Clinically relevant genetic variants of drug-metabolizing enzyme and transporter genes detected in Thai children and adolescents with autism spectrum disorder

Abstract: Single-nucleotide polymorphisms (SNPs) among drug-metabolizing enzymes and transporters (DMETs) influence the pharmacokinetic profile of drugs and exhibit inter- and intraethnic variations in drug response in terms of efficacy and safety profile. The main objective of this study was to assess the frequency of allelic variants of drug absorption, distribution, metabolism, and elimination-related genes in Thai children and adolescents with autism spectrum disorder. Blood samples were drawn from 119 patients, and DNA was extracted. Genotyping was performed using the DMET Plus microarray platform. The allele frequencies of the DMET markers were generated using the DMET Console software. Thereafter, the genetic variations of significant DMET genes were assessed. The frequencies of SNPs across the genes coding for DMETs were determined. After filtering the SNPs, 489 of the 1,931 SNPs passed quality control. Many clinically relevant SNPs, including CYP2C19*2, CYP2D6*10, CYP3A5*, and SLC01B1*, were found to have frequencies similar to those in the Chinese population. These data are important for further research to investigate the interpatient variability in pharmacokinetics and pharmacodynamics of drugs in clinical practice.

Keywords: Thai population, ADME, pharmacokinetics, autism spectrum disorder, microarray, pharmacogenetics

Introduction

Autism spectrum disorder (ASD) is a global health concern where the patient demonstrates three core features: social withdrawal, verbal and nonverbal communication impairment, and stereotype behavior with restricted and repetitive activities and/or interests. Results have shown that males are more likely to have autism than females, with a prevalence ratio of 4:1. Atypical antipsychotics, including risperidone and aripiprazole, both US Food and Drug Administration approved, have been used as a pharmacologic therapy for the treatment of behavioral symptoms (irritability and aggression) in addition to the psychoeducational therapy among children and adolescents. However, children and adolescents treated with antipsychotic drugs may be predisposed to side effects, such as weight gain, metabolic effects, endocrin dysregulation, and tardive dyskinesia. Genetic variations in drug-metabolizing enzymes (DMEs), drug transporters, and drug targets are important determinants of efficacy and toxicity in pharmacotherapy among patients. Individual variability in drug response poses a major challenge in drug therapy, drug development, and drug regulation. A better account of genetic variability and implementation of personalized treatment plans would help improve the clinical outcomes of drug therapy among children and adolescents.
medication are essential in individual patients to improve the drug therapy by enabling clinicians to prescribe the right medication in the right dose to achieve maximum therapeutic efficacy with minimum adverse drug reactions. Pharmacogenetics is the study of contribution of genetic differences to drug response between individuals. Advances in the field of molecular genotyping, such as DNA chips and microarrays, have facilitated the analysis of large genetic variations. Single-nucleotide polymorphisms (SNPs) are an important marker for pharmacogenetic studies, which can be used for phenotypic association with a functional variant and for optimizing personalized drug therapy. Investigations on animal models of autism have revealed the association between polymorphism in serotonin transporter (5-HTT) and autism. In humans, genetic studies in patients with ASD have revealed the polymorphisms in \textit{CYP1A2*1F} and its association with susceptibility to ASD, and another polymorphism contributing to ASD is \textit{COMT} Val158Met.

Polymorphisms in DMEs and transporters (DMETs) across different populations have been reported with varying frequencies of allelic variation, suggesting interethnic differences in response to drug therapy. Patients are classified as poor metabolizer (PM), intermediate metabolizer, extensive metabolizer, and ultrarapid metabolizer, leading to no activity, reduced activity, normal activity, and increased activity, respectively, based on the DME genetic polymorphisms. The most common cytochrome P450 polymorphisms are found in \textit{CYP2C9}, \textit{CYP2C19}, and \textit{CYP2D6} as identified to date (http://www.cypalleles.ki.se). The important Phase II enzymes exhibiting genetic polymorphisms, which determine the fate of the drugs, include uridine diphosphate glucuronosyltransferase (UGT), glutathione \textit{S}-transferase (GST), sulfotransferase, \textit{N}-acetylationtransferase (NAT), and thiopurine methyltransferase (TPMT). Some of the best characterized drug transporter genes implicated in drug metabolism and response include the adenosine triphosphate (ATP)-binding cassette (ABC) family, such as \textit{ABCB1}, \textit{ABCC1}, \textit{ABCC2}, and \textit{ABCG2}, and solute carrier (SLC) family proteins, such as \textit{OCT1}, \textit{OATP1B1}, and \textit{OAT}. Several pharmacogenetic biomarkers of DMETs are documented in PharmGKB (https://www.pharmgkb.org/), with evidence from different populations. There is a considerable difference in the frequency of genetic polymorphisms associated with drug response, across and within populations. The DMET genes have greater interindividual variability in expression as compared to non-DMET genes. A study investigating the frequencies of DMET SNPs among Thais as well as compared to other ethnic populations revealed significant differences in the distribution of several clinically important genetic polymorphisms among absorption, distribution, metabolism, and elimination genes. Integrating pharmacogenetics into clinical practice has proven to be a cost-saving and improved therapeutic outcome for patients, with the avoidance of medication adverse effects. There is a critical need to understand and establish the frequency of genetic variants and implement the knowledge of genetic variation in DMET genes in the Thai population to construct dosing guidelines, so as to improve the clinical efficacy and minimize the occurrence of adverse effects.

