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The recessive model of MRP2 G1249A polymorphism decrease the risk of drug-resistant in Asian Epilepsy: A systematic review and meta-analysis

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Summary ABCC2 gene polymorphisms have been shown to be associated with drug-resistant epilepsy. However, the published results were controversial. To comprehensively re-evaluate the association between ABCC2 gene polymorphisms and drug-resistant epilepsy in Asian, we carried out this meta-analysis, which included eight related studies. Studies were selected using PUBMED, Web of science, the Cochrane database of system reviews and Embase. Pooled odds ratio (OR) with 95% confidence interval (CI) was used to assess the association. Studies with 1302 drug-resistant cases and 1563 drug-sensitive controls were included. No significant association was detected by combined analyses for C-24T, G-1774delG, C3972T and G2934A. However, significant association was found in recessive model for G1249A polymorphism (GG *vs.* GA + AA: OR = 0.72, 95%CI = 0.53—0.96, $P = 0.03$), indicating the recessive model of G1249A in MRP2/ABCC2 might decrease the risk of drug resistance in Asian epilepsy.

Introduction

Multidrug resistance has been known to be a major clinical problem in the treatment of epilepsy. One-third of patients continued to have seizures after treatment of Antiepileptic drugs (AEDs) (Remy and Beck, 2006). The mechanism

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underlying the resistance to AEDs has not been clear yet. Preliminary data suggested that overexpression of efflux ATP-binding cassette (ABC) transporters at the blood—brain barrier (BBB) might result in drug-resistant epilepsy (Kwan and Brodie, 2005; Loscher et al., 2009). More importantly, genetic variants of drug transporter genes that associated with the efflux activity might contribute to drug resistant epilepsy.

The ABC transporters, including MDR1 (*p*-glycoprotein, ABCB1) and MRPs (multidrug resistance proteins, ABCCs), was the most studied candidate genes for drug resistant epilepsy in previous pharmacogenetic researches (Kutoba et al., 2006). A number of studies have supported the evidence of association between ABCB1 variant (C3435T) and drug-resistant epilepsy (Hung et al., 2005; Ebid et al., 2007). However, no significant association was identified by previous meta-analysis (Haerian et al., 2010; Bournissen et al., 2009). MRP2 (ABCC2) frequently showed low expression in normal brain tissue, but high expression in human epileptogenic brain tissues and MRP2-deficient rat model (Potschka et al., 2003). Recently, several association studies on ABCC2 variants and drug-resistant epilepsy had been performed in different ethnic populations. A variant (C-24T) in the 5′-UTR of ABCC2 gene was shown to be associated with low mRNA expression and drug-resistant epilepsy in Caucasian (Ufer et al., 2009), but the result could not be repeated in Asian populations. Meanwhile, two nearby SNPs, G1249A and C3972T, were significantly associated with reduced bioavailability of the ABCC2 substrates, which might contribute to the increased MRP2 activity (Haenisch et al., 2008). However, no association was observed between drug-resistant epilepsy and ABCC2 haplotypes containing 1249A allele and −24C allele in Japanese Epilepsy patients (Kim et al., 2009). Moreover, haplotypes containing the delG allele of G-1774delG variant, were reported to be associated with the mental retardation, but not with Japanese drug-resistant epilepsy (Seo et al., 2008).

Due to these controversial results, we should comprehensively re-assess the association between MRP2/ABCC2 polymorphisms and drug-resistant epilepsy. Therefore, a meta-analysis of all relevant published human studies was conducted to evaluate the role of MRP2/ABCC2 in response to antiepileptic drugs in Asian.

Materials and methods

Selection of studies

We searched literatures in Pubmed, Web of science, the Cochrane database of system reviews and Embase (last updated on May, 2014) using the key words (''ABCC2'' or ''MRP2'', polymorphisms or SNPs and epilepsy). Meanwhile, additional literatures were identified by cross-references within original or review articles. Only data from the full-published paper was recruited. Meeting or conference abstracts were excluded. Studies were not restricted to any particular language. A study was included in the current meta-analysis if it conformed to the following criteria: (i) the study regarding the ABCC2 polymorphisms and epilepsy; (ii) the design was unrelated case-control or case-cohort study and included data on ABCC2 genotypes for drug-sensitive and drug-resistant epilepsy patients; (iii) allele frequencies or genotypes were available. (IV) The studies were conducted in Asian populations.

Data extraction

Data was extracted from relevant articles, if original data of genotype frequencies were available. Two independent authors (L.T. and Y.W) extracted all data from each study. Any disagreements were resolved by discussion between the two authors. Information of first author, year of publication, type of study design, ethnicity, age, drug using, total sample size, number of cases and controls, frequencies of allele, genotypes, haplotypes containing SNPs C-24T, G1249A, C3972T, G2934A and G-1774delG were collected from each study.

Statistical methods

All the statistical analyses were conducted with program RevMan 5 (Oxford, UK) and STATA10.0. The Hardy—Weinberg equilibrium (HWE) was calculated for all the control groups of each study, and studies in which controls deviated from HWE ($P < 0.05$) were excluded. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated for each study. Variation and heterogeneity were evaluated using Cochran's *Q*-statistic (Egger et al., 1997; Davey and Egger, 1997). If significant heterogeneity was observed across studies ($P < 0.10$), the random effect model was used for meta-analysis. Otherwise, the fixed effect model (Mantel—Haenszel method) was used. The effect of heterogeneity was also measured using the I^2 value: $I^2 = 100\% \times (Q - \mathrm{df})/Q$ (Higgins and Thompson, 2002). Subgroup analyses were performed by ethnicity. The effect of publication bias was assessed by Egger's test and Begg's test. A *P* value <0.05 was considered significant of statistical publication bias.

Results

Characteristics of the studies

The characteristics of available studies meeting the inclusion criteria were shown in Table 1. There were 293 studies through the initial search. After browsing titles and abstracts, 95 studies were retrieved for duplicated data, 160 records were excluded for not case-control studies on ABCC2 and drug response, 27 studies were excluded for not exploring ABCC2 gene polymorphisms, and 3 studies were conducted in European populations (Ufer et al., 2009, 2011; Hilger et al., 2012). Therefore, a total of 8 studies conducted in Asian populations were incorporated in our meta-analysis (Kim et al., 2009, 2010; Seo et al., 2008; Kwan et al., 2011; Qu et al., 2012; Ma et al., 2014; Yi et al., 2013; Soobitha et al., 2013). Patients were classified by epilepsy syndrome (idiopathic, cryptogenic or symptomatic epilepsy) or seizure types (generalized seizure or partial seizure) in each study. And, only three studies (Kim et al., 2010; Yi et al., 2013; Soobitha et al., 2013) reported association between ABCC2 polymorphisms and monodrug (two studies for CBZ and one