Integrative analysis of rs717620 polymorphism in therapeutic response to anti-seizure medications

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ABSTRACT

Background: Previous studies have shown that the rs717620 polymorphism in *ABCC2*, the gene encoding multidrug resistance protein 2, influences the therapeutic response to anti-seizure medications (ASMs). However, this result is not consistent, and the mechanism by which rs717620 influences ASM responses is unclear.
Aims: The present study evaluated the association between rs717620 genotype and ASM efficacy, and examined the potential mechanisms.
Main: methods: We conducted a literature search of five electronic databases, Embase, Medline, Web of Science, China National Knowledge Infrastructure, and Wanfang, to identify relevant studies on response to ASM therapy among rs717620 genotypes. Expression quantitative trait loci analysis and drug–gene interaction analysis were also performed to assess the underlying mechanisms.
Key findings: The pooled results for 18 studies revealed a significant association between rs717620 genotype and ASM resistance under the recessive model (TT vs. CT + CC: OR = 1.68, 95 % CI = 1.27–2.21, I^2 = 3.1 %). A significant association was also found in the Asian population under the recessive model (TT vs. CT + CC: OR = 1.70, 95 % CI = 1.26–2.29, I^2 = 29.3 %). Further analysis revealed that rs717620 regulates the expression of *ABCC2* in human brain, while drug–gene interaction analysis suggested that ABCC2 interacts with oxcarbazepine and carbamazepine.
Significance: The rs717620 polymorphism influences ASM therapeutic responses by altering brain expression levels of *ABCC2*.

1. Introduction

Some forms of epilepsy have a genetic etiology, such as juvenile myoclonic epilepsy, Dravet syndrome, and childhood absence epilepsy [1]. Although a variety of anti-seizure medications (ASMs) are available for epilepsy therapy, 20%–30 % of patients do not achieve effective seizure control [2]. Therefore, it is essential to explore new therapeutic targets and treatment methods for epilepsy. Genetic background may also influence ASM response. Indeed, several recent studies have reported that gene polymorphisms can

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confer ASM resistance or promote adverse drug reactions in epilepsy patients [3–5]. However, these findings have been inconsistent across studies, in part due to limited sample size and statistical power.

The *ABCC2* gene located on chromosome 10 encodes a member of the ATP-binding cassette transporter superfamily involved in multidrug resistance. In humans, *ABCC2* harbors a single nucleotide polymorphism in the 5′ untranslated region (UTR), rs717620, that has been reported to influence the therapeutic response to ASMs [6,7]. For instance, the rs717620 genotype influenced plasma concentrations of the novel ASM lacosamide as well as treatment efficacy in the Chinese population [8]. However, this finding was not replicated in other studies [9–18]. For the practice of precision medicine, it is necessary to identify genetic factors influencing ASM responses in individual patients. Further, as new drugs are introduced and potential associations between genetics and drug efficacy emerge, it is necessary to conduct larger scale studies with greater statistical power and more rigorous quality control.

In this study, we compared the rs717620 genotype between 2305 drug-resistant and 2205 drug-responsive epilepsy patients of Asian and Caucasian ancestry to identify potential association with ASM efficacy. We also performed expression quantitative trait loci (eQTL) analysis and drug–gene interaction analysis to explore the potential mechanisms for associations between rs717620 genotype and ASM response.

2. Materials and methods

2.1. Literature search

A systematic search for studies examining the association between rs717620 genotype and ASM response was conducted using Embase, Medline, Web of Science, China National Knowledge Infrastructure, and Wanfang. Databases were searched up to April 9, 2023, using the following terms: (*ABCC2* OR *MRP2*) AND (polymorphism OR variant) AND (epilepsy OR seizure OR epileptic). There were no language restrictions.

2.2. Inclusion and exclusion criteria

Study inclusion criteria were as follows: (1) Studies related ASM therapeutic response; (2) Accurate genotyping data obtained; (3) Therapeutic outcome clearly described. Reviews and meta-analyses were excluded, as were studies in which the rs717620 genotype distribution of the control group did not conform to Hardy–Weinberg equilibrium (HWE).

2.3. Data extraction and quality assessment

The rs717620 genotype distribution, first author, year of publication, genotyping method, and ethnicity of the population were extracted and reviewed independently by two authors (Wang and Ding). Any disagreements during data extraction were resolved by a third researcher (Rao). The Newcastle–Ottawa quality assessment scale was used to assess the quality of all included studies [19].