In this study, we used the DMET™ Plus GeneChip microarray platform (Affymetrix Inc., Santa Clara, CA, USA), which is used to genotype markers across genes involved in drug pharmacokinetics. The main aim of this study was to investigate the frequency of DMET genetic variations in the Thai population. The genetic database derived from this study will help in determining the pattern of SNPs in DMET genes among Thai population and correlate the genetic information with the drug response and adverse side effects to produce the significant clinical associations.

Materials and methods

Participants

Blood samples were collected from the 119 Thai children and adolescents with ASD (according to the \textit{Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition} criteria) at Yuwprasart Waihayopathum Child and Adolescent Psychiatric Hospital. Participants were included who were prescribed with risperidone once or twice a day and the dosing was flexible as well. Patients with severe physical disabilities and currently being treated with other antipsychotic drugs were excluded from the study. However, stimulants were allowed in the case of co-occurring attention deficit/hyperactivity disorder. The purpose and experimental procedures were explained to the parents of the participants before obtaining written informed consent from all of the participants’ parents. The study was conducted in accordance with the principles of the Declaration of Helsinki and locally approved by the Ramathibodi Ethics Committee (Bangkok, Thailand).

Sample collection and genomic DNA (gDNA) extraction

Blood samples were collected into EDTA tubes with the assistance of a trained laboratory technician and were then brought to the laboratory of Pharmacogenomics and Personalized Medicine, Ramathibodi Hospital, in a well-insulated...
ice box. The samples were then stored at $<-70^\circ C$ for the subsequent extraction of gDNA.

gDNA was isolated from EDTA–whole blood using a MagNA Pure Compact System (Hoffman-La Roche Ltd., Basel, Switzerland), according to the manufacturer’s instructions, and quantified by a NanoDrop™ 1000 Spectrophotometer at 260 nm (Thermo Fisher Scientific, Waltham, MA, USA).

Genotyping and marker selection
Samples were genotyped using the DMET platform (DMET Plus) according to the standard protocol described by the manufacturer. The DMET™ Plus GeneChip enables the genotyping of 1,936 genetic variants (1,931 SNPs and five copy number variations) of 231 genes having functional significance in Phase I and Phase II DME genes and drug transporter coding genes. The DMET Plus platform examines the genetic variations, including biallelic and triallelic SNPs, copy number variations, and insertions/deletions. Genotype analysis using the DMET Plus platform is based on an efficient and comprehensive molecular inversion probe technology. DNA samples on the DMET Plus array were scanned with the GeneChip Scanner 3000 (Affymetrix Inc.). The genotype profile of 1,931 SNPs was generated by DMET™ Console Software® (Version 1.3; Affymetrix Inc.).

Quality control
Quality control of the samples and SNPs was performed as shown in Figure 1. Individual samples were considered passed or in bounds if they had genotyping calls >90%. The markers with genotyping call rate <95%, deviation from Hardy–Weinberg equilibrium (HWE) at $P>0.001$, minor allele frequency (MAF) <0.05, and variants on chromosome X were discarded.

Statistical analysis
Data are presented as median and ranges, or as otherwise specified. The Haploview 4.2 software was used for checking HWE, along with MAF, and filtering markers according to the criteria set for quality control.

Results
Patient characteristics and selection of markers
Most of the participants were males (87.1%) and had a median age of 8.8 years (range 3.3–18.3 years). A total of 1,681 SNPs passed the first quality control filter with call rate of >95%. Only 489 SNPs were included for the assessment of genetic prevalence after considering the quality control filter removing the SNPs that were not in HWE, MAF <0.05, and SNPs on the X chromosome (46 SNPs) (Figure 1). The average call rate of the sample was 99.23%.

