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Comparison of oxcarbazepine efficacy and MHD concentrations relative to age and BMI

Associations among ABCB1, ABCC2, UGT2B7, and SCN2A polymorphisms

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Abstract

Genetic polymorphisms are related to the concentration and efficacy of oxcarbazepine (OXC). 10-Hydroxycarbazepine (MHD) is the major pharmacologically active metabolite of OXC, and it exerts an antiepileptic effect. This study aimed to explore the connection between the MHD concentration and genes such as ATP-binding cassette B1 (ABCB1), ATP-binding cassette C2 (ABCC2), UDP-glucuronosyltransferase-2B7 and sodium voltage-gated channel alpha subunit 2 (SCN2A), which participate in the antiepileptic function of OXC.

Total 218 Chinese epileptic patients, were stratified into different groups according to their age, body mass index (BMI) and OXC efficacy. The genotypes of 7 single nucleotide polymorphisms in all subjects were determined by polymerase chain reaction-improved multiple ligase detection reaction assay. The MHD plasma concentration was detected by high-performance liquid chromatography and then standardized through dosage and body weight.

In general, the ABCC2 rs2273697 mutant ($P = .026$) required a significantly higher standardized MHD concentration. For age groups, carriers of the ABCC2 rs2273697 mutant showed a significantly higher standardized MHD concentration than noncarriers in the juvenile group ($P = .033$). In terms of BMI, a significantly higher standardized MHD concentration was found in the ABCB1 rs2032582 mutant of the normal weight group ($P = .026$). The SCN2A rs17183814 mutant required a significantly higher OXC maintenance ($P = .014$) in the low-weight group, while lower OXC maintenance dose ($P = .044$) and higher standardized MHD concentration ($P = .007$) in the overweight group.

The ABCC2 rs2273697 polymorphism was significantly associated with MHD plasma concentration in the whole patient cohort and in patients stratified by different ages, this finding provides potential theoretical guidance for the rational and safe clinical use of OXC.

Abbreviations: ABCB1 = ATP-binding cassette B1, ABCC2 = ATP-binding cassette C2, BMI = body mass index, LW = low-weight, MHD = 10-hydroxycarbazepine, NW = normal weight, OW = overweight, OXC = oxcarbazepine, SCN2A = sodium voltage-gated channel alpha subunit 2, UGT2B7 = UDP-glucuronosyltransferase-2B7.

Keywords: 10-hydroxycarbazepine, ABCB1, ABCC2, epilepsy, gene polymorphisms, oxcarbazepine, SCN2A, UGT2B7

1. Introduction

Epilepsy is one of the most common neurological diseases, and it affects approximately 50 million people worldwide.[1] It occurs in all strata of the population, but it primarily occurs in patients under 16 and over 60, accounting for 40% and 20%, respectively.[2] Oxcarbazepine (OXC), a new-generation antiepileptic drug (AED), has been widely used for the treatment of focal epilepsy syndromes.[3] Although it is effective in seizure inhibition, a big portion of patients (30–40%) exhibit drug resistance independent of drug noncompliance, significant precipitating factors, inappropriate drug administration or doses, and further development of nervous system diseases.[4,5]

Recent studies indicate that the main cause of OXC resistance is the genetic polymorphism existing in the genes encoding for proteins associated with OXC metabolizing enzymes, transporter proteins, or target proteins and receptors.[6] By checking the database (http://www.pharmgkb.org/do/) and literatures, we found 4 single nucleotide polymorphisms (SNPs) that were closely related to OXC, including ATP-binding cassette B1 (ABCB1) rs1045642,[7] ATP-binding cassette C2 (ABCC2) rs2273697,[8] ABCC2 rs717620,[9] and UDP-glucuronosyltransferase-2B7 (UGT2B7) rs7439366.[7] The ABCB1 rs1045642 mutant was found to be related to a higher normalized OXC concentration,[7] and meta-analyses have observed the close

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association between the ABCB1 rs1045642 polymorphism and drug resistance in Caucasian and Chinese patients.[10,11] The polymorphism of UGT2B7 rs7439366 exhibited a correlation with therapeutic efficacy, which is consistent with 2 other studies.[12,13] Carriers of the ABCC2 rs2273697 and ABCC2 rs717620 mutant alleles have been reported in association with higher OXC maintenance doses than noncarriers in Asian (Indian and Chinese) epileptic patients.[9,14]