2.4. Statistical analysis

All statistical analyses were performed using STATA version 11 (Stata-Corp LP, College Station, TX, U.S.A.) and a p-value <0.05 was considered statistically significant for all tests. Hardy–Weinberg equilibrium was confirmed in control groups by Chi-square test. The significance of pooled odds ratios (ORs) was evaluated using the Z test. Subgroup analyses were conducted according to ethnicity. A p-value <0.05 or $I^2 > 50$ % was considered to indicate significant heterogeneity. In such cases, a random-effect model was constructed for meta-analysis; otherwise, a fixed-effect model was applied. Sensitivity analysis was performed by removing one study at a time and evaluating the change in the pooled ORs and 95 % confidence intervals (CIs) of the remaining studies. Begg's test [20] and Egger's test [21] were performed to assess the effect of publication bias (p-value <0.05).

2.5. Expression quantitative trait loci (eQTL) analysis

The purpose of the Genotype-Tissue Expression project (GTEx, http://www.gtexportal.org/home/) is to evaluate how genetic variation regulates gene expression and function in normal human tissues and how this regulatory association influences the onset risk and development of diseases. To explore if rs717620 regulates the expression level of *ABCC2* in human brain tissues, we performed eQTL analysis using GTEx.

2.6. Evaluation of ABCC2 influences on ASM therapy

Although the influence of *ABCC2* on ASM therapy has been extensively studied, the results remain inconclusive. To further evaluate this, we performed drug–gene interaction analysis using the Drug–Gene Interaction Database [22].

3. Results

3.1. Characteristics of the included studies

The flow diagram of study selection is shown in Fig. 1. The initial search of five databases yielded 232 records, of which 120 were excluded as duplications. After the removal of review articles, meta-analyses, and conference abstracts, a total of 69 full-text articles were identified. Further evaluation revealed that 23 articles did not examine the association between rs717620 genotype and ASM therapy response, two articles did not provide genotype data, one article provided incorrect genotyping data, and the genotype distribution in the control group of two studies did not conform to HWE. Finally, 18 studies on the association between rs717620 and ASM therapy response were included. The characteristics of all studies are summarized in Table 1.

3.2. Meta-analysis results

A total of 4510 epileptic patients were included in the 18 studies evaluating the association between rs717620 genotype and response to ASM therapy. Pooled results indicated that the rs717620 TT genotype was associated with resistance to ASMs under the recessive model (TT vs. CT + CC: OR = 1.68, 95 % CI = 1.27–2.21, $I^2 = 3.1$ %) for the entire cohort (Fig. 2c) and the Asian subgroup (TT vs. CT + CC: OR = 1.70, 95%CI = 1.26–2.29, $I^2 = 29.3$ %) (Fig. 2c). However, no significant association between the rs717620 and therapeutic response to ASMs was observed under codominant and dominant model(Fig. 2a and b).

3.3. Publication bias and sensitivity analysis

Publication bias was not observed for either genetic model (Table 2) and funnel plots also showed no publication bias (Fig. 3). In sensitivity analysis, the significant association between rs717620 and response to ASM therapy was not eliminated by the removal of any single study (Fig. 4).

3.4. Expression quantitative trait loci (eQTL) analysis

The rs717620 genotype regulated *ABCC2* expression in the caudate ($P = 0.0028$), cerebellar hemisphere ($P = 0.0008$), cerebellum ($P = 0.000032$), cortex ($P = 0.041$), hippocampus ($P = 0.03$), putamen ($P = 0.024$), spinal cord ($P = 0.022$), and substantia nigra ($P = 0.041$) (Fig. 5).
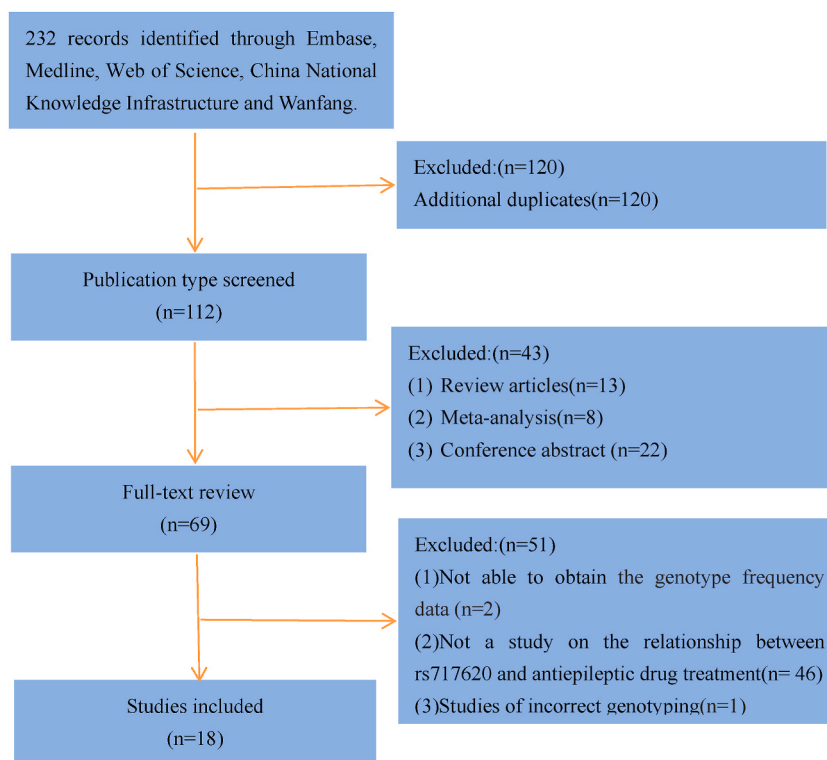

