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Meta-Analysis

Association of GABRG2 rs211037 gene polymorphism with epilepsies and Pharmacoresistance to Anti-Epileptic Drugs: A Meta-Analysis

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Abstract

Gamma-aminobutyric acid A receptor, gamma 2 (*GABRG2*) gene encodes the GABRG2 protein which is a crucial part of the GABA receptor. The exonic *GABRG2* (C588T) rs211037 gene polymorphism has been commonly investigated concerning the variable association to different types of epilepsies (and antiepileptic drugs (AEDs) response. The current meta-analysis study was designed to explore whether this genetic variant predicts susceptibility to different types of epilepsy and pharmacoresistance to AEDs. In this meta-analysis, from 2000 to 2023, twenty studies were included containing 3351 epileptic patients and 3649 controls to investigate the association of *GABRG2* rs211037 polymorphism with susceptibility to different types of epilepsy. Similarly, five studies comprising 632 responder patients and 401 non-responder patients were selected to evaluate the *GABRG2* rs211037 polymorphism to pharmacoresistance to AEDs. Results showed a significant link between *GABRG2* rs211037 polymorphism and susceptibility to all types of epilepsies in the total, Asian, and Caucasian populations in genetic models. Similarly, CC vs CT, CC vs TT, and CC vs CT+TT genetic models were also associated with idiopathic generalized epilepsy (IGE) and febrile seizure (FS) epilepsies in the total, Asian and Caucasian populations. The alleles also showed a significant association with epilepsy. Genetic models of CC vs CT, CC vs TT, and CC vs CT+TT were also associated with pharmacoresistance to AEDs ($P<0.05$) in the total, Asian and Caucasian populations. The publication bias was not significant ($P<0.05$) but the heterogenicity ($I^2\%$) was mostly more than 50%. This meta-analysis concluded that there exists a significant association of *GABRG2* rs211037 polymorphism with susceptibility to different types of epilepsies and pharmacoresistance to AEDs in all populations.

Key Words: *GABRG2* rs211037, Asian Population, Caucasian Population, Febrile seizure, Idiopathic generalized seizure, Pharmacoresistance to AEDs

1. Introduction

Epilepsy is a neurological disorder characterized by more than one, unprovoked seizures apart by 24 hours (Cowan 2002). Epilepsy has a diverse and heterogeneous nature. Genetic abnormalities are considered one of the prominent reasons for epilepsy (Prasad and Prasad 2001, Sigurdardottir and Poduri 2006). Gene mutations, especially single nucleotide polymorphisms (SNPs) are strongly associated with channelopathies, brain malformations, and various types of seizures that are sometimes tagged as resistant epilepsies (Sisodiya 2010). Approximately 20–30 % of epilepsy cases are caused by acquired conditions, but the remaining 70–80 % of cases are considered to be associated with one or more genetic factors (Hildebrand et al. 2013). However, there are

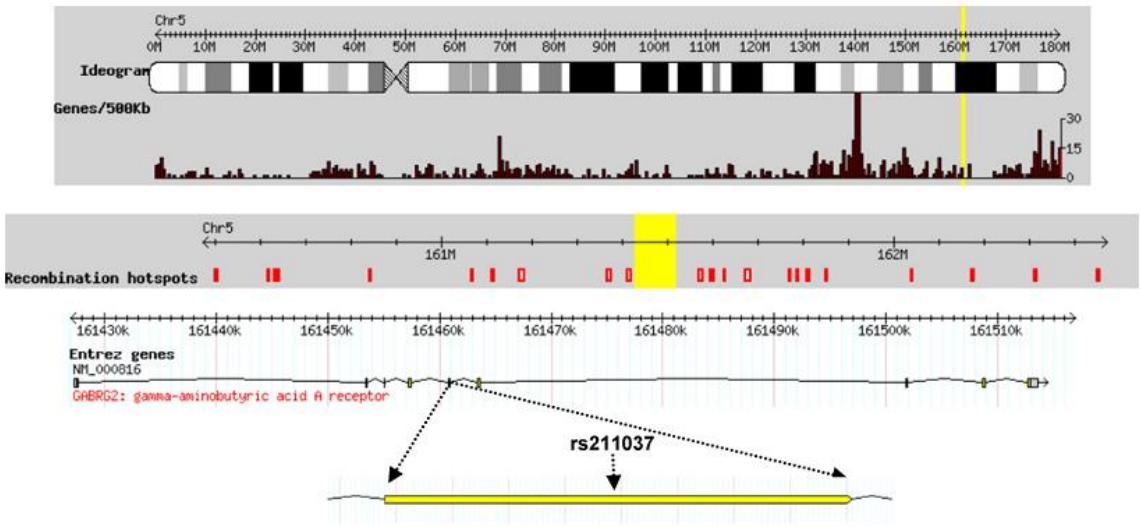

Figure 1: GABRG2 (rs211037) polymorphisms location on exon 5 of chromosome 5 (26).