Additionally, OXC is considered a prodrug, its anticonvulsant effect depends on its active 10-hydroxycarbazepine (MHD) metabolite,[15] and the concentration of MHD is often used as an indicator for evaluating the efficacy of OXC clinically.[16] To date, related findings about the correlation among this commonly studied SNPs and MHD concentration are scarce. One study failed to associate the SCN1A, ABCC2, and UGT2B7 mutant with the MHD concentration in Chinese patients with epilepsy,[12] this association failed to be replicated in a later study.[17] The association between the SNPs and MHD remains unclear. A study in German patients found that younger patients may tolerate higher MHD serum levels and higher OXC dosages per body weight than adult patients,[18] whereas Sánchez had the opposite result in the association between ABCB1 polymorphisms and drug resistance in Caucasian patients.[19] Moreover, the clearances and distribution volumes of OXC and MHD were found to be related to patient weight.[20] Fortunately, we found some interesting results by stratifying patients by age and BMI based on the above studies. In addition, as a 10-keto analog of carbamazepine (CBZ), the mechanism of action and efficacy of OXC are comparable to those of CBZ based on structural similarities, so we also explored ABCB1 rs2032582,[21] UGT2B7 rs28365063,[22,23] and SCN2A rs17183814,[24] which are associated with CBZ.

To evaluate the associations between these genetic mutants and the MHD concentration, the present study aimed to identify the effects of candidate SNPs in ABCB1 rs1045642, ABCB1 rs2032582, ABCC2 rs2273697, ABCC2 rs717620, UGT2B7 rs7439366, UGT2B7 rs28365063, and SCN2A rs17183814 on the plasma MHD concentrations and therapeutic efficacy in patients overall or in different stratified groups of patients.

2. Materials and methods

2.1. Subjects

This study was conducted from May 2014 to September 2015 in epileptic outpatients at the Department of Neurology at Xiangya Hospital. As shown in Figure 1, a total of 218 old diagnosed patients (120 males and 98 females) with epilepsy, aged between 1 and 60 years old, were eventually selected for the study. The patients were treated with OXC tablet (0.15 g, Novartis Farma S. p.A, Italy, H20140098) monotherapy for at least 1 month until the plasma concentration of MHD had reached a steady state, and the dosage for all patients was adjusted by bodyweight according to drug instruction. The patients were enrolled in this study have a valid clinical examination of epilepsy (electroencephalography and magnetic resonance imaging) proved by a doctor. Any subject who neglected the treatment regimen or presented any exclusion criteria: alcohol or any other pathological drugs intake, adverse drug reactions, poor treatment compliance, were excluded from the study. According to the guidelines of the International League Against Epilepsy,[25] patients were divided into an OXC-resistant group (occurrence of at least 4 seizures over a period of 1 year during treatment with OXC, N = 133) and an OXC responsive group (seizure-free for at least 1 year during treatment with OXC, N = 85). The patients were also grouped according to the age[19,26] and BMI[27,28] classification criteria of China, including 2 age categories: juvenile group (N = 114) and adult group (N = 104), and 3 BMI groups: low body weight (LW) group (N = 62), normal weight (NW) group (N = 100), and overweight (OW) group (N = 56). Follow-up was conducted every 3 months and continued for 1 year to obtain the following information, including gender, BMI, OXC maintenance dose (mg/kg), standardized MHD concentration (maintenance dose adjusted concentration, μg/ml per mg/kg), the age of first epilepsy occurrence (years), epilepsy duration (years), and duration of OXC treatment (months), types of epilepsy and the number of seizures.

The study was approved by the Ethical Committee of Xiangya Hospital of Central South University (Approval No. 201404364)