Fig. 1. Flow diagram of selection of studies.

Table 1
Characteristics of studies included in the meta-analysis.

Author and year	Region	Number of NR/R	Method of Genotyping	HWE test P value
Zhou et al. (2015)	China	156//234	BeadChip scanning and GoldenGate assay	0.83
Xue et al. (2016)	China	104/150	PCR-RFLP	0.71
Qu et al. (2012)	China	217/320	PCR-RFLP	0.51
Seo et al. (2008)	Japan	133/146	PCR-RFLP	0.98
Subenthiran et al. (2013)	Malaysia	152/162	TaqMan	0.64
Wan et al. (2015)	China	22/58	DNA sequencing	0.06
Grover et al. (2012)	India	88/128	Direct sequencing	0.34
Yang et al. (2019)	China	133/85	PCR-improved multiple ligase detection	0.44
Zhao et al. (2023)	China	65/166	DNA sequencing	0.11
Yang et al. (2018)	China	41/163	PCR-RFLP	0.11
Yun et al. (2015)	China	22/58	PCR-RFLP	0.06
Zhang et al. (2011)	China	93/88	SNaPshotSNP	0.85
Eitan et al. (2019)	Jordan	171/124	MassARRAY	0.19
Hilger et al.(2012)	Austria	337/44	TaqMan	0.65
Sporis et al.(2013)	Croatia	50/44	PCR-RFLP	0.25
Ufer et al.(2009)	German	118/103	PCR-RFLP	0.56
Ufer et al.(2011)	German	176/32	Pyrosequencing	0.59
Nava-Cedeño et al.(2022)	Spanish	227/100	MassARRAY	0.12

Abbreviations: R: response to ASM therapy; NR: no response to ASM therapy; HWE, Hardy–Weinberg Equilibrium; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.
p-values were calculated based on Chi-square test.

3.5. Evaluation of ABCC2 in the therapy of epilepsy

After screening the Drug–Gene Interaction Database [22], we found that *ABCC2* interacts with the ASMs oxcarbazepine and carbamazepine, suggesting the role of *ABCC2* in ASM therapy. However, further research is needed to confirm the underlying mechanisms.

4. Discussion

Previous studies on the association between rs717620 genotype and response to ASM therapy have yielded inconsistent results, partly due to relatively small sample sizes. To address this controversy, we conducted a pooled analysis of 18 studies selected based on strict quality criteria and including >4000 patients. In addition, we conducted eQTL and drug–gene interaction analyses to identify potential mechanisms. Collectively, this study suggest that the rs717620 genotype alters *ABCC2* expression in human brain, thereby influencing the therapeutic response to ASMs.

According to the ALFA project (https://www.ncbi.nlm.nih.gov/snp/rs717620#frequency_tab), the rs717620 T allele frequency is higher in Asians than Caucasians, which may contribute to the differential responses to some ASMs. Our findings are in contrast to several previous investigations. For instance, Grover et al. reported that rs717620 increased the risk of ASM resistance under both dominant and co-dominant models [23], while we found a significant association only under the recessive model, in accord with Qian et al. [24]. Another recent study reported a correlation between rs717620 and ASM therapy response under the dominant model [25], again at odds with our findings, while another found no association [26], partly due to differences in the genetic models. After careful analyses of these studies, we speculate that (1) lack of Hardy–Weinberg equilibrium in the control group and (2) large differences in sample numbers between responsive and unresponsive groups may have contributed to these disparities. Larger-scale studies with strict quality control are needed to resolve this issue.

However, Egger's test revealed potential publication bias under the recessive model ($P = 0.05$), so we conducted trim and fill analysis to identify the source but found no evidence of publication bias. Sensitivity analysis also showed no significant changes in the pooled ORs and 95 % CIs for the remaining studies after separately removing each individual study. Therefore, the results of our study are stable.