more than 12 genes that have an established association with epilepsies (Weber and Lerche 2008). Among the associated genes *GABRG2* is an important one and has been explored in many populations for linkage with different types of epilepsies. GABA-A receptor is a ligand-gated ion channel complex receptor that regulates the chloride channel with the help of a major inhibitory neurotransmitter called Gamma-aminobutyric acid (GABA). GABA-A receptor is very common in the mammalian brain and initiates most of the fast synaptic inhibition (Macdonald and Olsen 1994). GABRG2 receptors have five subunits (two α, two β, and one γ) that are expressed by *GABRA1*, *GABRB2*, and *GABRG2* genes, respectively. Important functions like impaired channel gating, reduced mRNA stability, the aberration in subunit folding, and glycosylation which result in abnormal receptor assembly and trafficking are associated with various mutations in these above genes (Shivers et al. 1989, Arslan 2006, Mulligan et al. 2012). The *GABRG2* gene is located in 5q34 and is highly expressed in the brain (Kostrzewa et al. 1996). *GABRG2* (rs211037) gene polymorphisms are related to susceptibility to FS or idiopathic generalized epilepsy (IGE) and other types of epilepsies in different populations, however, the results were inconsistent (Table 1 and Fig. 1) (Kananura et al. 2002, Madia et al. 2003, Chou et al. 2007, Chou et al. 2003, Nakayama et al. 2003, Kinirons et al. 2006, Ma et al. 2006, Kumari et al. 2010, Shi et al. 2010, Salam, Rahman, and Karam 2012, Gitaí et al. 2012, Balan et al. 2013, El Ella et al. 2018, Butilă et al. 2018). The genetic variation in the *GABRG2* gene (rs211037) is also studied to find the association with pharmacoresistance to AEDs (Table 2) (Kumari et al. 2010, Balan et al. 2013, El Ella et al. 2018, Butilă et al. 2018). The association of *GABRG2* (rs211037) gene polymorphisms with epilepsies and pharmacoresistance to AEDs are variable without any solid conclusion. Therefore, the current meta-analysis study aims to find the association of *GABRG2* (rs211037) gene polymorphisms with different types of epilepsies and to pharmacoresistance to AEDs in different populations for a reasonable conclusion.

2. Methods & Materials

2.1. Search Strategy & Selection

The current meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al. 2010) (Figure

Table 1: Allele and genotype distribution of GABRG2 rs211037 polymorphism in the included studies in various epilepsies.

No	Author	Year	Ethnicity	Epilepsy	Definition	Sample Size (N)		Genotypes						Alleles				Assoc
						Cases	Control	CC		CT		TT		C		T		
								Cases	Control	Cases	Control	Cases	Control	Cases	Control	Cases	Control	
1	Kananura et al.	2002	German	IGE	ILAE	135	154	83	104	47	42	5	8	213	250	57	58	No
2	Madia F et al.	2003	Italian	SMEI (FS + AFS)	ILAE	53	96	28	48	21	49	4	8	77	136	29	56	No
3	Chou et al.	2003	Taiwanese	FS	ILAE	104	83a	17	9	55	32	31	42	89	50	117	116	yes
4	Nakayama et al.	2003	Japanese	FS	Freeman JM, 1980	94	106	24	23	50	58	20	25	98	104	90	108	No
5	Kinirons et al.	2006	British	All	ILAE	569	330	342	203	187	114	40	13	871	520	267	140	No
6	Kinirons et al.	2006	British	FS	ILAE	84	330	46	203	35	114	3	13	127	520	41	140	No
7	Kinirons et al.	2006	British	IGE	ILAE	78	330	48	203	24	114	6	13	120	520	36	140	No
8	Kinirons et al.	2006	Irish	All	ILAE	699	283	376	170	262	99	31	14	1014	439	324	127	No
9	Kinirons et al.	2006	Irish	FS	Other	80	283	43	170	35	99	2	14	121	439	39	127	No
10	Kinirons et al.	2006	Irish	IGE	ILAE	117	283	67	170	48	99	2	14	182	439	52	127	No
11	Ma et al.	2006	American	FE+ FS	Not Def	74	118	73	113	1	5	0	0	147	231	1	5	No
12	Chou et al.	2007	Taiwanese	IGE	ILAE	77	83a	17	9	38	32	22	42	72	50	82	116	No
13	Ritu Kumari et al.	2010	India	all types	ILAE	395	199	211	117	168	73	16	9	591	307	199	91	No
14	XiuYu Shi	2010	Japanese	All types	ILAE	140	48	35	9	67	24	38	15	137	42	143	54	yes
15	Salam et al.	2012	Egyptian	IGE+FS	ILAE	100	120	26	12	42	46	32	62	94	70	106	170	yes
16	Lívia ,et al.	2012	Brazilian	Myoclonic	ILAE	98	130	41	47	45	45	14	8	63	69	36	30	No
17	Shabeesh], et al.	2013	Indian	FS	ILAE	240	267	307	150	113	99	18	16	727	399	149	131	yes
18	Soheir S et al.	2018	Egyptian	IGE	ILAE	100	100	46	68	42	40	12	2	134	176	66	44	yes
19	Anamaria et al.	2018	Romanian	FS	ILAE	54	153	12	79	24	57	18	17	49	70	61	29	yes
20	Anamaria et al.	2018	Romanian	IGE	ILAE	60	153	31	79	24	57	5	17	86	70	34	29	yes

FE= Focal Epilepsy, IGE= Idiopathic Generalized Epilepsy, FS= Febrile Seizure, SMEI=severe myoclonic epilepsy of infancy, AFS=afebrile seizure, ILAE=International League Against Epilepsy, Assoc=Association

Table 2: Allele and genotype distribution of GABRG2 rs211037 polymorphism with AEDS response in various epilepsies.

