statistical heterogeneity, and the Q-statistic test with $p < 0.1$ was used to define a significant degree of heterogeneity. The double of the usual significance threshold (2×0.05) has been considered for the Q-statistic test to increase the power of the heterogeneity test in meta-analysis. Fixed-effects summary measures were calculated as inverse-variance-weighted averages of the log OR if there was no heterogeneity ($p > 0.1$) and random-effects where substantial heterogeneity ($p < 0.1$) existed. Sensitivity analyses were performed to assess the stability of the results of the meta-analysis. All probability values are 2-sided, and values of $p < 0.05$ were considered statistically significant. Statistical analyses were performed using validated Meta-analysis Made Easy (MIX) version 1.7.[20]

3. Results

Characteristics of the included studies are listed in Table 1. The initial search with the keywords and the subject terms identified 51 abstracts, all published in English. Of these abstracts, 27 were excluded because they were irrelevant to rs211037 or to epilepsy. In the next step, the full texts of the 24 remaining articles were evaluated, yielding eight, including 3258 subjects (1871 epilepsy patients and 1387 controls) that met our eligibility criteria for meta-analysis (Fig. 2). Amongst the included studies, only three reports—two Taiwanese[13,17] and one Egyptian[18]—were associated with susceptibility to FS or IGE.

There was a considerable diversity of epilepsy types among the eight included studies.[11–18] The control group in the Taiwanese

Table 2
Meta-analysis of *GABRG2* rs211037 and susceptibility to FS, IGE, and all epilepsies under alternative genetic models.

Allele/genotype	FS ($N = 6$)				IGE ($N = 4$)				All epilepsies ($N = 8$)[a]			
	OR 95% CI	p	I^2 (%)	p_{het}	OR 95% CI	p	I^2 (%)	p_{het}	OR 95% CI	p	I^2 (%)	p_{het}
T vs. C												
All	0.77 (0.54–1.11)	0.16	71	<0.01	0.90 (0.63–1.29)	0.57	68	0.03	0.79 (0.56–1.11)	0.17	85	<0.01
Asian	0.62 (0.42–0.90)	0.01	63	0.07	–	–	–	–	0.54 (0.33–0.87)	0.01	81	<0.01
Caucasian	–	–	–	–	1.07 (0.86–1.35)	0.54	0	0.84	1.1 (0.95–1.28)	0.19	0	0.75
TT vs. CC												
All	0.47 (0.30–0.73)	0.0008	29	0.22	0.64 (0.25–1.65)	0.36	63	0.04	0.62 (0.30–1.28)	0.20	83	<0.01
Asian	0.41 (0.25–0.68)	0.0004	50	0.14	–	–	–	–	0.31 (0.13–0.74)	0.009	76	0.02
Caucasian	–	–	–	–	1.01 (0.51–1.99)	0.98	44	0.17	1.21 (0.81–1.82)	0.36	0	0.44
TT vs. CT												
All	0.59 (0.42–0.83)	0.003	0	0.57	0.65 (0.28–1.51)	0.32	59	0.06	0.80 (0.61–1.05)	0.11	40	0.13
Asian	0.59 (0.41–0.86)	0.005	23	0.27	–	–	–	–	0.63 (0.44–0.90)	0.01	0	0.45
Caucasian	–	–	–	–	0.78 (0.24–2.52)	0.67	63	0.07	1.11 (0.73–1.68)	0.64	31	0.22
TT vs. CC + CT												
All	0.54 (0.39–0.75)	0.0002	0	0.43	0.67 (0.29–1.54)	0.35	63	0.05	0.74 (0.45–1.20)	0.22	69	<0.01
Asian	0.52 (0.37–0.74)	0.0003	37	0.20	–	–	–	–	0.49 (0.29–0.83)	0.008	58	0.09
Caucasian	–	–	–	–	0.98 (0.50–1.91)	0.95	54	0.11	1.16 (0.75–1.78)	0.51	10	0.34
CT + TT vs. CC												
All	0.79 (0.48–1.28)	0.33	64	0.02	1.04 (0.80–1.36)	0.75	39	0.18	0.72 (0.47–1.11)	0.14	83	<0.01
Asian	0.56 (0.36–0.85)	0.007	43	0.17	–	–	–	–	0.4 (0.2–0.8)	0.01	74	0.02
Caucasian	–	–	–	–	1.14 (0.87–1.50)	0.35	0	0.76	1.11 (0.93–1.33)	0.24	0	0.66

Abbreviations: FS, febrile seizure; IGE, idiopathic generalized epilepsy.
[a] Since the control samples of Chou et al.[12] and Chou et al.[16] were the same, only one control group was included in this meta-analysis.