The rs717620 polymorphism is within the *ABCC2* gene promoter, and similar to other non-coding single nucleotide polymorphisms, likely influences ASM response by regulating gene expression level [27]. Here we present evidence that rs717620 regulates *ABCC2* expression in multiple brain regions, suggesting that rs717620 may influence the efficacy of ASM therapy by regulating *ABCC2* expression. In fact, drug–gene interaction analysis revealed that *ABCC2* interacts with oxcarbazepine and carbamazepine, frequently prescribed ASMs with similar chemical structures [28]. Both suppress seizures by blocking voltage-dependent sodium channels [29], but oxcarbazepine is often used as an alternative therapy for patients who cannot tolerate carbamazepine [30,31]. Altered ABCC2 may influence transport, thereby affecting therapeutic efficacy.

Although we provide evidence for a substantial influence of rs717620 genotype on ASM response, there are limitations that need to be addressed in future studies. First, the pooled sample sizes are still relatively small, particularly for analyzing associations between rs717620 genotype and responses to specific ASMs. Second, the precise underlying mechanisms are still unknown.
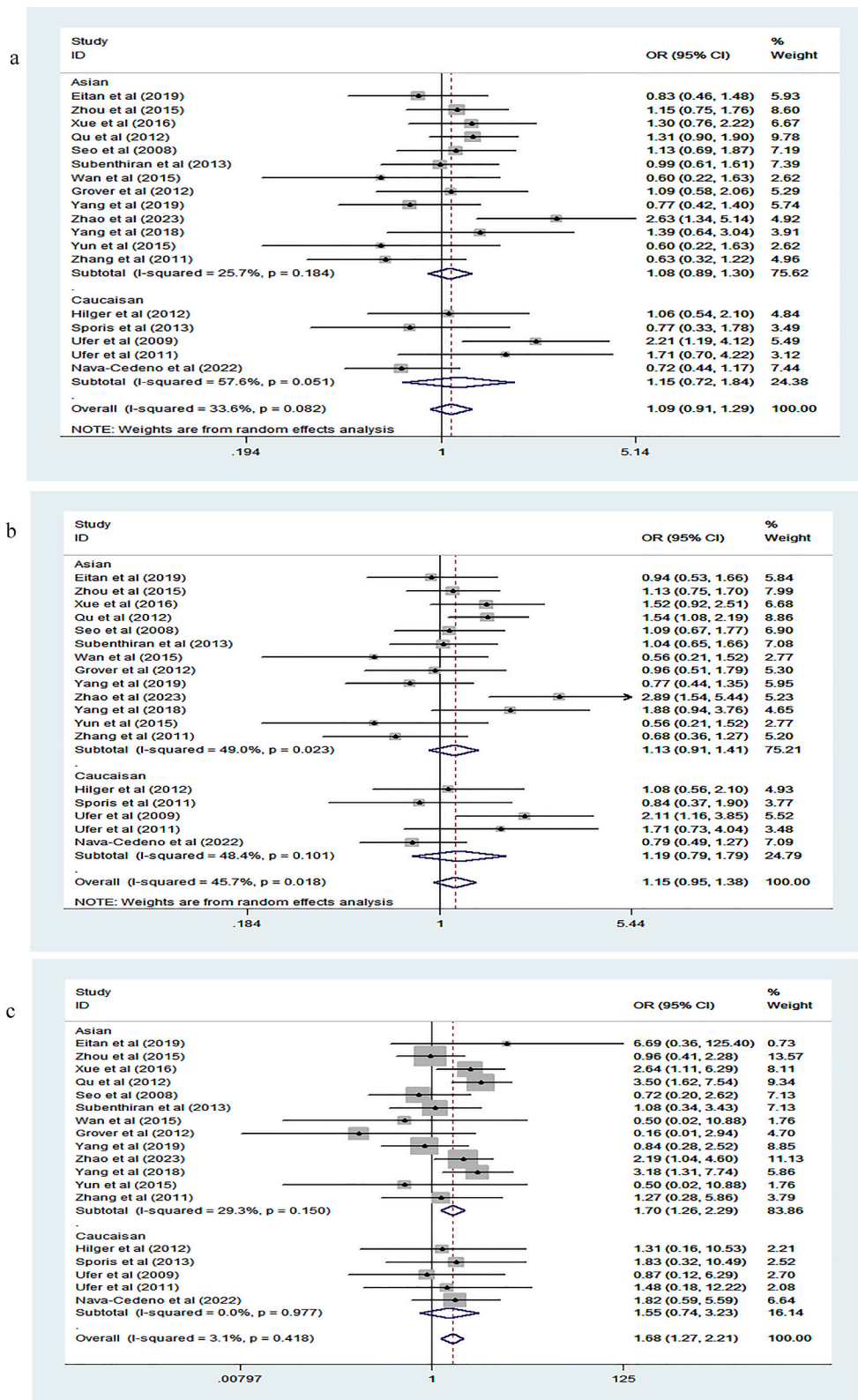
Fig. 2. Forest plots showing the associations between rs717620 genotype and ASM therapy response. (a) Based on the CTvs.CC model. (b) Based on the TT + CT vs.CC model. (c) Based on the TT vs. CT + CC model.