No	Author	Year	Ethnicity	Epilepsy	Definition	AEDs	Sample Size (N)		Genotypes						Alleles				Ac
							Responsive	Non-Responsive	CC		CT		TT		C		T		
									Responsive	Non-Responsive	Responsive	Non-Responsive	Responsive	Non-Responsive	Responsive	Non-Responsive	Responsive	Non-Responsive	
1	Kumari	2010	India	all	ILAE	No	259	122	137	66	109	53	13	3	383	185	135	59	N
2	Shabeesh	2013	India	FS	ILAE	No	240	198	165	142	66	47	9	9	394	331	84	65	N
3	Anamaria	2018	Romanian	FS	ILAE	No	38	16	10	2	22	3	7	11	42	7	36	25	ye
4	Anamaria	2018	Romanian	IGE	ILAE	No	49	11	30	1	17	7	2	3	77	9	21	13	ye
5	Soheir S	2018	Egyptian	IGE	ILAE	Not	46	54	30	16	16	26	0	12	76	58	16	50	ye

IGE= Idiopathic Generalized Epilepsy, FS= Febrile Seizure, ILAE=International League Against Epilepsy, Assoc=Association

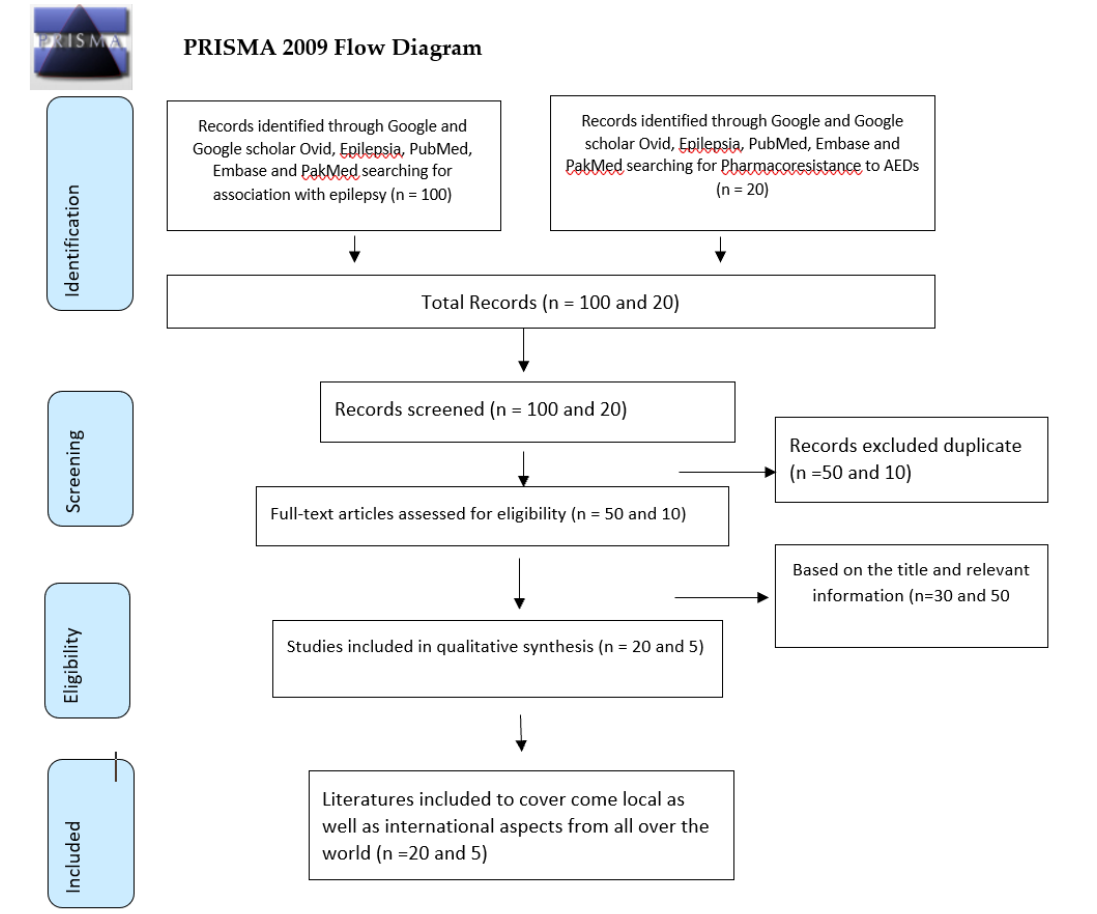

Figure 2: Flow diagram taken from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting, items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit www.prisma-statement.org.

2). The published studies were searched by using the MeSH terms ''epilepsy,'' ''polymorphism,'' ''variant,'' ''GABRG2,'' ''rs211037,'' ''rs211037 C>T,'' ''Crs211037T,'' " C588T" and ''susceptibility,'' "Resistant epilepsy" Pharmacoresistance to Anti-epileptic drugs", " Pharmacogenetics and Pharmacogenomic of AEDs with respected to GABRG2 gene polymorphism", in google scholar, PubMed, Ovid, Epilepsia, MEDLINE, Embase, and the Cochrane Database of Systematic Reviews without language limitation, the last search being updated in 2023. The reference lists were hand-searched for other relevant publications.

2.2. Data Extraction /Inclusion and Exclusion Criteria

The first author name, year of publication, ethnicity of patients, numbers of epilepsy patients and of controls with each genotype, and type of epilepsy were selected from each publication according to the following inclusion criteria: (1) examining the association between *GABRG2* (rs211037) gene polymorphism and epilepsy; (2) the study used control in the study; (3) Calculation of odd ration (OR (95%CI) were possible of genotype frequencies of the *GABRG2* (rs211037) gene polymorphism. The review or case studies, duplicated studies, studies without a control group, or overlapping cases and/or

