**ABCC2 rs2273697 and rs3740066 polymorphisms and resistance to antiepileptic drugs in Asia Pacific epilepsy cohorts**

**Aim:** One third of new epilepsy patients do not respond to treatment; therefore, we aimed to examine the relationship of ABCC2 rs2273697 and rs3740066 polymorphisms with drug resistance in 2056 Malaysian (55%), Hong Kong (32%) and Japanese (13%) epilepsy patients. **Results:** Significant association of the rs2273697 allele was observed in Chinese females with epilepsy, Malaysian Chinese subjects with generalized seizure and Japanese subjects with partial seizure and for genotypes (AA vs GG) and Malaysian Chinese with generalized seizure (GA vs GG and autosomal dominant). Significant association of the rs3740066 allele was observed in Malaysian females of Malay origin with cryptogenic epilepsy and Chinese subjects with partial seizure and for genotypes in Malay with cryptogenic epilepsy (CT vs CC and autosomal dominant). Significant results were also seen for their haplotypes in different groups. After Bonferroni correction for multiple comparisons, the GT haplotype in Chinese subjects with epilepsy remained significant. Hence, this haplotype might be a risk for resistance to medication in this ethnicity.

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**KEYWORDS:** epilepsy drug responsiveness polymorphism

Lack of responsiveness to antiepileptic drugs (AEDs) is a common problem in epilepsy treatment [1]. Many AEDs are highly permeable compounds that are transported by multidrug resistance proteins at the blood–brain barrier (BBB) [2]. One of the major causes of resistance to drugs is increase in the activity or amount of MRP2 (ABCC2). ABCC2 is a member of the ATP-binding cassette (ABC) transporter superfamily. This protein is localized on the luminal side of BBB endothelial cells and couples ATP hydrolysis to extrude various organic anions out of the cell. Overexpression of ABCC2 transporters on BBB cells may increase efflux of AEDs to the capillary lumen, leading to a reduction of the AED concentration in the brain to a level that may be inadequate to control seizures [3,4]. While in vitro studies have indicated that some common AEDs such as carbamazepine (CBZ), valproate (VPA), levetiracetam, phenytoin (PHT), lamotrigine and phenobarbital are not substrates of the ABCC2 transporter [5,6], CBZ and PHT are reported to be substrates for this transporter [2,7]. Furthermore there is pharmacogenetic evidence indicating that functional genetic variability in ABCC2 is associated with adverse effects of CBZ [7]. Precise mechanisms of ABCC2 actions in drug responsiveness in epilepsy have been obscure. SNPs in the ABCC2 gene may alter its expression and function, resulting in resistance to AEDs. The nonsynonymous rs2273697 (Val417Ile) and the silent rs3740066 (Ile1324 Ile) polymorphisms have received attention in genetic association studies. Some reports suggested that the mutated allele of the exonic rs2273697 variant is associated with neurological adverse drug reactions as a result of taking CBZ or oxcarbazepine in patients from Germany [8] with partial epilepsy, and in Koreans with epilepsy [7], but no association was reported from Austrian epilepsy patients [9]. Functional studies showed that this SNP selectively reduced CBZ transport across the cell membrane. Moreover, rs3740066 was reported to be involved in resistance to AEDs in patients from China [10], whereas studies from Japan [11] and Austria [9] did not support this result. Finally, the TGT (rs717620–rs2273697–rs3740066) haplotype was reported to affect AEDs responsiveness in patients from China [10]. The rs717620–rs2273697–rs3740066 haplotype of the ABCC2 gene showed a significant link with drug resistance epilepsy. The TGT haplotype in drug nonresponders was more frequent than drug responders. This haplotype was also related to decreased irinotecan clearance in cancer treatment [12,13]. A recent meta-analysis of eight studies reported an association of rs17620 with drug responsiveness in epilepsy [14]. Such inconsistencies among various epilepsy studies may be caused by differences in prevalence of this locus among ethnic groups and also by
Materials & methods
This study was a multicenter collaboration between University of Malaya Medical Centre (UMMMC, Kuala Lumpur, Malaysia), Universiti Kebangsaan Malaysia Medical Centre (UKMMC, Kuala Lumpur, Malaysia), General Hospital Kuala Lumpur (GHKL, Kuala Lumpur, Malaysia), the Chinese University of Hong Kong (CUHK, Hong Kong), and Kumamoto Saishunso National Hospital (Kumamoto University, Japan). The study protocol was approved by the ethics committees of the centers involved. Patients recruited from the participating epilepsy clinics were eligible for inclusion if they had been prescribed with AEDs for at least a year. Phenotyping of patients from the Malaysian, Hong Kong and Japanese cohorts into either drug resistant or drug responsive groups was thoroughly discussed and agreed upon prior to the study, and classifications were based upon International League Against Epilepsy (ILAE) criteria [15,16]. Patients not classified as either resistant or responsive were excluded from analysis.

