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ARTICLE

UGT1A1 polymorphisms associated with prolactin response in risperidone-treated children and adolescents with autism spectrum disorder

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Abstract

The aim of this study was to investigate the association of drug-metabolizing enzyme and transporter (DMET) polymorphisms with the risperidone-induced prolactin response using an overlapping gene model between serum prolactin level and hyperprolactinemia in autism spectrum disorder (ASD) patients. Eighty-four ASD patients who were receiving risperidone for at least 1 month were recruited and then assigned to either the normal prolactin group or the hyperprolactinemia group based on their serum prolactin level. The genotype profile of 1936 (1931 single nucleotide polymorphisms (SNPs) and 5 copy number variation (CNVs) drug metabolism markers was obtained using the Affymetrix DMET Plus GeneChip microarray platform. Genotypes of SNPs used to test the accuracy of DMET genotype profiling were determined using TaqMan SNP Genotyping Assay kits. Eighty-four patients were selected for the allelic association study after microarray analyses (51 in the normal prolactin group, and 33 in the hyperprolactinemia group). An overlapping allelic association analysis of both analyses discovered five DMET SNPs with a suggestive association ($P < 0.05$) with risperidone-induced prolactin response. Three *UGT1A1* SNPs (*UGT1A1**80c.-364C > T, *UGT1A1**93 c.-3156G > A, and *UGT1A1* c.-2950A > G, showed a suggestive association with the risperidone-induced prolactin response and found to be in complete linkage disequilibrium (D′ value of 1). In this DMET microarray platform, we found three *UGT1A1* variants with suggestive evidences of association with the risperidone-induced prolactin response both measured by hyperprolactinemia and by prolactin level. However, due to the lack of validation studies confirmation and further exploration are needed in future pharmacogenomic studies.

Introduction

Autism spectrum disorder (ASD) is characterized by communication impairment, social reciprocity, and

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repetitive behaviors or restricted interests [1]. Risperidone is approved by the Food and Drug Administration (FDA) for the treatment of irritability including aggression and self-injury, in children with ASD [2]. Several studies have demonstrated the efficacy and safety of risperidone in improving behavioral problems associated with ASD [3–5]. However, evidences suggest the link between risperidone treatment and serum prolactin level elevations among ASD children [6–9]. The clinical manifestations of hyperprolactinemia are menstrual disturbances, amenorrhea, infertility, and galactorrhea in women and gynecomastia, decreased libido, and impotence in men. Because the dopamine D_2 receptor in the anterior pituitary gland plays an important role in regulating prolactin secretion, blocking of this receptor by risperidone is one of the major underlying causes of hyperprolactinemia [10]. Genetic variability among individuals likely contributes to the prolactin elevations by risperidone exposure [11].

Risperidone is metabolized in the liver mainly by cytochrome P450 (CYP) 2D6 (CYP2D6) and to a lesser level by CYP3A4 and CYP3A5 to 9-hydroxyrisperidone, which has pharmacodynamic properties similar to that of risperidone [12–14]. Both risperidone and 9-hydroxyrisperidone are good substrates for the ABCB1 (P-glycoprotein) transporter [15]. The interindividual genetic alterations in drug-metabolizing enzymes and transporters (DMET) are associated with predicting the side-effect profile to a drug exposure [16]. Several authors have reported the association between single nucleotide polymorphisms (SNPs) of *CYP2D6* and hyperprolactinemia in risperidone treated patients [17]. Pharmacogenetic studies of susceptibility to hyperprolactinemia focused on SNPs in selected candidate pharmacokinetic genes in *CYP2D6* and *ABCB1* have been reported, but these studies have yielded discrepant results [10, 11, 18].

A broad approach in assessing the impact of multiple DMET polymorphisms for risperidone induced hyperprolactinemia might provide a better understanding of their etiological mechanisms. The Affymetrix DMET Plus GeneChip microarray platform investigates 1936 (1931 SNPs and 5 CNVs) drug metabolism markers in 225 genes including 47 phase I enzymes, 80 phase II enzymes, 52 transporters, and 46 other genes [19]. The advantage of microarray studies is the possible identification of unexpected biomarkers which do not have an established biological pathway with the prolactin regulation [20]. To date, there have not been any association studies between multiple DMET genetic variants and the risks of risperidone-induced prolactin response in the Thai population. Therefore, the objective of the present study is to investigate hypothesis-free the association of the risperidone-induced prolactin response which is assessed as hyperprolactinemia and prolactin level with DMET SNPs by use of the DMET microarray platform among risperidone treated Thai children and adolescents with ASD.