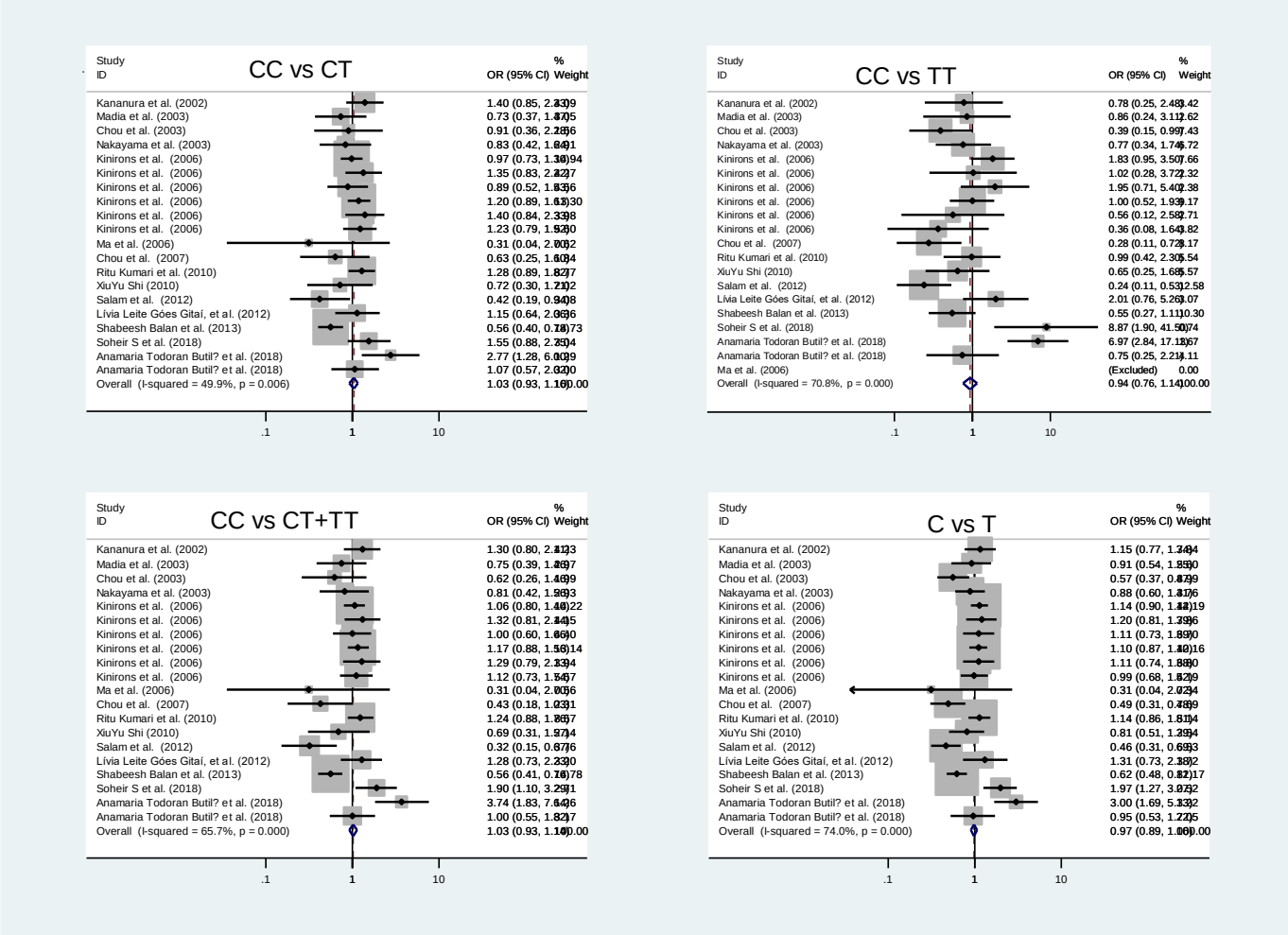

Figure 3: Forest plot of the association of different genetic models of GABRG2 rs211037 with all types of epilepsies in all population. Since the control samples of two Chou et al. studies12,16 was the same, only one control group was included in this meta-analysis. For each study, the position of the 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.

control were excluded from the current meta-analysis.

2.3. Definition of Drug Resistance and Responsiveness

Drug resistance is defined as the occurrence of at least three/four episodes of seizures over one year with three rational AEDs at maximum tolerated doses (Siddiqui et al. 2003, Lakhan et al. 2009). Patients who had undergone surgeries for seizure control were considered refractory irrespective of their outcome after surgery. The epilepsy patients who had complete freedom from seizures for at least one year from the last follow-up visit were considered drug-responsive.

2.4. Statistical Analysis

The strength of the association between *GABRG2* rs211037 polymorphism and epilepsy susceptibility was assessed by ORs with 95% CIs. The pooled ORs were performed for the allele model (C vs. T), codominant model (CC vs CT), and dominant model (CC vs CT+TT). Moreover, a Chi-square test was used to determine whether the observed frequencies of