Studies from Malaysia, Hong Kong and Japan were independently performed within three different populations. Definition of drug responder or drug nonresponder in the three cohorts was consistent across the populations. Drug responsiveness was defined as being free of seizures for at least 1 year. Drug nonresponse was defined as treatment failure with at least two or more drugs because of adverse reactions and/or a lack of efficacy at maximum tolerated dose [11,17,18]. Since prescribed drug dosage varies substantially between patients and depends on patient characteristics such as bodyweight or epilepsy features such as seizure or etiology types, we included patients with any dosage of AEDs in this study. We also included patients on first-line AED (CBZ, VPA and PHT) monotherapy or polytherapy. Patients were excluded from this study because of following criteria: unreliable record of seizure frequency, significant psychiatric comorbidity, history of pseudo seizures, alcohol or drug abuse and presence of progressive or degenerative neurological or systemic disorders.

Written informed consent was obtained from all subjects before participating in this study. An established epilepsy database was created to record demographic details, clinical information on seizure types and epilepsy syndromes, and any relevant family history. Patient’s DNA was extracted from either whole blood or buccal swabs. The three cohorts independently analyzed genotypes of ABCC2 polymorphisms by different strategies, because of varied facilities available. The rs2273697 and rs3740066 loci were genotyped by using the MALDI-TOF mass spectrometry (MassARRAY®, Sequenom, CA, USA) method at the Hong Kong University Genome Research Centre (Pokfulam, Hong Kong) in patients from both Malaysia and Hong Kong and by using the PCR-RFLP technique in patients from Japan. Quality control of the genotype data was performed by randomly replicating 5–10% of the samples [11].

All values were expressed as mean ± standard deviation and frequency for continuous and categorical data, respectively. Prior to statistical calculation, the distributions of continuous variables were checked for normality using the Kolmogorov–Smirnov test. The nonparametric Mann–Whitney U-test or the Kruskal–Wallis rank sum test was used to compare the ages of participants at study entry and onset of seizure (not normally distributed variables) between drug responder and nonresponder groups. χ² test was used to calculate the difference of categorical data, including gender, seizure type and epilepsy syndrome between races. A goodness-of-fit χ² test with one degree of freedom was applied to test the Hardy–Weinberg equilibrium (HWE); p < 0.05 indicated a lack of agreement with HWE. Adjusted binomial logistic regression analysis for covariates, including ethnicity, gender, age at recruitment, age at onset of epilepsy, seizure type and epilepsy syndrome was used to obtain odds ratios with 95% CI. Haplotype and linkage disequilibrium (LD) analysis for the SNPs was performed with the SHEsis [19] and corrected for multiple testing by using 100,000 permutations for each SNP and haplotype. The Bonferroni procedure was used for correction of multiple comparisons. p-values of less than 0.05 in two-sided tests of statistical significance were considered statistically significant. Statistical analyses in this study were performed using SPSS version 16.0 (SPSS Inc., IL, USA).

Results
Study population
The demographic characteristics of 2056 epilepsy patients (1124 from Malaysia, 653 from Hong Kong and 279 from Japan) in this study are shown in Table 1. Out of these patients, 1065 (52%) were Chinese, followed by 422 (20%) Malays, 290 (14%) Indians and 279 (14%) Japanese. Of 1065
Chinese patients recruited, 412 (39%) were from Malaysia and 653 (61%) were from Hong Kong. Of the 2056 patients, 987 (48%) patients were drug nonresponders and the remaining were drug responders since patients not classified into either of these two categories were excluded from this study. Out of all the patients studied, 36 and 64% of patients were on AED monotherapy (CBZ, VPA or PHT) and polytherapy treatment, respectively. Most patients on polytherapy were on a combination of some common AEDs including levetiracetam, PHT, lamotrigine and phenobarbital.