Allele frequency distribution of common functional polymorphisms of Phase I enzymes
The observed minor allele frequencies of common polymorphisms in CYP enzymes with their clinical or functional relevance are presented in Table 1. We identified 32 CYP genes with different markers prevalent in the Thai population. The prevalence rates of some pharmacologically and clinically relevant CYP polymorphisms observed were as follows: CYP1A1*2C (30.3%), CYP1A2*1F (23.9%), CYP2A6*9 (15.3%), CYP2B6*4 (32.8%), CYP2B6*6 (28.4%), CYP2C19*2 (33.2%), CYP2C19*3 (5%), CYP2D6 100C>T (41.2%), CYP2D6 2850C>T (10.1%), CYP3A4*3 (37%), and CYP3A7*2 (35.8%).

Allele frequency distribution of common functional polymorphisms of Phase II DMEs
We detected different allele frequencies of common Phase II DMEs, with a wide frequency range from 5% to 49% in...
Table 1 Minor allele frequencies of common functional polymorphisms in major human CYP genes in Thai children and adolescents with autism spectrum disorder (sample size =119)

| Gene    | dbSNP RS ID | Common name                  | Minor allele frequency | Clinical relevance |
|---------|-------------|-------------------------------|------------------------|--------------------|
| CYP1A1  | rs1048943   | CYP1A1*2C>254A>G(i462V)       | 0.303                  | -                  |
|         | rs4646422   | CYP1A1*13G>A(G45D)            | 0.08                   | -                  |
| CYP1A2  | rs2069514   | CYP1A2*IC->3860G>A(Promoter)  | 0.303                  | -                  |
|         | rs762551    | CYP1A2*IF->163C>A(Promoter)   | 0.239                  | -                  |
|         | rs2470890   | CYP1A2_3374T>C(N516N)         | 0.206                  | -                  |
| CYP2A6  | rs28399433  | CYP2A6*9_G>48T>G(Promoter)    | 0.153                  | -                  |
|         | rs1137115   | CYP2A6*5G>A(V17V)             | 0.261                  | -                  |
|         | rs4079369   | CYP2A6*3570C>G                | 0.076                  | -                  |
|         | rs8192729   | CYP2A6*5336G>A                | 0.076                  | -                  |
| CYP2B6  | rs8192709   | CYP2B6*2_64C>T(R22C)          | 0.055                  | -                  |
|         | rs4803418   | CYP2B6*14593C>G               | 0.382                  | -                  |
|         | rs2279343   | CYP2B6*2_18053A>G(K262R)      | 0.328                  | -                  |
|         | rs3745274   | CYP2B6*6_15631G>T(Q172H)      | 0.284                  | -                  |
|         | rs2279344   | CYP2B6*18273G>A               | 0.286                  | -                  |
|         | rs8192719   | CYP2B6*21563C>T               | 0.282                  | -                  |
| CYP2C19 | rs4244285   | CYP2C19*2_19154G>A(P227P)     | 0.332                  | -                  |
|         | rs4986893   | CYP2C19*3_17948G>A(W212X)     | 0.05                   | -                  |
| CYP2D6  | rs1135840   | CYP2D6*4180G>C(S486T)         | 0.298                  | -                  |
|         | rs16947     | CYP2D6_2850C>T(R296C)         | 0.101                  | -                  |
|         | rs1058164   | CYP2D6_1661G>C(V136V)         | 0.286                  | -                  |
|         | rs1065852   | CYP2D6_100C>T(P34S)           | 0.412                  | -                  |
|         | rs1080985   | CYP2D6_1584C>G                | 0.071                  | -                  |
|         | rs2836052   | CYP2D6_2178G>A                | 0.397                  | -                  |
| CYP2A6  | rs776746    | CYP3A5*2_6986A>G(SpliceDefect) | 0.37                  | -                  |
|         | rs2257401   | CYP3A7*2_26041C>G(T409R)      | 0.358                  | -                  |

Note: dbSNP RS ID is an identification tag assigned by the National Center for Biotechnology Information to a group of single nucleotide polymorphisms (SNPs) that map to an identical location in the SNP database.

this Thai population, as shown in Table 2. Among UGT1A1 polymorphisms, UGT1A1*60 was the most prevalent (36.1%) in this study group. The prevalence rates of other notably clinically significant variants among several Phase II enzymes were as follows: UGT2B7*2 (31.5%), UGT1A7*12 (15.1%), GSTA5 c.-31+2057C>T (35.7%), GSTP1*B (27.5%), GSTT1 c.94G>A (39.5%), NAT2*13 (45.4%), and NAT2*6 (27.7%).