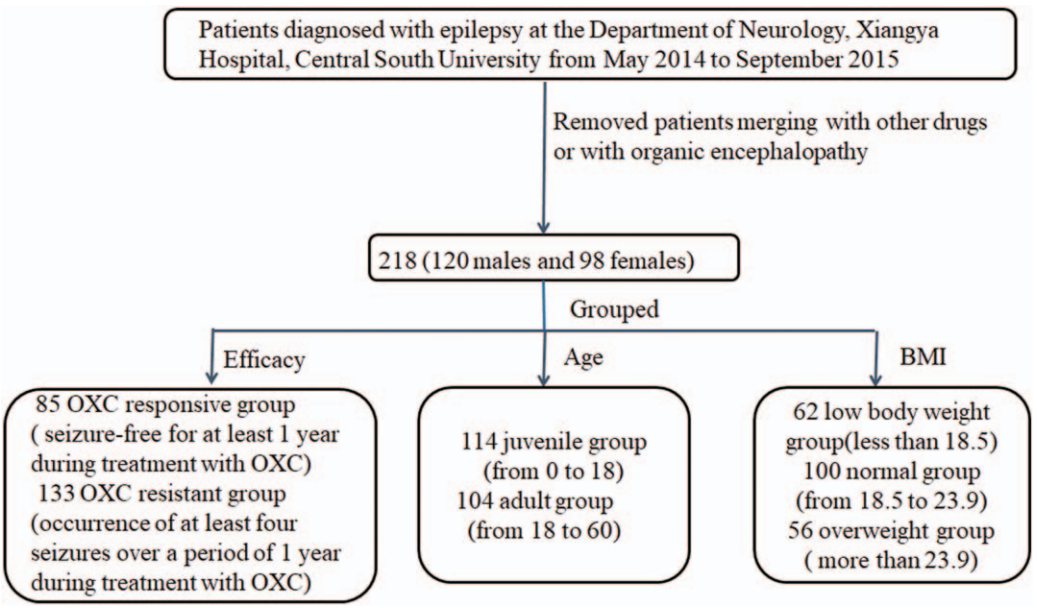

Figure 1. Sample enrollment and grouping.

and registered in the China Clinical Trial Register (registration number: ChiCTR-OCH-14004528). All procedures in this study were strictly based on the Declaration of Helsinki. All patients provided written informed consent.

2.2. Determination of OXC and MHD plasma concentrations

For each patient, a 2 ml sample of venous blood was obtained for the drug assays just before the morning OXC dose (approximately 12 hours after the evening dose, trough concentration). The samples were then centrifuged for 5 minutes at 3000 r/min and stored at –80°C until the MHD analysis, DNA extraction and genotyping. The MHD plasma concentrations were determined by HPLC (SHIMADZU Inc, Japan) in the therapeutic drug monitoring center of the Department of Pharmacy, Xiangya Hospital, Central South University. The analytical range for MHD was 0.234 to 38.044 μg/ml. The method had an excellent linear correlation ($r = 0.999$) and specificity (intra and interday precision ranged from 0.58–16.67% for MHD). The standardized concentration of MHD (μg/ml per mg/kg) was used to eliminate the influence of body weight and administered dosage.[7]

2.3. Genotyping

Genomic DNA was extracted from whole blood using the phenol-chloroform method. Seven SNPs, including ABCB1 rs1045642, ABCB1 rs2032582, ABCC2 rs717620, ABCC2 rs2273697, UGT2B7 rs7439366, UGT2B7 rs28365063, and SCN2A rs17183814, were selected for the current project. The SNP positions were obtained from http://hapmap.ncbi.nlm.nih.gov. Genetic polymorphisms were detected using polymerase chain reaction-improved multiple ligase detection reactions according to the manufacturer's instructions (Center for Genetic & Genomic Analysis, Genesky Biotechnologies Inc, Shanghai) by Shanghai Tianhao Biotechnology Co, Ltd.

2.4. Statistical analysis

The measurable data were expressed as the mean and standard deviation. The statistical analysis was performed using SPSS version 19.0 software (SPSS Inc, Chicago, IL). The genotype frequencies were checked with Hardy–Weinberg equilibrium using the χ^2 test. The clinical characteristics of drug-responsive/resistant patients were compared by t test or $\chi 2$ test. Multivariable linear regression[29] were conducted to analyze the association among each polymorphism and OXC maintenance dose, standardized MHD concentration in different groups. The age, BMI, epilepsy duration, and the age of first epilepsy occurrence were served as covariates. Binary logistic regression was used to analyze the association between each polymorphism and OXC-resistance/response. The age, BMI, epilepsy duration, OXC maintenance dose, and MHD concentration were served as covariates. A 2-sided P-value less than .05 was considered statistically significant.