Mean age at study entry did not significantly differ between patients from Hong Kong, Japan and Malaysia (p > 0.05), whereas mean age of onset of epilepsy in patients from Japan was significantly lower than in patients from Malaysia and Hong Kong (p < 0.05). Epilepsy started at a significantly later age in the drug nonresponders than in the drug responders amongst Malays, Malaysian Chinese, Hong Kong and Japanese (p = 0.004, p = 0.01, p < 0.001 and p < 0.001, respectively). The male ratio in Hong Kong drug nonresponders was significantly more than in the drug responders (p = 0.03).

Partial seizure was predominant in Malay, Malaysian Chinese, Hong Kong and Japanese patients, but it was less commonly diagnosed in Indian subjects. Partial seizure was significantly more frequent in drug nonresponders than drug responders in the three ethnic subgroups from Malaysia as well as in Chinese from Japan (p < 0.05). Cryptogenic epilepsy was significantly more common than symptomatic epilepsy in the Malay drug nonresponders as compared with drug responders, while idiopathic epilepsy was more frequent than cryptogenic epilepsy in Indian and Hong Kong drug nonresponders as compared with responders (p < 0.05). In drug nonresponders from Japan, idiopathic epilepsy and symptomatic epilepsy were more and less common than cryptogenic epilepsy, respectively, as compared with drug responders (p < 0.05).

### Association study

Genotype and allele analyses of ABCC2 rs2273697 and rs3740066 in epilepsy overall and in idiopathic and symptomatic epilepsy were performed for each of the five ethnographic groups, as well as in all Chinese and in all subjects (Tables 2–4). Genotype distributions for these two SNPs were in HWE for these seven ethnographic groups (p > 0.05). Since distribution of seizure types and epilepsy syndromes was different among these groups, we performed subanalysis data by gender and ethnicity for each type of seizure and epilepsy syndrome in each subgroup (see Supplementary Material: www.futuremedicine.com/doi/suppl/10.2217/pgs.13.239). Significant association was observed for the rs2273697 allele in all Chinese females with epilepsy, Malaysian Chinese subjects with generalized seizure and Japanese subjects with partial seizure, as well as for genotypes in all females with epilepsy (AA vs GG) and Malaysian Chinese with generalized epilepsy (GA vs GG and GA+AA vs GG). Similar results were obtained for the rs3740066 allele for the male ratio in Hong Kong drug nonresponders as compared with responders in the three ethnic subgroups from Malaysia and Hong Kong remained significant. This haplotype was less frequent in Chinese subjects with epilepsy than in controls (16 vs 24%). Therefore, this haplotype probably acts as a protective factor against epilepsy in the Chinese population. A variable degree of LD between the two loci was seen among different groups (see Supplementary Material).

### Discussion

In this study, we examined association of rs2273697 and rs3740066 polymorphisms and their haplotypes with drug responsiveness in a pooled data of epilepsy patients from Malaysia, Hong Kong and Japan. Drug resistance is a major problem in the clinical outcome of epilepsy [20]. Reduction in the levels of AEDs in brain tissues is one potential mechanism for pharmacoresistance in epilepsy. Studies have indicated that overexpression of the ABCC2 transporter mainly in endothelial cells of the BBB, liver, intestine, kidney, placenta and lungs is a risk factor for resistance to drugs in diseases such as epilepsy, cancer and tuberculosis-induced hepatitis [7,10,21–25]. Reduced expression of the ABCC2 protein contributed to increased extracellular brain levels of PHT in MRP2-deficient TR-rats as compared with the normal background strain [2]. However, the precise nature of the mechanism of ABCC2 in drug
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Malaysian Malay</th>
<th>Malaysian Chinese</th>
<th>Malaysian Indian</th>
<th>Hong Kong</th>
<th>Japan</th>
<th>All subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>33 ± 15</td>
<td>36 ± 18</td>
<td>36 ± 16</td>
<td>38 ± 16</td>
<td>21 ± 11</td>
<td>34 ± 16</td>
</tr>
<tr>
<td>Age at seizure onset (years), mean ± SD</td>
<td>11 ± 12</td>
<td>16 ± 17</td>
<td>16 ± 13</td>
<td>21 ± 17</td>
<td>6 ± 5</td>
<td>15 ± 13</td>
</tr>
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**Gender**