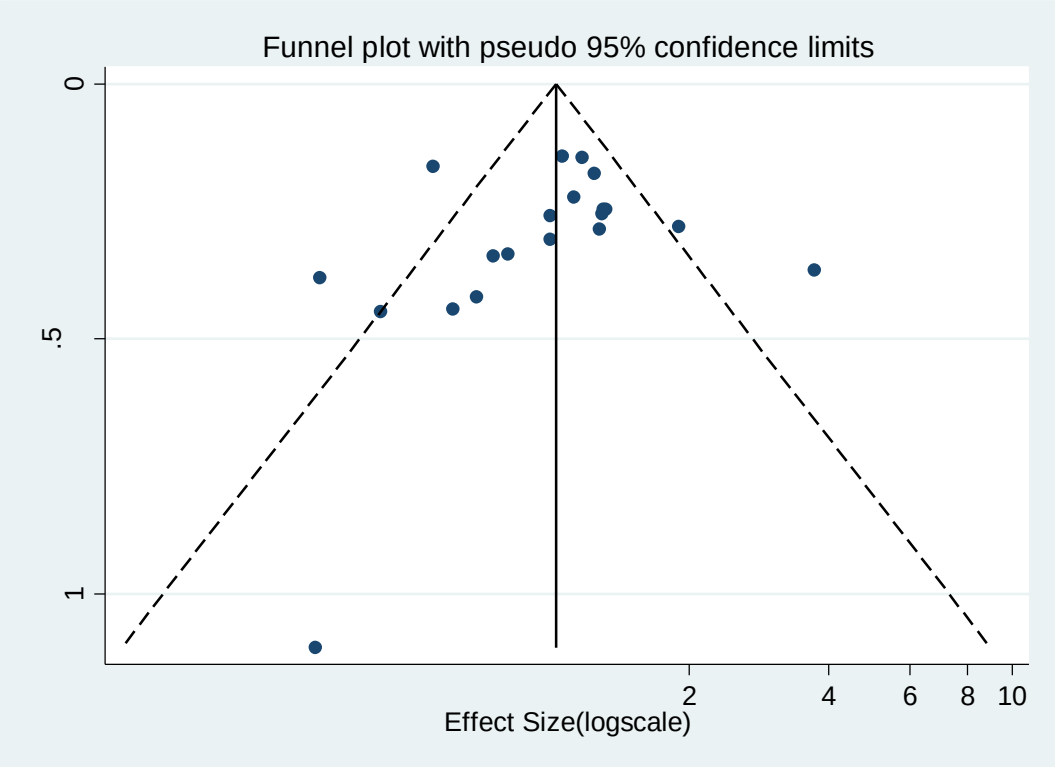

Figure 4: Funnel Plot different genetic models of GABRG2 rs211037 with all epilepsies in all population. Since the control samples of two Chou et al. studies12,16 was the same, only one control group was included in this meta-analysis. For each study, the position of the square is the OR, the horizontal 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.

the genotypes in the controls conformed to Hardy–Weinberg Equilibrium (HWE) expectations. The random effect model was used when I^2 was greater than 50% and the fixed effect model was used when I^2 was less than 50%.

Heterogeneity among the studies was quantized by the I^2 statistics. $I^2 > 50\%$ indicated an obvious between-study heterogeneity (Higgins et al. 2003), and the pooled OR was calculated by the random effects model (DerSimonian and Laird 1986); otherwise, the fixed effects model was used (Mantel and Haenszel 1959). Additionally, sensitivity analyses were performed to assess the stability of the meta-analysis results by sequential removal of each study. Finally, Egger's tests were used to analyze the publication bias (Egger et al. 1997, Furuya-Kanamori et al. 2020, Tsuji et al. 2020). All statistical analyses were conducted using Stata 12.0 (Stata Corp, College Station, TX). A p-value less than 0.05 was considered statistically significant.

3. Results

Characteristics of the included studies are listed in Table 1. The initial search with the keywords and the subject terms identified 100 abstracts, all published in English. Of these abstracts, 50 were excluded because they were irrelevant to rs211037 or epilepsy. In the next step, the full texts of the 50 remaining articles were evaluated, yielding 20, including 3351 epileptic patients and 3649 control that met our eligibility criteria for meta-analysis (Fig. 2). Twelve studies were about the FS or IGE (Chou et al. 2003, Nakayama et al. 2003, Kinirons et al. 2006, Chou et al. 2007, Salam, Rahman, and Karam 2012, Balan et al. 2013, El Ella et al. 2018, Butilă et al. 2018). There