Table 2
Test for publication bias.

Genetic model	Begg's test (p)	Egger's test (p)
CT vs.CC	0.47	0.57
TT + CT vs.CC	0.52	0.39
TT vs. CT + CC	0.24	0.05
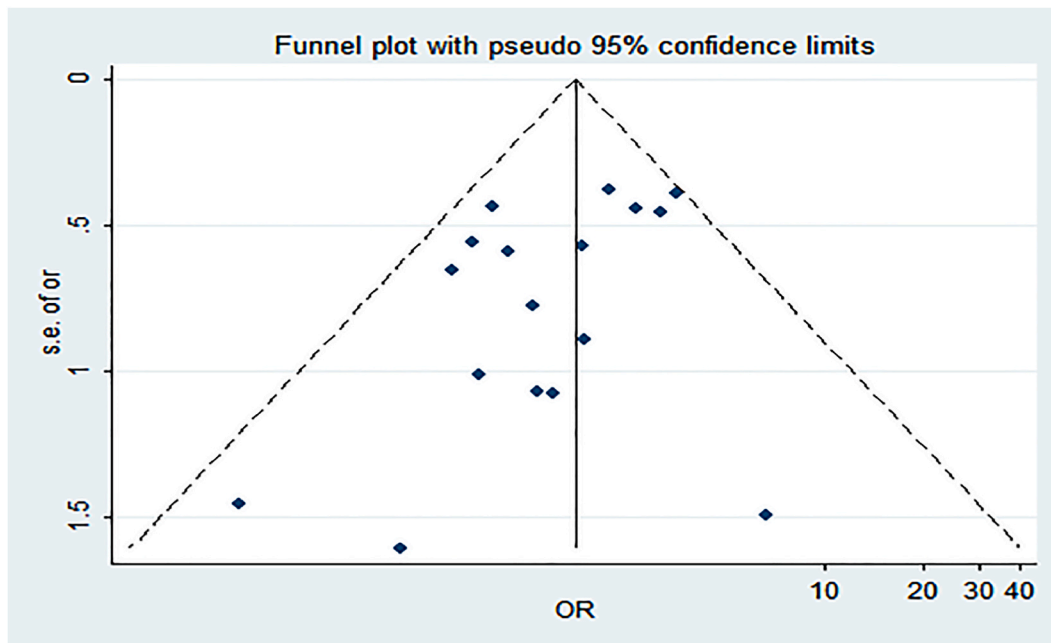
Fig. 3. Funnel plot of publication bias for studies on the association between rs717620 genotype and risk of ASM resistance under the recessive model.

5. Conclusion

The rs717620 genotype may influence the response to ASM therapy by regulating the expression of ABCC2 in human brain. However, further research on the underlying mechanisms and validation in independent populations are needed before these findings can be applied for ASM selection according to individual patient genotype.

Funding

Data Availability

All data and materials are available from the corresponding author upon reasonable request.

Ethics declaration

Informed consent was not required for this study because we did not include new participants.