3. Results

3.1. Patient characteristics based on OXC efficacy and MHD concentration

The characteristics of drug-responsive and drug-resistant patients are shown in Table 1. Significant differences between drug-responsive and drug-resistant patients were found in the epilepsy course ($P = .004$), OXC maintenance dose ($P < .0001$) and standardized MHD concentration ($P < .001$). For age groups, the juvenile group required a higher OXC maintenance dose, while the adult group had a higher standardized MHD concentration (Fig. 2a and b). In terms of BMI groups, the LW group required the highest OXC maintenance dose and the lowest standardized MHD concentration, the OW group had the lowest OXC maintenance dose and the highest standardized MHD concentration, and the NM group was in the middle (Fig. 2c and d).

Table 1

Characteristics of drug-responsive and drug-resistant patients.

Characteristics	Drug-responsive group	Drug-resistant group	*P*-value
Gender (male/female)	47/38	73/60	.533
Age, yr	18.23 ± 12.72	20.33 ± 13.15	.241
BMI	20.30 ± 3.67	20.71 ± 3.71	.492
Age of first epilepsy occurrence, yr	13.17 ± 11.18	12.54 ± 11.44	.688
Epilepsy duration, yr	5.06 ± 5.60	7.80 ± 7.38	.004
OXC treatment duration, mo	16.54 ± 9.14	17.41 ± 9.55	.504
OXC maintenance dose, mg/kg	12.76 ± 5.31	17.02 ± 8.72	<.0001
MHD concentration, μg/ml	9.14 ± 4.70	12.02 ± 5.39	<.001
Standardized concentration of MHD, μg/ml per mg/kg	0.60 ± 0.39	0.60 ± 0.40	.947
Partial/generalized seizures	79/6	116/17	.181

Gender was presented as the number. The comparison between 2 groups were performed by t test or χ^2 test. The rest of the data was presented as the mean ± standard deviation.
BMI = body mass index, MHD = 10-hydroxycarbazepine, OXC = oxcarbazepine.

3.2. Genetic polymorphisms and standardized MHD concentrations

Six of the 7 genotype distributions were consistent with the Hardy–Weinberg equilibrium proportions (Supplemental Table 1, http://links.lww.com/MD/C882), this was similar to the previous studies with Han Chinese samples.[9,29,30] Across all patients, only ABCB2 rs2273697 and UGT2B7 rs28365063 showed a correlation with the MHD concentration (Fig. 3). Carriers of the mutant ABCB2 rs2273697 allele required a higher MHD concentration than noncarriers ($R = 0.14$, 95% confidence interval [CI]: 0.02–0.26, $P = .026$) (Fig. 3a). Regrettably, UGT2B7 rs28365063 was not in Hardy–Weinberg equilibrium, further expansion of sample research is necessary in the future.

Considering the influence of patients age and BMI, patients were grouped accordingly. In terms of age groups, patients with ABCC2 rs2273697 mutant showed a higher standardized MHD concentration ($R = 0.18$, 95%CI: 0.01–0.30, $P = .033$) in the juvenile group (Fig. 4a). Furthermore, the mutant of UGT2B7 rs28365063 showed significant lower standardized MHD concentration in the adult group ($R = –0.26$, 95%CI: –0.93 to –0.13, $P = .009$) (Fig. 4b). For BMI groups, the mutant of SCN2A rs17183814 was associated with higher OXC maintenance dose in the LW group ($R = 6.04$, 95%CI: 1.28–10.80, $P = .014$), and higher standardized MHD concentration in the OW group ($R = 0.24$, 95%CI: 0.07–0.41, $P = .007$) (Fig. 4c and f). While patients with SCN2A rs17183814 mutant showed lower OXC maintenance dose in the OW group (R = –4.67, 95%CI: –9.21 to –0.11, $P = .044$) (Fig. 4e). In the NW group, the mutant of ABCB1 rs2032582 was related to a higher standardized MHD concentration ($R = 0.23$, 95%CI: 0.03–0.39, $P = .026$) (Fig. 4d).