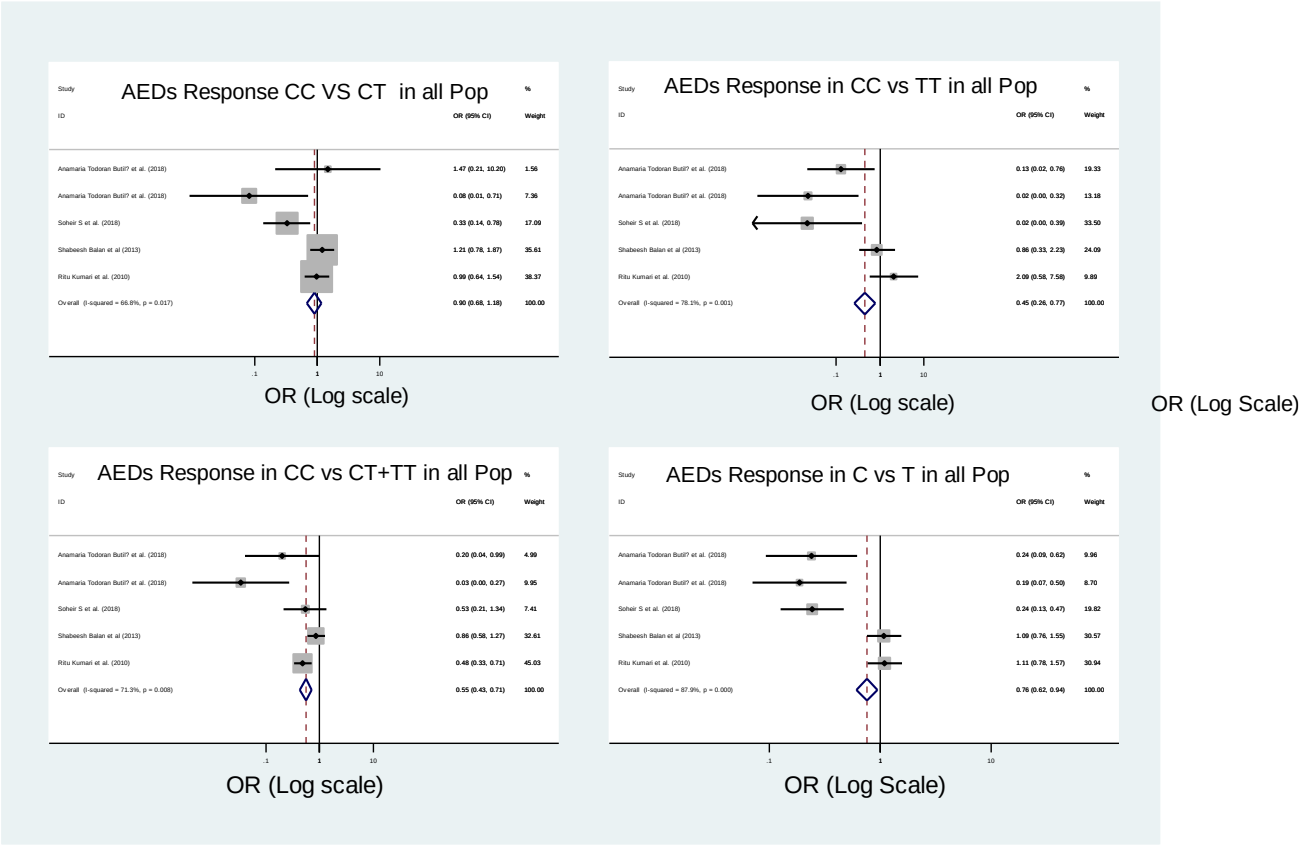

Figure 5: Forest Plot of the association of different genetic models of GABRG2 rs211037 with pharmacoresistance to AEDs in all types of epilepsies in all population. For each study, the position of the square is the OR, the horizontal line spans the 95% CI of the OR, and the area of the square is inversely 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.

was a considerable diversity of epilepsy types among the eight included studies (Kananura et al. 2002, Chou et al. 2007, Madia et al. 2003, Nakayama et al. 2003, Salam, Rahman, and Karam 2012, Chou et al. 2003, Kinirons et al. 2006, Ma et al. 2006, Kumari et al. 2010, Shi et al. 2010, Gitaí et al. 2012, Balan et al. 2013, El Ella et al. 2018, Butilă et al. 2018). The control group in the Taiwanese studies was shared, therefore only one control group of the two studies was included in the meta-analysis of all studies (Table 3 and Fig. 3) (Kinirons et al. 2006, Madia et al. 2003). Studies were classified into two categories: FS (6 studies: 789 patients vs. 1450 controls) (Kananura et al. 2002, Chou et al. 2007, Madia et al. 2003, Nakayama et al. 2003, Salam, Rahman, and Karam 2012, Chou et al. 2003, Kinirons et al. 2006, Ma et al. 2006, Kumari et al. 2010, Shi et al. 2010, Gitaí et al. 2012, Balan et al. 2013, El Ella et al. 2018, Butilă et al. 2018) and IGE (5 studies: 567 patients vs. 1103 controls) (Kananura et al. 2002, Kinirons et al. 2006, Chou et al. 2007, El Ella et al. 2018, Butilă et al. 2018). In two reports, patients had either FS or IGE, hence that study was split and included in either FS or IGE meta-analyses (Salam, Rahman, and Karam 2012, Butilă et al. 2018). Meta-analysis data of FS, IGE, and all studies are shown in Table 3. Similarly, five studies were included for pharmacoresistance to AEDs are listed in Table 2. There were 20 abstracts identified and all were published in English. Of these ten were excluded due to irrelevancy to pharmacoresistance to AEDs. In

the next step full text of 10 publications was evaluated and the final selection of 5 publications with 632 responder patients and 401 non-responder patients to AEDs (Balan et al. 2013, Kumari et al. 2010, Butilă et al. 2018, El Ella et al. 2018) (Table 2 and Figure 2). Meta-analysis data of pharmacoresistance to AEDs studies of all types of epilepsies are shown in Table 4. The stratification was not possible in these selected publications due to the low number of publications. Three publications, two from the Romanian population and the Egyptian population showed resistance to AEDs (Table 2) (Butilă et al. 2018, El Ella et al. 2018). The codominant model (CC vs CT and CC vs TT) showed a significant association (OR (95%CI), p, 1.03 (0.9-1.2), p0.006; 0.93 (0.8-1.2), p=0.0001; 0.86 (0.7-1.0), p=0.011; 0.67 (0.5-0.9), p=0.000) with all types of epilepsies in all population, and Asian population respectively shown in Table 3, Figure 3 and supplementary figures (S1-S2). However, there was no association in the Caucasian population. However, the dominant model (CC vs CT+TT) also showed a significant association (OR (95%CI), p; 1.03 (0.9-1.4), p=0.001; 0.62 (0.5-0.7), p= 0.001; 1.05 (0.9-1.2), p= 0.000) with all types of epilepsies in all, Asian and Caucasian population shown in Table 3, Figure 4 and Supplementary figures (S1-S2). The allelic model (C vs T) also showed a significant association with all types of epilepsies in all Asian populations (Table 3). Publications bias was less than $p<0.05$ shown in funnel plot (Figure 4).

Similarly, significant association ($p<0.05$) with IGE existed under the codominant model (CC vs CT and CC vs TT) in all epilepsies in all Asian populations but dominant (CC vs CT+TT) in genotype models in all epilepsies in all, Asian and Caucasian population (Table 3 and Supplementary figures (3S-6S).

However, the codominant model (CC vs CT) showed only association ($p<0.05$) with FS in all populations (Table 3 and 6S-8S) while the other codominant model (CC vs TT) showed a significant ($p<0.05$) association in all and Caucasian populations shown in Table 3 and supplement figures (6S-8S). A significant ($p<0.05$) association with FS existed in the dominant model (CC vs CT+TT) only in all populations (Table 3).