Allele frequency distribution of common functional polymorphisms of drug transporters

Table 3 shows the allele frequencies of drug transporter genes in Thai population. Among the important efflux ABCB1 transporters, the MAF of ABCB1 1236C>T and 3435C>T exhibited prevalence rates of 34.5% and 43.7%, respectively. Other ABC SNPs with clinical relevance exhibited prevalence rates of rs212091 (15.7%), rs717620 (22.3%), rs2273697 (6.7%), rs3740066 (24.3%), and 30.7% for ABCG2 421C>A.

The uptake SLC transporters (OCT1, OCT2, OATP1A2, and OATP1B2) were present with at least one variant allele in this study group (data for all variants not shown). Among the OCT1 family, the two variants rs628031 (Val408Met, 1222G>A) and rs1867351 (Ser52Ser, 156T>C) had higher frequency of 33.9% and 31.9%, respectively. The pharmacologically important variants SLCO1B1*1B, SLCO1B1*5,
Table 2 Minor allele frequencies of common functional polymorphisms in major human Phase II drug-metabolizing enzyme genes in Thai children and adolescents with autism spectrum disorder (sample size = 119)

| Gene      | dbSNP RS ID | Common name                                      | Minor allele frequency | Clinical relevance                                                                 |
|-----------|-------------|--------------------------------------------------|------------------------|-----------------------------------------------------------------------------------|
| UGT1A1    | rs4148323   | UGT1A1*6_c.211G>A(G71R)                          | 0.067                  | • UGT1A1*6 is associated with increased risk of neutropenia when treated with irinotecan²⁴ |
|           | rs4124874   | UGT1A1*60_c.-327T>G(Promoter)                    | 0.361                  |                                                                                  |
|           | rs10929303  | UGT1A1*76_c.*211C>T(3’UTR)                       | 0.088                  | • UGT1A1*93 is associated with increased risk of hematologic toxicity in irinotecan-treated patients³³ |
|           | rs8330      | UGT1A1*79_c.*440C>G(3’UTR)                       | 0.082                  |                                                                                  |
|           | rs887829    | UGT1A1*80_c.-364T                                  | 0.13                   |                                                                                  |
|           | rs10929302  | UGT1A1*93_c.-3156G>A(Promoter)                   | 0.126                  |                                                                                  |
| UGT1A7    | rs7586110   | UGT1A7*12_c.-57T>G(5’UTR)                        | 0.151                  | • UGT1A7*12 is associated with increased risk of hyperbilirubinemia when treated with atazanavir²⁴ |
| UGT2B7    | rs7439366   | UGT2B7*2_c.802C>T(H268Y)                         | 0.315                  | • Genotype TT shows better response to lorazepam and valproic acid as compared to genotype CC in UGT2B7*2 polymorphism¹⁰ |
|           | rs12233719  | UGT2B7*3_c.211G>T(A71S)                          | 0.084                  | • UGT2B7*3 is associated with decreased clearance of carvediol³¹ |
| GSTA5     | rs4715354   | GSTA5_c.-31+2057C>T                               | 0.357                  | • rs4715354 and rs7746993, both combined, are associated with decreased busulfan clearance³² |
|           | rs7746993   | GSTA5_c.-852G>T                                  | 0.147                  |                                                                                  |
| GSTP1     | rs1695      | GSTP1*B_c.313A>G(I105V)                          | 0.275                  | • GSTP1*B is associated with increased response and decreased severity of toxicity among patients with breast cancer treated with cyclophosphamide and epirubicin³³ |
| GSTZ1     | rs1046428   | GSTZ1_c.245C>T(T82M)                             | 0.055                  | • rs7975 and rs1046428 are associated with clearance of dichloroacetic acid³⁵ |
|           | rs7975      | GSTZ1_c.94G>A(A32K)                              | 0.395                  |                                                                                  |
| NAT2      | rs1799929   | NAT2_c.481C>T(L161L)                             | 0.078                  | • rs1799929 variant is associated with hepatotoxicity when treated with antituberculosis drugs³⁶ |
|           | rs1801280   | NAT2_c.341T>C(114T)                              | 0.092                  |                                                                                  |
|           | rs1799930   | NAT2_c.590G>A(R197Q)                             | 0.277                  | • NAT2*5, *6, *7 and *13 influence the metabolism of isoniazid³⁷ |
|           | rs1799931   | NAT2_c.857G>A(G286E)                             | 0.176                  |                                                                                  |
|           | rs1041983   | NAT2*13_c.282C>T(Y94Y)                           | 0.454                  |                                                                                  |

Note: dbSNP RS ID is an identification tag assigned by the National Center for Biotechnology Information to a group of single nucleotide polymorphisms (SNPs) that map to an identical location in the SNP database.

and SLCO1B1*17 had frequencies of 26.9%, 12.2%, and 8.4%, respectively.