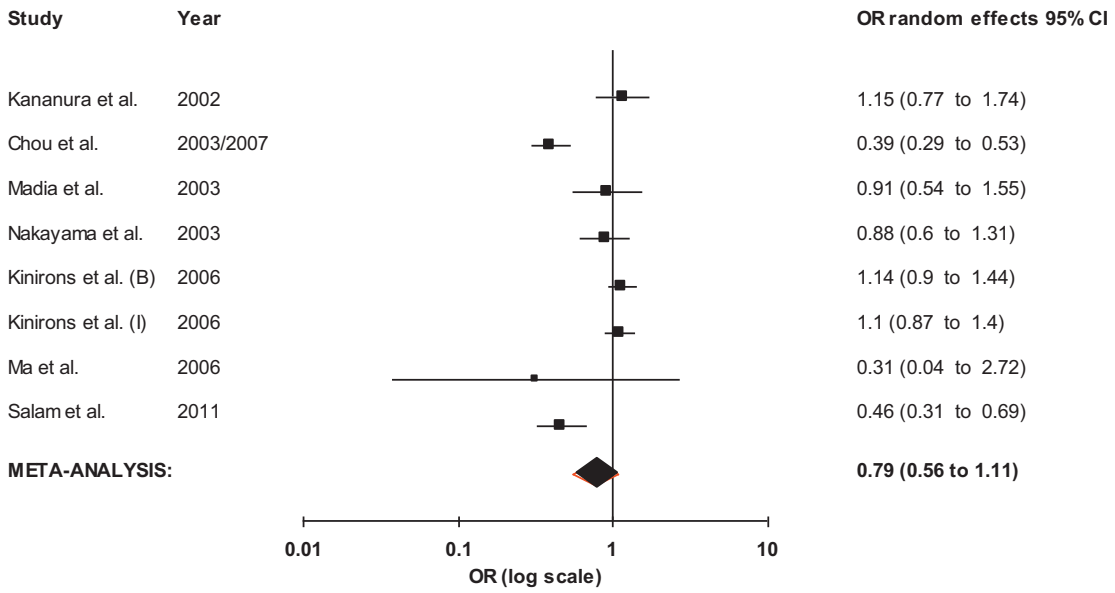

Fig. 3. Meta-analysis of the association of the T vs. C allele of rs211037 with all epilepsies. Since the control samples of two Chou et al. studies[12,16] were the same, only one control group was included in this meta-analysis. For each study, the position of the square is the OR, the horizontal line spans the 95% CI of the OR, and the area of the square is inversely proportional to the variance of the log OR. The position of the diamond is the overall OR, and the horizontal span of the diamond represents the 95% CI of the OR. B, British; I, Irish.

studies was shared, therefore only one control group of the two studies was included in the meta-analysis of all studies (Table 2 and Fig. 3).[13,17] Studies were classified into two categories: FS (6 studies: 535 patients vs. 1040 controls)[13–16,18] and IGE (4 studies: 407 patients vs. 850 controls).[15–7] In one report, patients had either FS or IGE, hence that study was split and included in either FS or IGE meta-analyses.[15]

Meta-analysis data of FS, IGE, and all studies are shown in Table 2. Neither allele nor genotype association was observed with IGE or with all epilepsy (Table 2 and Fig. 3). However, significant association with FS existed under codominant (Fig. 4, TT vs. CC, OR 0.47, 95% CI 0.30–0.73, $p = 0.0008$ and TT vs. CT, OR 0.59, 95% CI 0.42–0.83, $p = 0.003$) and dominant (OR 0.54, 95% CI 0.39–0.75, $p = 0.0002$) genotype models. A sensitivity analysis which excluded each study in turn demonstrated an increase of the pooled OR from 0.47 to 0.63 (TT vs. CC), 0.59 to 0.67 (TT vs. CT), and 0.54 to 0.82 (TT vs. CC + CT) and eliminated the significance of the associations (95% CI 0.37–1.06, $p = 0.08$; 95% CI 0.45–1.02, $p = 0.06$; and 95% CI 0.47–1.41, $p = 0.47$, respectively) when the Egyptian (for TT vs. CC or dominant) or Taiwanese study (for TT vs. CT or dominant) was excluded. Therefore, significant association in FS meta-analysis was caused by the large effect size of these two studies.