The codominant model (CC vs CT and CC vs TT) showed a significant association (OR (95%CI), p; 0.89 (0.7-1.2), p=0.017; 0.95 (0.7-1.3), p=0.031; 0.32 (0.1-1.2), p=0.04) with pharmacoresistance to AEDs shown in Table 4 and Figure 5. The dominant model (CC vs CT+TT) showed the association (OR (95%CI), p; 0.55 (0.4-0.7), p=0.008) with pharmacoresistance to AEDs shown in Table 4 and supplementary figure (9S-12S). The stratification was not possible for FS and IGE due to the small number of publications. Egger's test did not indicate statistically significant asymmetry of the plot ($p<0.05$), suggesting no evidence of publication bias.

4. Discussion

Of twenty publications, seven showed that *GABRG2* rs211037 polymorphism has an association with different types of epilepsies. There are two studies from Egyptian about FS and IGE, one study from the Taiwanese about FS, one Japanese study about all types of epilepsies, one Indian study about FS, and two Romanian studies about IGE and FS showed the susceptibility to these epilepsies. Meta-analysis demonstrates that *GABRG2* rs211037 polymorphism in codominant (CC vs CT and CC vs TT) and dominant model (CC vs CT+TT) is associated with different types of epilepsies in all populations and Asian populations. Taiwanese, Egyptian, Indian, Japanese, and Romanian studies contributed much to the significance. Similarly, the meta-analysis also demonstrated that *GABRG2* rs211037 polymorphism in codominant (CC vs CT and CC vs TT) and dominant model (CC vs CT+TT) is associated with pharmacoresistance to AEDs in all types of epilepsies in the total population. Among the five studies, three studies showed

Table 3: Meta-analysis of GABRG2 rs211037 susceptibility to FS, IGE, and all epilepsies under different genetic models.

Allele/genotype	All Epilepsies (N=20, 8, 12)				IGE (N=7,2,4)				FS (N=8,3,5)			
	OR 95% CI	p	I^2 (%)	P_{het}	OR 95% CI	p	I^2 (%)	P_{het}	OR 95% CI	p	I^2 (%)	P_{het}
CC vs CT Genotypes												
All	1.03 (0.9-1.2	0.006	49.4%	0.675	1.16 (0.9-1.4)	0.518	0%	0.197	0.87 (0.7-1.1)	0.001	73%	0.697
Asian	0.86 (0.7-1.0)	0.011	59.8%	0.872	1.20 (0.7-1.9)	0.106	61.7%	----	0.56 (0.4-0.7)	0.460	0.0%	0.841
Caucasian	1.15 (1.0-1.3)	0.292	16.0%	0.976	1.15 (0.8-1.5)	0.664	0.0%	0.538	1.48 (1.1-2.0)	0.195	36.2%	0.683
CC vs TT Genotypes												
All	0.93 (0.8-1.2)	0.0001	70.8%	0.886	0.91 (0.6-1.4)	0.003	72.3%	0.407	0.73 (0.5-1.0)	0.000	82.5%	0.763
Asian	0.67 (0.5-0.9)	0.000	71.3%	0.085	0.99 (0.5-1.9)	0.000	93.1%	----	0.38 (0.2-0.6)	0.308	15.1%	0.686
Caucasian	1.32 (0.9-1.7)	0.009	58.7%	0.233	0.85 (0.5-1.5)	0.279	22.0%	0.162	2.31(1.3-4.1)	0.005	81.2%	0.074
CC vs CT+TT Genotypes												
All	1.03 (0.9-1.4)	0.001	65.7%	0.524	1.83 (1.5-2.3)	0.001	76.0%	0.247	1.13 (0.9-1.4)	0.000	93.0%	0.589
Asian	0.62 (0.5-0.7)	0.001	68.2%	0.783	1.11 (0.7-1.7)	0.051	73.8%	------	0.48 (0.3-0.6)	0.973	0.0%	0.898
Caucasian	1.054 (0.9-1.2)	0.000	94.4%	0.025	2.22 (1.7-2.9)	0.015	71.2%	0.848	4.59 (3.2-6.5)	0.620	0.0%	0.656
C vs T Alleles												
All	0.97 (0.8-1.1)	0.000	74.0%	0.960	1.04 (0.8-1.3)	0.002	73.4%	0.811	0.80 (0.7-0.9)	0.000	83.0%	0.558
Asian	0.80 (0.7-0.9)	0.000	81.1%	0.776	1.00 (0.7-1.4)	0.000	94.5%	-----	0.56 (0.5-0.7)	0.473	0.0%	0.479
Caucasian	1.13 (1.0-1.3)	0.168	29.2%	0.953	1.01 (0.9-1.3)	0.92	0.0%	0.745	1.37 (1.1-1.8)	0.015	71.2%	0.887

Phet= Publication heterogenicity (egger test was used)

Table 4: Meta-analysis of GABRG2 rs211037 pharmacoresistance response to AEDs in FS, IGE, and all epilepsies using different genetic models.