CRediT authorship contribution statement

Shitao Wang: Conceptualization, Resources, Supervision, Writing – original draft, Funding acquisition. **Zongyou Li:** Data curation, Formal analysis, Software, Validation. **Zhibo Gao:** Investigation, Writing – review & editing. **Mengen Zhang:** Formal analysis, Methodology, Writing – review & editing. **Feng Rao:** Formal analysis, Visualization. **Jinghong Lu:** Writing – review & editing. **Hui Xu:** Software, Writing – review & editing. **Zhenrong Xie:** Funding acquisition, Writing – review & editing. **XiangQian Ding:**
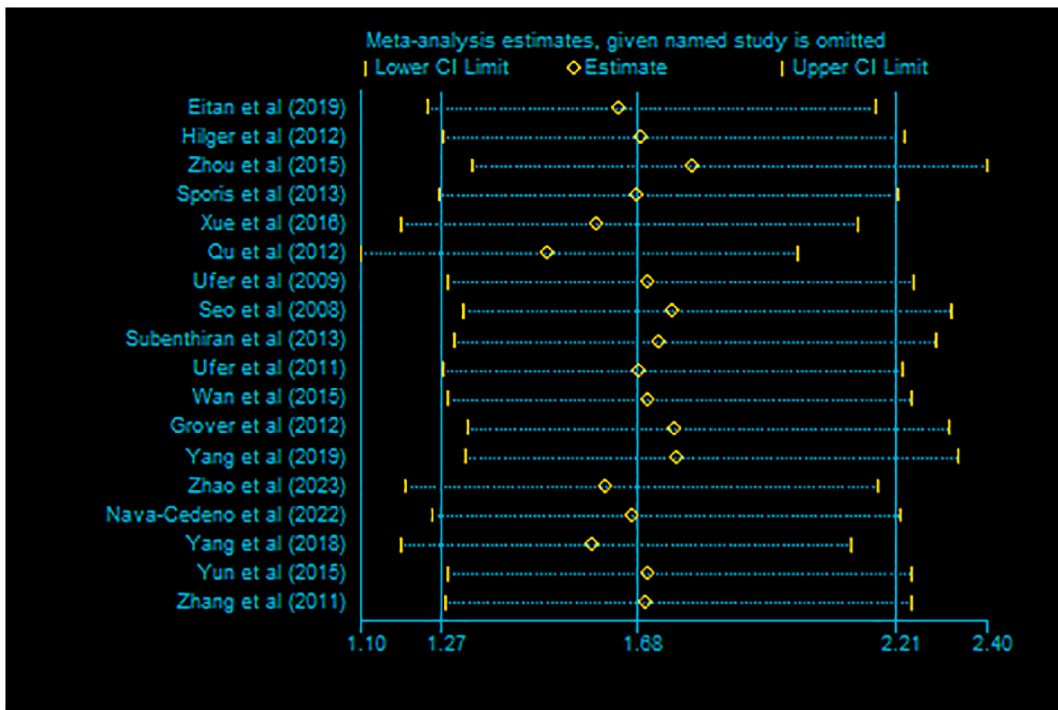
Fig. 4. Sensitivity analysis of studies on the association between rs717620 genotype and risk of ASM resistance under the recessive model.
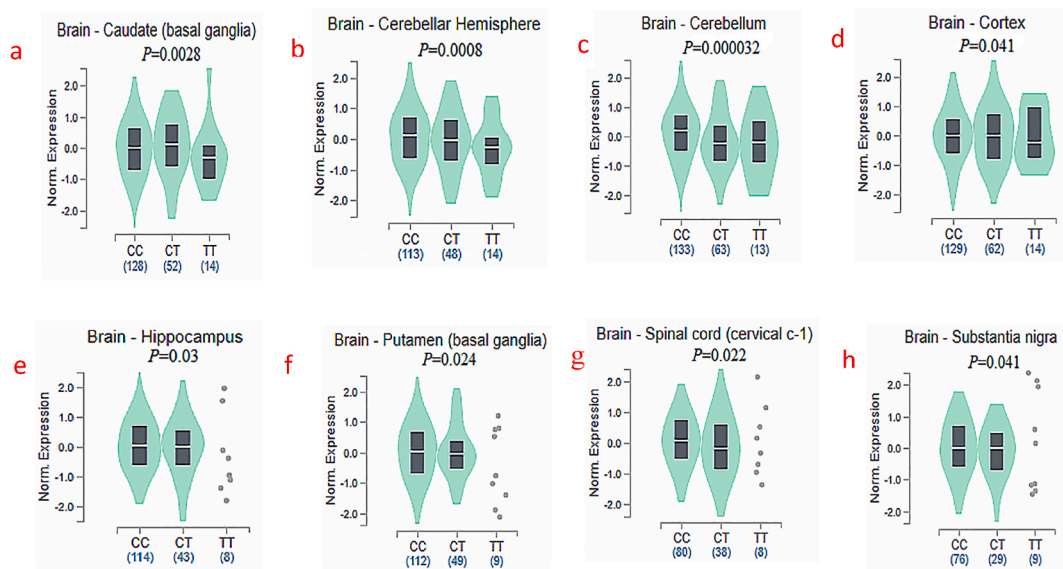

Fig. 5. Regional regulation *ABCC2* expression by rs717620 genotype in human brain: (a) caudate, (b) cerebellar hemisphere, (c) cerebellum, (d) cortex, (e) hippocampus, (f) putamen, (g) spinal cord, and (h) substantia nigra. Data were retrieved from the Genotype-Tissue Expression project (GTEx).

Conceptualization, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] I.E. Scheffer, S. Berkovic, G. Capovilla, M.B. Connolly, J. French, L. Guilhoto, E. Hirsch, S. Jain, G.W. Mathern, S.L. Moshé, D.R. Nordli, E. Perucca, T. Tomson, S. Wiebe, Y.-H. Zhang, S.M. Zuberi, ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology, Epilepsia 58 (4) (2017) 512–521.