Sub-analysis by ethnicity was carried out for FS, IGE, and all epilepsies. The number of Caucasian studies in FS or Asian studies in IGE categories was not enough to do subgroup meta-analysis. No allele or genotype association with IGE was seen in Caucasians or all studies. However, there was significant allele association with FS in Asians (T vs. C, OR 0.62, 95% CI 0.42–0.90, $p = 0.01$). Additionally, genotype association with FS was observed in codominant (TT vs. CC, OR 0.41, 95% CI 0.25–0.68, $p = 0.0004$ and TT vs. CT, OR 0.59, 95% CI 0.41–0.86, $p = 0.005$), dominant (OR 0.52, 95% CI 0.37–0.74, $p = 0.0003$), and recessive (OR 0.56, 95% CI 0.36–0.85, $p = 0.007$) models. Altogether, the effect size of the Egyptian and Taiwanese FS studies in the Asian sub-group resulted in significant association not only in Asians, but also in all epilepsies.

There was significant heterogeneity for FS in the allele (all studies, $I^2 = 71\%$, $p < 0.01$ and Asian studies, $I^2 = 63\%$, $p = 0.07$) and

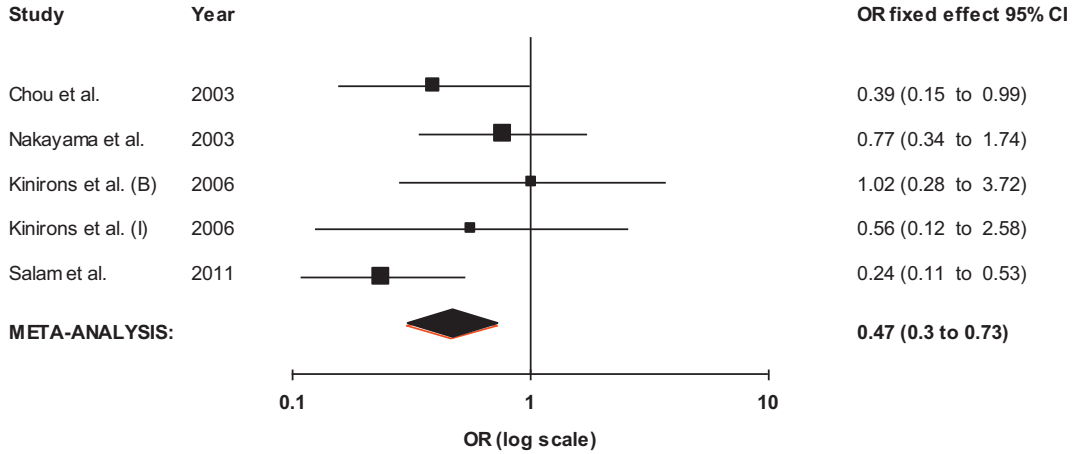

Fig. 4. Meta-analysis of the association of the TT vs. CC genotype of rs211037 with febrile seizures. For each study, the position of the square is the OR, the horizontal line spans the 95% CI of the OR, and the area of the square is inversely proportional to the variance of the log OR. The position of the diamond is the overall OR, and the horizontal span of the diamond represents the 95% CI of the OR. B, British; I, Irish.

in the autosomal recessive model (all studies, $I^2 = 64\%$, $p = 0.02$). In the IGE category, heterogeneity was significant in the allele (all studies, $I^2 = 68\%$, $p = 0.03$), codominant (TT vs. CC, all studies, $I^2 = 63\%$, $p = 0.04$; TT vs. CT, all studies, $I^2 = 59\%$, $p = 0.06$; Caucasian studies, $I^2 = 63\%$, $p = 0.07$) and dominant (all studies, $I^2 = 63\%$, $p = 0.05$) models (Table 2). The funnel plot for T vs. C in all studies was basically symmetric, and Egger's test did not indicate statistically significant asymmetry of the plot (intercept = −1.85, 95% CI −7.68–3.97, $p = 0.47$), suggesting no evidence of publication bias.