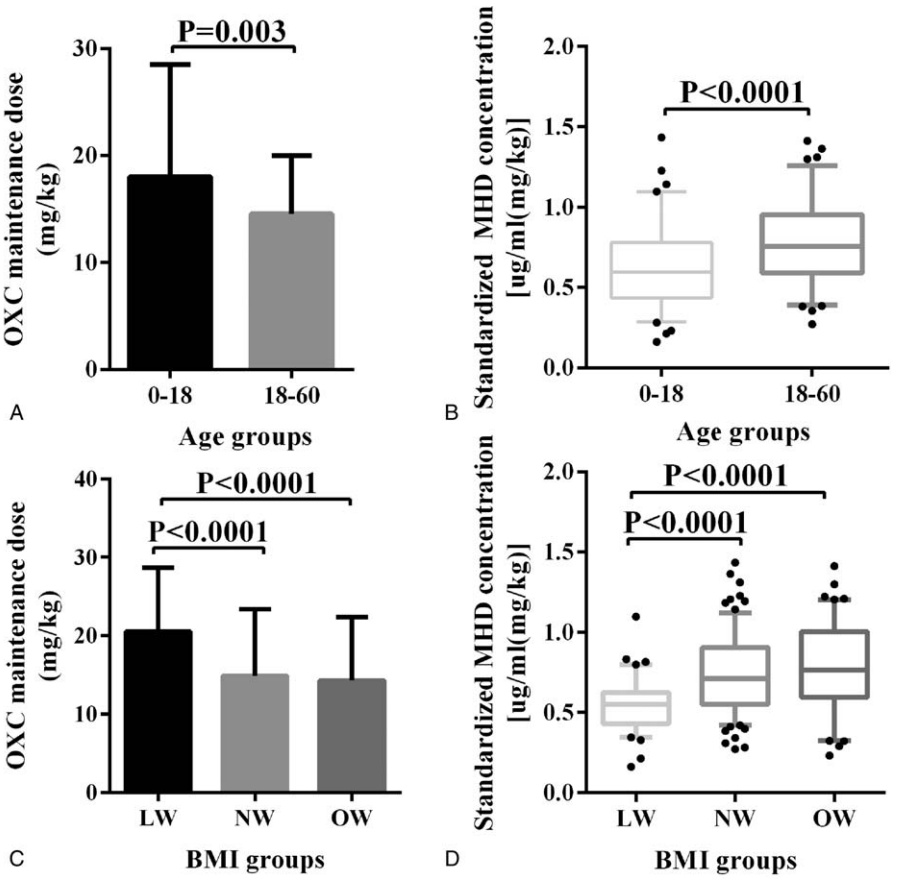

Figure 2. Graphical representations of various age groups and BMI groups associated with (a, c) OXC maintenance dose (mg/kg) and (b, d) standardized MHD concentration (μg/ml per mg/kg). The statistical significance for difference of means is shown (*P* values, *t* test, or χ^2 test). MHD = 10-hydroxycarbazepine.

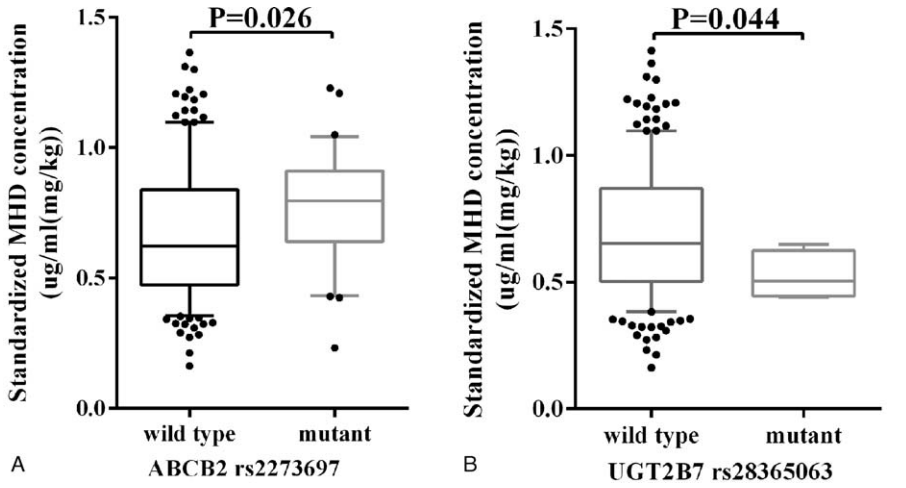

Figure 3. Graphical representations of ABCB2 rs2273697 and UGT2B7 rs28365063 associated with (a, b) standardized MHD concentration (μg/ml per mg/kg). The statistical significance for the difference of the means is shown (*P* values, multivariable linear regression). The age, BMI, epilepsy duration and the age of first epilepsy occurrence were served as covariates. ABCB2 = ATP-binding cassette C2, MHD = 10-hydroxycarbazepine, UGT2B7 = UDP-glucuronosyltransferase-2B7.