[2] S.M. Sisodiya, C. Marini, Genetics of antiepileptic drug resistance, Curr. Opin. Neurol. 22 (2) (2009) 150–156, https://doi.org/10.1097/WCO.0b013e32832923ec.

[3] Y.Y. Chen, Y.Y. Feng, Y.N. Chen, Y.M. Cao, C.Z. Ai, C.L. Bi, Y. Liu, W. Li, Association between ABCB1 C3435T polymorphism and antiepileptic drug resistance in epilepsy: an updated meta-analysis based on 62 studies, Int J Clin Pharmacol Ther 60 (3) (2022) 146–158, https://doi.org/10.5414/CP204045.

[4] B. Sarecka-Hujar, Is there a relation between 677C>T polymorphism in the MTHFR gene and the susceptibility to epilepsy in young patients? A meta-analysis, Brain Sci. 11 (10) (2021) 1327, https://doi.org/10.3390/brainsci11101327.

[5] X. Fan, Y. Chen, J. Lu, W. Li, X. Li, H. Guo, Q. Chen, Y. Yang, H. Xia, AS3MT polymorphism: a risk factor for epilepsy susceptibility and adverse drug reactions to valproic acid and oxcarbazepine therapy in children from South China, Front. Neurosci. 15 (2021), 705297.

[6] J. Qu, B.T. Zhou, J.Y. Yin, X.J. Xu, Y.C. Zhao, G.H. Lei, Q. Tang, H.H. Zhou, Z.Q. Liu, ABCC2 polymorphisms and haplotype are associated with drug resistance in Chinese epileptic patients, CNS Neurosci. Ther. 18 (8) (2012) 647–651, https://doi.org/10.1111/j.1755-5949.2012.00336.x.

[7] T. Xue, Z.N. Lu, Association between the polymorphisms in the ATP-binding cassette genes ABCB1 and ABCC2 and the risk of drug-resistant epilepsy in a Chinese Han population, Genet. Mol. Res. 15 (4) (2016), https://doi.org/10.4238/gmr15048752.

[8] T. Zhao, H.J. Li, J. Feng, H.L. Zhang, W. Ting-Ting, L. Ma, J. Yu, W.B. Zhao, L. Sun, L.H. Yu, Y. Sun, Impact of ABCC2 1249G.A and 224C.T polymorphisms on lacosamide efficacy and plasma concentrations in Uygur pediatric patients with epilepsy in China, Ther. Drug Monit. 44 (3) (2022) 455–464. Epub 2023 Oct 8.

[9] L.N. Al-Eitan, I.M. Al-Dalalah, M.M. Mustafa, M.A. Alghamdi, A.K. Elshammari, W.H. Khreisat, H.A. Aljamal, Effects of MTHFR and ABCC2 gene polymorphisms on antiepileptic drug responsiveness in Jordanian epileptic patients, Pharmgenomics Pers Med 12 (2019) 87–95.

[10] E. Hilger, E.M. Reinthaler, E. Stogmann, C. Hotzy, E. Pataraia, C. Baumgartner, A. Zimprich, F. Zimprich, Lack of association between ABCC2 gene variants and treatment response in epilepsy, Pharmacogenomics 13 (2) (2012) 185–190, https://doi.org/10.2217/pgs.11.143.

[11] T. Seo, T. Ishitsu, K. Oniki, T. Abe, T. Shuto, K. Nakagawa, ABCC2 haplotype is not associated with drug-resistant epilepsy, J. Pharm. Pharmacol. 60 (5) (2008) 631–635, https://doi.org/10.1211/jpp.60.5.0009.

[12] D. Sporis, N. Bozina, S. Basić, M. Lovrić, T. Babić, I. Susak, I. Marković, Lack of association between polymorphism in ABCC2 gene and response to antiepileptic drug treatment in Croatian patients with epilepsy, Coll. Antropol. 37 (1) (2013) 41–45.

[13] S. Subenthiran, N.R. Abdullah, J.P. Joseph, P.K. Muniandy, B.T. Mok, C.C. Kee, Z. Ismail, Z. Mohamed, Linkage disequilibrium between polymorphisms of ABCB1 and ABCC2 to predict the treatment outcome of Malaysians with complex partial seizures on treatment with carbamazepine mono-therapy at the Kuala Lumpur Hospital, PLoS One 8 (5) (2013), e64827.

[14] M. Ufer, I. Mosyagin, H. Muhle, T. Jacobsen, S. Haenisch, R. Häsler, F. Faltraco, C. Remmler, S. von Spiczak, H.K. Kroemer, U. Runge, R. Boor, U. Stephani, I. Cascorbi, Non-response to antiepileptic pharmacotherapy is associated with the ABCC2 – 24C > T polymorphism in young and adult patients with epilepsy, Pharmacogenet Genomics 19 (5) (2009) 353–362.