4. Discussion

Of eight reports, three supported the hypothesis that the synonymous *GABRG2* rs211037 polymorphism is a risk factor for epilepsy: one study in Egypt for susceptibility to FS and two studies in Taiwan for susceptibility to FS or IGE. Meta-analysis showed significant association between rs211037 and FS under co-dominant and dominant genotype models, with the Egyptian and/or Taiwanese studies contributing much of the significance. However, meta-analysis did not show significant association between IGE and either alleles or genotypes. It is plausible that the association with FS is either a true positive or a false positive obtained by chance.

Ethnicity might explain the association with FS. The prevalence of variants and linkage disequilibrium with other risk-associated variants varies among geographical populations. This genetic difference interacts with environmental factors such as regional climate, culture, and pathogens and results in a variety of adaptations of populations or individuals.[21–23] The incidence of FS varies in the world. In Western Europe and USA, the incidence of FS is less than Asia (2–5% vs. 5–10% in India, and 9% in Japan).[24] In this study, the CC genotype in the Asians with FS was more frequent than in controls (23 and 14%, respectively), while it did not differ between Caucasians with FS and controls (44 and 45%, respectively). It is possible that the CC genotype acts as a causal factor for susceptibility to FS in Asians (Chinese and Egyptians) but not in Caucasians due to differences in environment, genetic background, or linkage disequilibrium of rs211037 with other variants contributing to epilepsy risk. Verification of this finding awaits future studies.

On the other hand, the results of the Taiwanese and Egyptian FS studies may be false due to small sample size and uncontrolled genotyping quality phenomena. Sample size is a crucial determinant of the power to detect a causal variant in genetic association studies of multi-factorial polygenic diseases. To increase the power of these studies, large sample sizes are needed to give enough power for identifying the common causal loci with small effect sizes.[25,26] The range of sample sizes within the 6 FS association studies was 187–414 (mean = 263). Of the two FS studies with significant association, one had the minimum subject number (187) and the other had less than the average sample size (220).[13,18] Rigorous quality control (QC) is a crucial component of association studies since subtle biases in raw data can produce false positives.[27] In the FS group, the three studies with significant association used the same method and protocol for genotype analysis (polymerase chain reaction-restriction fragment length polymorphism or PCR-RFLP),[13,17,18] while the studies with opposite results used single-strand confirmation polymorphism (SSCP) analysis or Applied Biosystems Taqman technology.[14–16] The three articles with significant association did not state whether they controlled the PCR-RFLP product quality by other techniques, however the studies that used SSCP or Taqman technology duplicated some genotype data by other techniques. A replication stage using alternative standard methods is a key factor in controlling genotype quality and reducing false positive results.[27] However, despite of doing QC for genotyping; the error of some techniques such as SSCP cannot be ignored. For example, a study which was performed in European American samples, reported a very low frequency of minor allele frequency in both cases and controls (0.007 and 0.02, respectively).[16]

Some limitations of our meta-analysis should be acknowledged. First, the criteria for the selection of patients and controls in the included studies were heterogeneous for parameters such as definitions for FS, seizure type, and family history of FS. There are two definitions of FS, published by the National Institute of Health (NIH) and the International League Against Epilepsy (ILAE). The NIH and ILAE definitions are very similar, but they differ in the lower age limit (three vs. one month, respectively).[24] Among the six studies of FS, four used the ILAE definition of FS.[13,15,18] Seizures are a clinical component of FS and consist of two different types: simple (generalized tonic–clonic) and complex (focal).[28] Of the FS studies, three were carried out on patients with simple FS[18] and all or 90%[16] of patients with complex FS,[14] respectively, but the remaining studies did not identify the type of seizure in the FS patients. Positive family history for FS increases the risk of developing FS up to 25–40%, as compared with acquired FS. Because the molecular mechanisms of familial FS differ from those of acquired FS, a heterogeneous population composed of both hereditary and nonhereditary FS produces underpowered results.[29] Out of six FS studies, three reported positive family history of FS in 28.5%,[18] 86%,[14] and 100% of FS patients,[16] but the remaining studies did not report the family history of FS patients. Second, the small number of studies of Caucasians with FS and Asians with IGE made it impossible to perform a complete stratified analysis by ethnicity. Third, the two Taiwanese studies used the same controls in their analysis. In conclusion, despite significant association between the *GABRG2* rs211037 polymorphism and susceptibility to FS, a possible false positive result cannot be excluded. Future studies with larger sample sizes are required to verify the results.

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