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<th>Characteristics</th>
<th>Malaysian Malay</th>
<th>Malaysian Chinese</th>
<th>Malaysian Indian</th>
<th>Hong Kong</th>
<th>Japan</th>
<th>All subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>105 (50)</td>
<td>89 (43)</td>
<td>69 (47)</td>
<td>165 (46)</td>
<td>67 (46)</td>
<td>495 (46)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>107 (50)</td>
<td>111 (53)</td>
<td>88 (47)</td>
<td>134 (45)</td>
<td>193 (54)</td>
<td>469 (47)</td>
</tr>
</tbody>
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**Seizure type**

<table>
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<th>Characteristics</th>
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<th>Hong Kong</th>
<th>Japan</th>
<th>All subjects</th>
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</thead>
<tbody>
<tr>
<td>Generalized, n (%)</td>
<td>105 (55)</td>
<td>100 (53)</td>
<td>83 (47)</td>
<td>80 (22.5)</td>
<td>47 (33)</td>
<td>415 (41)</td>
</tr>
<tr>
<td>Partial, n (%)</td>
<td>87 (45)</td>
<td>88 (47)</td>
<td>78 (40)</td>
<td>193 (54)</td>
<td>195 (59)</td>
<td>601 (59)</td>
</tr>
<tr>
<td>Unspecified, n</td>
<td>20</td>
<td>18</td>
<td>8</td>
<td>3</td>
<td>4</td>
<td>53</td>
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</table>

**Etiology**

<table>
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<th>Characteristics</th>
<th>Malaysian Malay</th>
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<th>Malaysian Indian</th>
<th>Hong Kong</th>
<th>Japan</th>
<th>All subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptogenic, n (%)</td>
<td>83 (40)</td>
<td>78 (38)</td>
<td>32 (22)</td>
<td>144 (40)</td>
<td>66 (45)</td>
<td>403 (38)</td>
</tr>
<tr>
<td>Idiopathic, n (%)</td>
<td>76 (36)</td>
<td>64 (31)</td>
<td>73 (30)</td>
<td>60 (17)</td>
<td>42 (29)</td>
<td>315 (30)</td>
</tr>
<tr>
<td>Symptomatic, n (%)</td>
<td>50 (24)</td>
<td>64 (31)</td>
<td>40 (28)</td>
<td>154 (43)</td>
<td>38 (26)</td>
<td>346 (32)</td>
</tr>
<tr>
<td>Unspecified, n</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>4</td>
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</table>

*Excluded from analysis.

NR: Nonresponder; R: Responder; SD: Standard deviation.
responsiveness is still unclear. Previous studies showed significant association of rs2273697 and rs3740066 with resistance to AEDs in epilepsy patients from China and Germany [7,8,10], whereas the associations found in studies from Japan and Austria did not reach significance [9,11]. Regards rs2273697 in LD with rs717620 is physiologically more sensitive in increasing the risk of drug resistance especially to CBZ [7,26].

Our cohort data from Malaysia, Hong Kong and Japan on the role of ABCC2 polymorphisms and drug responsiveness showed an association for rs2273697–rs3740066 GT haplotype in Chinese epilepsy patients. Therefore, this haplotype might be a risk for resistance to AEDs in this epilepsy population.

Our results for rs2273697 and rs3740066 loci were consistent with negative findings from Austria, China, South Korea and Japan [11,17,26-28], but not with positive associations reported from Germany, north India and China [8,10,23]. Our results also did not reveal evidence supporting strong associations of these loci with resistance to AEDs in subjects with idiopathic or symptomatic epilepsy from Malaysia, Hong Kong and Japan except for the GT haplotype data in all Chinese subjects with epilepsy.

There was a high variation in distribution of epilepsy syndromes among patients from Malaysia, Hong Kong and Japan. Symptomatic epilepsy was more frequent in patients from Hong Kong (54%) and Japan (41%) as compared with Malays, Indians and Chinese subjects from Malaysia (30, 35 and 28%, respectively) while idiopathic epilepsy in patients from Hong Kong (11%) and Japan (18%) was less common than in Malays, Indians and Chinese from Malaysia (33, 28 and 42%, respectively). Discrepancy between our results and those of some previous studies might be explained by factors discussed in the following paragraphs.

It is possible that inadequate number of samples in studies that reported association between these loci and drug responsiveness may affect the results. Small sample size can cause false-positive or -negative results and may not provide sufficient power to detect small to moderate effects [29-33]. To reduce this effect, we analyzed the pooled data from Malaysia, Hong Kong and Japan to give a larger sample size with more reliable results. However, this strategy created a heterogeneous epilepsy population with different ratios of epilepsy syndromes from five major ethnic groups as the second limitation. Therefore, we included results of subanalysis by epilepsy syndrome for each ethnic group to this study.