[15] M. Ufer, C. von Stülpnagel, H. Muhle, S. Haenisch, C. Remmler, A. Majed, H. Plischke, U. Stephani, G. Kluger, I. Cascorbi, Impact of ABCC2 genotype on antiepileptic drug response in Caucasian patients with childhood epilepsy, Pharmacogenet Genomics 21 (10) (2011) 624–630.

[16] Z. Wan, H. Meng, Y. Bai, Y. Bai, Y. Dong, M. Liang, Y. Guo, Lack of association between ABCC2 polymorphisms and plasma carbamazepine concentrations or pharmacoresistance in Chinese patients with epilepsy, Neurol. Asia 20 (3) (2015) 221–227.

[17] X. Yang, Y. Yan, S. Fang, S. Zeng, H. Ma, L. Qian, X. Chen, J. Wei, Z. Gong, Z. Xu, Comparison of oxcarbazepine efficacy and MHD concentrations relative to age and BMI associations among ABCB1, ABCC2, UGT2B7, and SCN2A polymorphisms, Medicine (Baltim.) 98 (12) (2019), e14908.

[18] L. Zhou, Y. Cao, H. Long, L. Long, L. Xu, Y. Zhang, B. Xiao, ABCB1, ABCC2, SCN1A, SCN2A, GABRA1 gene polymorphisms and drug resistant epilepsy in the Chinese Han population, Pharmazie 70 (6) (2015) 416–420.

[19] A. Stang, Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses, Eur. J. Epidemiol. 25 (9) (2010) 603–605.

[20] C.B. Begg, M. Mazumdar, Operating characteristics of a rank correlation test for publication bias, Biometrics 50 (4) (1994) 1088–1101.

[21] M. Egger, G. Davey Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, BMJ 315 (7109) (1997) 629–634, https://doi.org/10.1136/bmj.315.7109.629.

[22] K.C. Cotto, A.H. Wagner, Y.Y. Feng, S. Kiwala, A.C. Coffman, G. Spies, A. Wollam, N.C. Spies, O.L. Griffith, M. Griffith, DGIdb 3.0: a redesign and expansion of the drug-gene interaction database, Nucleic Acids Res. 46 (D1) (2018) D1068–D1073, https://doi.org/10.1093/nar/gkx1143.

[23] S. Grover, R. Kukreti, A systematic review and meta-analysis of the role of ABCC2 variants on drug response in patients with epilepsy, Epilepsia 54 (5) (2013) 936–945.

[24] L. Qian, S. Fang, Y.L. Yan, S.S. Zeng, Z.J. Xu, Z.C. Gong, The ABCC2 c.-24C > T polymorphism increases the risk of resistance to antiepileptic drugs: a meta-analysis, J. Clin. Neurosci. 37 (2017) 6–14.

[25] X. Zan, G. Yue, Y. Hao, X. Sima, A systematic review and meta-analysis of the association of ABCC2/ABCG2 polymorphisms with antiepileptic drug responses in epileptic patients, Epilepsy Res. 175 (2021), 106678.

[26] Y. Wang, L. Tang, J. Pan, J. Li, Q. Zhang, B. Chen, The recessive model of MRP2 G1249A polymorphism decrease the risk of drug-resistant in Asian Epilepsy: a systematic review and meta-analysis, Epilepsy Res. 112 (2015) 56–63.

[27] S. Wang, X. Cai, S. Liu, Q. Zhou, T. Wang, S. Du, D. Wang, F. Yang, Q. Wu, Y. Han, A novel BCL11A polymorphism influences gene expression, therapeutic response and epilepsy risk: a multicenter study, Front. Mol. Neurosci. 15 (2022), 1010101.

[28] S. Schwabe, Oxcarbazepine: clinical development program, Epilepsia 35 (Suppl 5) (1994), https://doi.org/10.1111/j.1528-1157.1994.tb05968.x. S51–53.

[29] K. Wellington, K.L. Goa, Oxcarbazepine: an update of its efficacy in the management of epilepsy, CNS Drugs 15 (2) (2001) 137–163.

[30] S.C. Schachter, Oxcarbazepine: current status and clinical applications, Expert Opin Investig Drugs 8 (7) (1999) 1103–1112, https://doi.org/10.1517/13543784.8.7.1103.

[31] R. Maiti, B.R. Mishra, S. Sanyal, S. Mohapatra, S. Parida, A. Mishra, Effect of carbamazepine and oxcarbazepine on serum neuron-specific enolase in focal seizures: a randomized controlled trial, Epilepsy Res. 138 (2017) 5–10.