3.3. Genetic polymorphisms and OXC therapeutic efficacy

All SNPs of ABCB1, ABCC2, UGT2B7, and SCN2A did not differ significantly between the OXC responsive group and the OXC-resistant group ($P > .05$) (Supplemental Table 2, http://links.lww.com/MD/C882). A multivariate logistic analysis was also performed to evaluate the combined effects of SNPs and nongenetic factors on OXC responsiveness, only the epilepsy course had a significant impact on OXC responsiveness ($P = .009$).

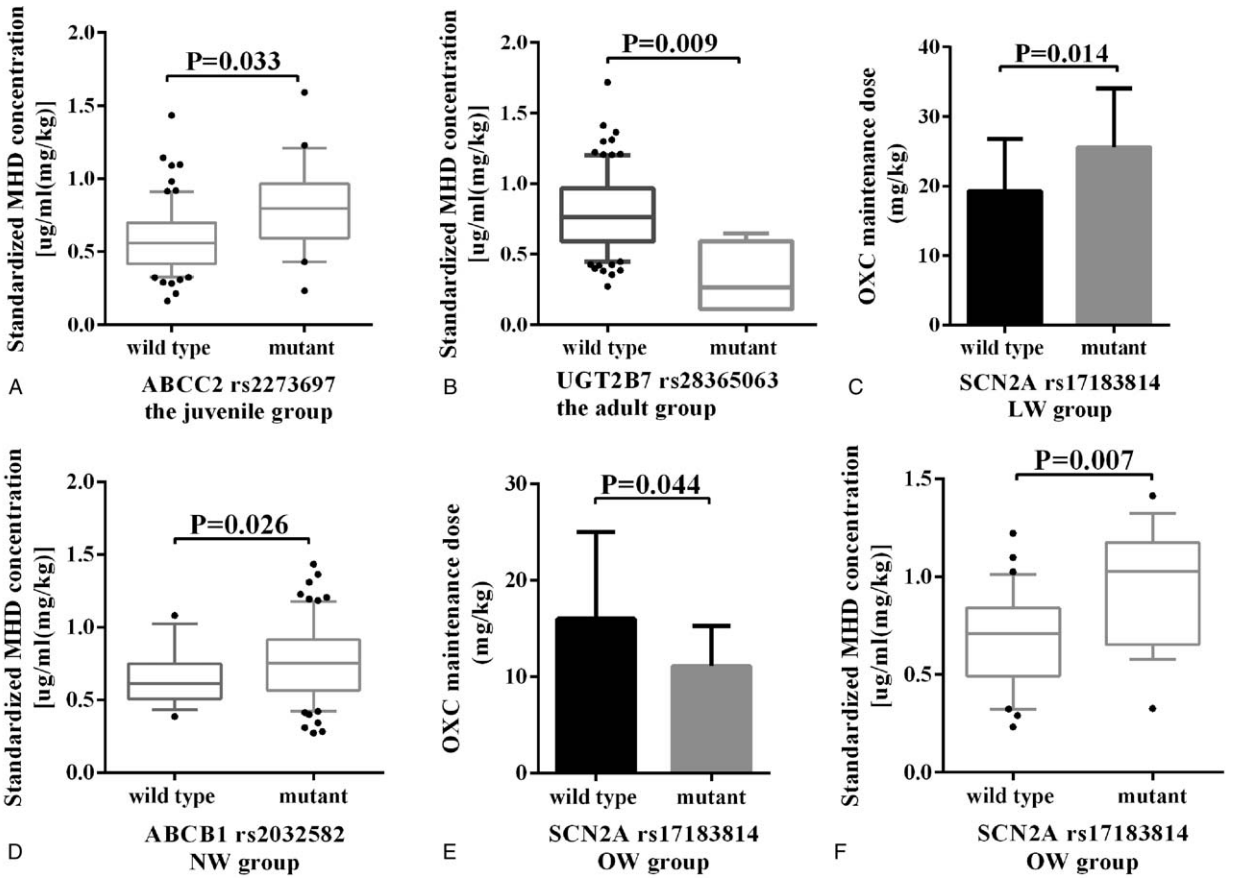

Figure 4. Graphical representations of different SNPs associated with OXC miantenance dose (mg/kg) and standardized MHD concentration (μg/ml per mg/kg) in various age and BMI groups. ABCB2 rs2273697 and UGT2B7 rs28365063 were associated with (a, b) standardized MHD concentration (μg/ml per mg/kg) in various age groups. SCN2A rs17183814 and ABCB1 rs2032582 were associated with (c, e) OXC maintenance dose (mg/kg), (d, f) standardized MHD concentration (μg/ml per mg/kg) in various BMI groups. Statistical significance for the difference of the means is shown (*P* values, multivariable linear regression). The age, BMI, epilepsy duration and the age of first epilepsy occurrence were served as covariates. ABCB1 = ATP-binding cassette B1, ABCB2 = ATP-binding cassette C2, BMI = body mass index, MHD = 10-hydroxycarbazepine, SNPs = single nucleotide polymorphisms, UGT2B7 = UDP-glucuronosyltransferase-2B7.

4. Discussion

Our study mainly investigated the associations between polymorphisms related to AED transportation proteins (encoded by the ABCB1 and ABCC2 genes), metabolizing enzymes (encoded by the UGT2B7 gene), and targeting proteins (encoded by the SCN2A gene) both in a crude analysis and after stratifying through patient age or BMI. When all patients were analyzed as a whole, only the ABCC2 rs2273697 polymorphism was significantly associated with standardized MHD concentration. After stratification, significant associations between higher standardized MHD concentrations and polymorphisms were found in ABCC2 rs2273697 of the juvenile group, SCN2A rs17183814 of the OW group and ABCB1 rs2032582 of the NW group. For age groups, the juvenile group shows highest OXC maintenance dose, while the adult group had the highest standardized MHD concentration. Based on the calculation of standardized MHD concentration (maintenance dose was adjusted concentration), as the average OXC maintenance dose was 0.807-fold in adult compared with juvenile group, may be the reason of highest standardized MHD concentration in adults.