Allele/genotype	All Epilepsies (N=5,3, 2)				IGE (N=2,1,1)				FS (N=2,1,1)			
	OR 95% CI	p	I^2 (%)	P_{het}	OR 95% CI	p	I^2 (%)	P_{het}	OR 95% CI	p	I^2 (%)	P_{het}
CC vs CT Genotypes												
All	0.89 (0.7-1.2)	0.017	66.8%	0.248	0.25 (0.1-0.5	0.238	28.2%	---	1.21 (0.7-1.8)	0.849	0.0%	----
Asian	0.95 (0.7-1.3)	0.031	71.2%	0.144	---- a	---- a	---- a	----	---- a	---- a	---- a	----
Caucasian	0.32 (0.1-1.2)	0.049	74.3%	-----	---- a	---- a	---- a	----	---- a	---- a	---- a	----
CC vs TT Genotypes												
All	0.44 (0.3-0.8)	0.001	78.1%	0.193	0.02(0.0-0.2)	0.988	0.0%	----	0.53 (0.2-1.2)	0.064	70.9%	----
Asian	0.62 (0.3-1.1)	0.011	77.8%	-----	---- a	---- a	---- a	----	-----	---- a	---- a	----
Caucasian	0.08 (0.0-0.4)	0.282	13.6%	-----	---- a	---- a	---- a	----	-----	---- a	---- a	----
CC vs CT+TT Genotypes												
All	0.55 (0.4-0.7)	0.008	71.3%	0.105	0.24(0.1-0.5)	0.013	83.9%	----	0.77 (0.5-1.1)	0.082	66.9%	----
Asian	0.63 (0.5-0.8)	0.109	54.8%	0.811	---- a	---- a	---- a	----	---- a	---- a	---- a	----
Caucasian	0.08 (0.0-0.3)	0.176	45.3%	----	---- a	---- a	---- a	----	---- a	---- a	---- a	----
C vs T Alleles												
All	0.76 (0.6-0.9)	0.000	87.9%	0.013	0.22 (0.1-0.3)	0.668	0.0%	----	0.87 (0.6-1.2)	0.003	88.3%	----
Asian	0.88 (0.7-1.1)	0.000	88.6%	0.003	---- a	---- a	---- a	----	---- a	---- a	---- a	----
Caucasian	0.21 (0.1-0.4)	0.729	0.0%	-------	---- a	---- a	---- a	----	---- a	---- a	---- a	----

a= one study is available from Asia and Caucasian Population

association with pharmacoresistence, two Romanian and one Egyptian study. However, the association of *GABRG2* rs211037 polymorphism with pharmacoresistance to AEDs was not found for FS and IGE in Asian and Caucasian populations due to the limited number of studies in the existing literature. More, prescribed AEDs (e.g. carbamazepine, valproic acid, etc.) were not mentioned in these studies. Therefore, it is important to conduct such types of studies on specific AEDs in different populations. Such studies will help find a clear sense of association with pharmacoresistance to AEDs.

GABRG2 rs211037 polymorphism is variable among geographical populations. This genetic polymorphism interacts with environmental factors such as regional climate, culture, and pathogens and results in a variety of adaptations of populations or individuals (Jorde and Wooding 2004, Campbell and Tishkoff 2008, Sabeti et al. 2006). The incidence of FS in Western Europe and the USA is less than the Asian population (2-5% vs 5-10%) in India and (9% in Japan) (Waruiru and Appleton 2004).

In this meta-analysis, the CC genotype is more common in the FS of the Asians compared to controls (19 and 10% respectively), while this difference is not too high for Caucasians' FS compared to controls (7 and 10%). This difference may be due to differences in environment, genetic background, or linkage disequilibrium of rs211037 with other variants contributing to epilepsy risk. This needs further exploration with bigger studies. On the other hand, the small sample size and uncontrolled genotyping quality phenomena of the Taiwanese and Egyptian FS studies may affect the overall result of the study. The 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 to identify the common causal loci with a small effect sizes (Tan, Mulley, and Berkovic 2004, Spencer et al. 2009). The range of sample sizes within the 7 FS association studies was 80–240 (mean = 115). Of the two FS studies with significant association, one had the minimum subject number (87) and the other sample size (240)(El Ella et al. 2018, Balan et al. 2013). Rigorous quality control (QC) is a key factor during association studies because a minor bias in the data leads to false positive results (Dequeker et al. 2001).

The significant association in three studies in FS was genotyped through polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) (Madia et al. 2003, Kinirons et al. 2006, Ma et al. 2006), while the studies with opposite results used single-strand conformational polymorphism (SSCP) analysis or Applied Biosystems TaqMan technology (Nakayama et al. 2003, Salam, Rahman, and Karam 2012, Chou et al. 2007). Some articles with a significant association did not mention 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.

To control the genotype quality and minimize the false positive results a replication stage using an alternative standard method was used (Dequeker et al. 2001). The SSCP error cannot be ignored in QC for genotyping. A study that was performed in European American samples reported a low frequency of minor alleles in both patients and controls (0.007 and 0.02, respectively) (Chou et al. 2007).

A meta-analysis itself has some limitations which must be considered like the criteria of patients and control selection in the included studies are different for parameters such as definition of epilepsies (FS, IGE) classification of seizure, and family history. Commonly two systems; the National Institute of Health (NIH) and the International League Against Epilepsy (ILAE) are used to classify and diagnose

epilepsies with some differences in the guidelines (Waruiru and Appleton 2004, Madia et al. 2003, Salam, Rahman, and Karam 2012, Ma et al. 2006, Reid et al. 2009, Nakayama et al. 2003, Chou et al. 2007). Sometimes proper diagnosis and classification become cumbersome such as the molecular mechanisms of familial FS differ from those of acquired FS, a heterogeneous population composed of both hereditary and nonhereditary FS produces underpowers results (Thomas, Witte, and Biomarkers 2002). 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 for association with epilepsy and AED response. Third, the two Taiwanese and one Romanian study used the same controls in their analysis. In conclusion, despite the 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.

Conflict of Interest

The authors declare that they have no competing interests.

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Study Approval

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Authors Contribution

SU & SA conceptualized the study, NA, MZ, and MI helped in the literature review and analysis, MN and SU helped write the first draft, and SU& SA supervised the whole project and wrote the final manuscript.

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