Discussion

In this study population of 119 Thai children and adolescents with ASD, we have reported allele frequency of clinically relevant DMET SNPs. Among the 1,931 markers genotyped by the DMET assay, we detected ~26% of SNPs distributed along the pharmacokinetic genes. Although, 87% of SNPs passed the 95% call rate criteria, many of the SNPs were discarded because they were monomorphic and had a prevalence of <5%. Our study sample was comprised of mostly males (87%), and hence 46 SNPs on the X chromosome were excluded, as well. The SNPs reported in this study could serve as informative data in assessing the potential risk of therapeutic failure or adverse events in the Thai population, where there is little information available about the prevalence of variations across DMET genes. The DMET microarray technique proved to be a powerful tool enabling us to characterize the clinically important genetic variants among DMET genes.

The frequency of some alleles in this study showed similar prevalence with previous studies conducted in the Thai population. The allele frequencies of CYP2C19*3 (PM), CYP2D6*2, and CYP2D6*10 (decreased enzyme activity) were 5%, 10%, and 41%, respectively, in this study. Similar findings were reported by the group studying CYP2C19 and CYP2D6 polymorphisms and tamoxifen efficacy in Thai patients with breast cancer.²⁸ CYP2C19*2, a PM, which has been shown to cause severe acute adverse drug reactions among Thai children treated with phenobarbital,²⁹ showed a higher frequency of 33.2% in
this study, which is in line with the previously reported frequency of 27%. CYP2B6 variants, c.516G>T and c.785A>G, which were strongly correlated with plasma efavirenz levels in the Thai population, are not reported in the findings of this study. Another variant of a major CYP2B6 enzyme, c.64C>T, which is also associated with efavirenz plasma concentration, was present at a frequency of 0.055, which is also reported by the earlier study to occur at similar prevalence of 0.06.

Polymorphisms in Phase II metabolic enzymes and transporters are of clinical significance, because of altered function affecting the drug safety and drug efficacy. UGT enzyme polymorphisms have been associated with several drug substrates and widely studied among several ethnic groups. The prevalence of UGT1A1*6, which is more commonly observed in Asian populations and absent among Caucasians, resembled earlier studies that reported a frequency of 9%. A previous study of UGT2B7*2 among Thai patients with breast cancer reported an allele frequency of 28%, which is similar to the 31.5% reported in this study. CYP1A2*1F was associated with an increased risk of cholangiocarcinoma (CCA), while NAT2*6 and *7 were associated with a lower risk of CCA in a study by Prawan et al, who evaluated the relationship between CYP1A2 and NAT2 alleles and CCA among individuals living in the northeastern region of Thailand. The allelic frequencies of CYP1A2*1F, NAT2*6, and NAT2*7 in this study group were found to be 23.9%, 27.7%, and 17.6%, respectively. Genetic variants of
a widely documented polymorphic enzyme TPMT did not pass quality control in this study group with the exception of one variant, TPMT_c.474C>T, with a prevalence of 22.7% (data not shown).

Among the genetic polymorphisms of ABC and SLC transporters, we found a modest replication of allele frequency, as was reported in a previous comprehensive study of the frequency of several functional variants known to affect plasma concentration of anti-human immunodeficiency virus drugs among the Thai population, including ABCB1 (1236C>T, 2677G>T, and 3435C>T), ABCG2 421C>A, and SLC1B1 521T>C.39

Limitations in this study include lack of validation data for the markers extracted from the DMET assay. Second, we did not evaluate the clinical role of DMET SNPs in determining the influence on the ASD symptoms. A study by Jiao et al40 has accumulated the evidence of the role of SNPs in the classification of symptom severities among ASD children. It is necessary to analyze the effects of genetic polymorphisms in DMET genes on clinical efficacy and adverse events to amplify the strength of this study. Finally, the small size and inability to compare with the diverse ethnic Thai populations may limit the scope of application of our findings. Further inclusion of control population would have provided more evidence for translating the findings from this study into clinical practice, which was lacking in this study.

Conclusion
In this study, we have analyzed the DMET SNPs that are increasingly significant in identifying the predicted drug metabolizer phenotypes among individuals. Knowledge of these variations and implementation of this information to correlate these variants with drug response in the Thai population will help us to understand the interindividual variations in response to pharmacological agents. Identification of several functional SNPs in the clinical setting, rather than just the few widely studied SNPs, will provide more concise and predictive value for pharmacotherapy.

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Disclosure
The authors report no conflicts of interest in this work.

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