MDR1 (encoded by the ABCB1 gene) and MRPs (encoded by the ABCC genes) are important for the transport of AEDs across the blood–brain barrier.[31] All CBZ analogs and metabolites including OXC and MHD are thought to be active substrates of ABC transporters in in vitro transport studies.[32,33] Studies have found that the overexpression of ABCC2 transporters on blood–brain barrier cells may increase the amount of AED efflux, leading to a reduction in the AEDs concentration in the brain to a lower level, thereby participating in epilepsy resistance.[34] In our study, the ABCC2 rs2273697 polymorphism was significantly associated with the standardized MHD concentration not only in the overall patient group but also in the stratified analysis by age, which is consistent with opinions in the past.[35] In our study, we for the first time grouped patients by age or BMI in multiple polymorphisms analysis. A study[36] on 40 Chinese patients with epilepsy failed to find a correlation between ABCB1 rs1045642 and the standardized MHD concentration, which was consistent with our results. For the BMI groups, the ABCB1 rs2032582 polymorphism was significantly associated with standardized MHD concentration in the NW group, which was inconsistent with Wang et al.[36] In addition, the SCN2A rs17183814 polymorphism was significantly associated with the OXC maintenance dose and standardized MHD concentration in the LW group and the OW group, which is consistent with the north Indian populations.[24,37] However, contrasting results have been reported in Malaysia and Hong Kong.[38] The possible explanation for the difference above is the ethnic difference or patient stratification.

At present, there are many studies investigating the associations between genetic polymorphisms and drug transportation

proteins, drug-metabolizing enzymes, drug-targeting proteins, and drug-resistance, based on the predecessors' study, we found some known and unknown associations between SNPs and standardized MHD concentration, which may provide potential theoretical guidance for the rational and safe clinical use of OXC. Moreover, BMI and age were important and necessary subgroup factors not only in studies of AEDs, such as in intensive pharmacokinetic studies of tenofovir in a large, diverse cohort of HIV-infected women.[39] Our study suggests that stratification by age and BMI could contribute to unmasking the association between gene polymorphisms and drug resistance in epilepsy. The development of a genetic algorithm-guided population pharmacokinetic model is needed to evaluate the consistency between the recommended doses and the reference range for trough concentration of MHD, especially when considering age and weight.

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Writing the Manuscript: X Yang, ZJ Xu.

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