Some administered AEDs in treatment of epilepsy may not be ABCC2 substrates, thus this issue may have an effect on association data in various studies, especially in monotherapy treatment. These drugs probably control seizure through interaction with other transporters or targets. For example, PHT transporting is mediated by P-glycoprotein in BBB and CBZ and PHT block voltage-dependent sodium channels in the neurons [34,35].

Definition of seizure control, duration of treatment, and AED monotherapy or polytherapy may also affect drug responsiveness and thereby have an effect on association studies data. Consideration of 1-year of AED(s) treatment is not enough for some epilepsy syndromes such as symptomatic epilepsy to classify patients into drug responders or drug nonresponders. In these patients seizure control takes longer whereas this period is shorter in patients with idiopathic epilepsy. Patients with symptomatic epilepsy are also more resistant to AEDs as compared with other types of epilepsy [36]. Therefore, definition of drug responder and drug nonresponder varies among the association studies, which may lead to differences in patient classification and final results. A standardized clinical classification should be executed among clinicians.

Previous association studies were performed on patients with AED polytherapy or combination of both monotherapy and polytherapy treatments. Competition of AEDs used in polytherapy in such patients may lead to drug interactions. Certain AEDs used may cause enzyme
induction or inhibition and eventually result in a reduction in the serum concentration of drugs that are substrates for the same enzymes. Therefore, drug interactions may influence the efficacy of AEDs used in seizure control [37,38].

ABCC2 rs2273697 and rs3740066 may not be functional alone but can act in combination to result in resistance to AEDs in epilepsy as we showed for the GT haplotype. These loci may also possibly affect drug responsiveness through interaction with other SNPs in this gene or with other genes, and this interaction may vary according to ethnicity or clinical factors.

Our present study had three unavoidable limitations. First is the heterogeneous epilepsy populations in this international study. As a consequence of having a large sample size with broad inclusion criteria, it is inevitably limited by heterogeneous subgroups. To address the effect of such variability, we carried out subanalysis by epilepsy syndrome and seizure type for each ethnicity although this strategy resulted in small sample sizes, which were underpowered for subgroup analysis. Therefore, future studies with larger sample size are needed to replicate the current findings. The second limitation was polytherapy treatment in most of the patients in the three cohorts, which may affect the results through drug interactions. A further limitation was that we have not investigated all functional SNPs in the ABCC2 gene, including SNPs in the promoter sequence such as rs717620, rs2804402 and rs1885301 and their haplotypes may certainly have provided further information on the role of genetic variability in ABCC2 in determining response to AEDs [23,39,40]. In conclusion, results of the present study suggest that the rs2273697–rs3740066 GT haplotype might be a risk factor for resistance to AEDs in Chinese epilepsy patients.

Conclusion & future perspective
Since the role of ABCC2 rs2273697 and rs3740066 polymorphisms and their haplotypes in resistance to AEDs on epilepsy is challenging, three cohorts from Malaysia, Hong Kong and Japan have been analyzed in this study to examine this relationship in symptomatic and idiopathic epilepsy among the five ethnic groups. Overall results and stratified analysis by ethnicity and epilepsy syndrome identified a significant association between the GT haplotype and drug responsiveness in Chinese subjects. Future larger studies on these SNPs and their haplotypes in epilepsy are suggested.

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Financial & competing interests disclosure
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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research
The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Relationship between ABCC2 gene polymorphisms & response to treatment in epilepsy
- Approximately 30–40% of newly diagnosed epilepsy patients do not respond to antiepileptic drugs (AEDs).
- Evidence showed reduced expression of the ABCC2 transporter in resistance to AEDs.
- In the present study, association of ABCC2 rs2273697 and rs3740066 polymorphisms and their haplotypes with AED responsiveness was evaluated in epilepsy patients from Malaysia, Hong Kong and Japan.

Significant association of rs2273697 & rs3740066 GT haplotype with resistance to AEDs was found
- Results from three sites showed significant GT haplotype association with response to AEDs in Chinese subjects.

Conclusion
- The rs2273697–rs3740066 GT haplotype might be a risk factor for resistance to AEDs in Chinese epilepsy patients.
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- of interest
- of considerable interest

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