Subjects and methods

Patients

This study is an observational-retrospective study. Patients were recruited from Yuwaprasart Waithayopathum Child and Adolescent Psychiatric Hospital, Samut Prakarn, Thailand. The parents or guardians of the patients provided written informed consent to participation in this pharmacogenomic study, after the study was approved by the ethics committee of the Ramathibodi Hospital, Bangkok, Thailand.

The inclusion criteria for the patients were (1) clinically diagnosed with ASD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, (2) treated with risperidone for at least one month to achieve steady state plasma levels, and (3) had complete record of dose and duration of risperidone therapy. Exclusion criteria were patients with severe physical disabilities and receiving concomitant medications that could potentially affect pharmacokinetics of risperidone. Drugs affecting pharmacokinetics of risperidone include CYP2D6 and/or CYP3A4 inhibitors (quinidine, clozapine, fluoxetine, and paroxetine) and CYP2D6 and/or CYP3A4 inducers (carbamazepine, phenytoin, and rifampicin) [21].

The sample size was calculated according to the equation $n = [(Z_{\alpha/2})^2\ (p)(1-p)]/d^2$ where $Z_{\alpha/2}$ represents the value for a 95% confidence interval = 1.96, p represents the prevalence of risperidone-induced hyperprolactinemia in Thailand [7] = 0.45, and d represents the allowed error of the test = 0.15. According to the calculation, at least 43 samples should be collected for statistical validity.

Risperidone dosing among the ASD patients was based on body weight. Risperidone dosing followed the guidelines where the starting dose of risperidone for the treatment of irritability associated with autistic disorder is 0.25 mg/day for patients weighing <20 kg and 0.5 mg/day for patients weighing 20 kg or more, with the target dose of 0.5 mg/day (<20 kg) and 1 mg/day (20 kg or more) (Risperdal® prescribing information, revised version 2014). Drug intake records were assessed by the nursing staff of the hospital. All the medications that were in concomitant use with risperidone were recorded. The treatment for co-occurring disease conditions with medications were allowed to continue.

Serum prolactin measurement

Blood samples were drawn after an overnight fast and collected into EDTA anticoagulation tubes. Serum prolactin

concentration was measured by IMMULITE 1000 enzyme-amplified chemiluminescent immunoassay (Siemens Healthcare GmbH, Germany). Hyperprolactinemia was defined as a serum prolactin level greater than the 97.5th percentile value of age- and sex-matched control subjects [22]. The cutoff points for the 97.5th percentile values by patient age and sex for prolactin levels were: 14.43, 24.81, 13.44, 16.37, 13.54, 18.63, 17.55, 19.81, 15.09, 16.51, and 15.71 ng/ml in males and 20.14, 16.37, 26.37, 44.20, 15.47, 22.78, 31.13, 20.52, 20.71, 17.78, and 39.53 ng/ml in females for ages of 4–6, 7–8, 9–10, 11, 12, 13, 14, 15, 16, 17, and 18–19 years old, respectively according to Elmlinger et al. [7, 8, 18, 22].

Preparation and processing of the drug-metabolizing enzyme and transporter platform (DMET)

Genomic DNA was isolated from whole blood using MagNA Pure Compact Nucleic Acid Isolation Kit (Hoffman-La Roche Ltd., Basel, Switzerland), which is based on magnetic-bead technology. SNPs were genotyped with the Affymetrix DMET GeneChip microarray platform. The microarray platform is based on molecular inversion probes (MIP) technology [23]. Firstly, a multiplex polymerase chain reaction (mPCR) is used to preamplify some markers from regions containing pseudogenes and close homologs. PCR products which have the polymorphic markers of interest are then preferentially amplified through the highly selective MIPs. The quality of amplified MIPs is checked through a first quality control (QC) gel which should be a single band. To improve the samples, smaller DNA fragments are added by fragmentation reagents and DNA fragment size is determined on the second QC gel. Target DNA is then labeled and hybridized [24, 25]. Washing and staining of DMET arrays were performed using Affymetrix fluidic stations and scanned by the Affymetrix GeneChip® Scanner 3000 (Affymetrix Inc, Santa Clara, CA, USA).

Quality control

Genotype call rates of DMET SNPs were generated with Affymetrix DMET™ Console software® (version 1.3; Affymetrix Inc.). A test of concordance between the genetic and reported sex was carried out to identify the errors in labeling samples. Haploview was used to generate sample and marker quality data [26]. Samples with genotype call rate >95% were retained for the analysis. SNPs were removed if their individual genotype call rate were <95%. Moreover, SNPs with minor allele frequency (MAF) <0.05, SNPs that were not in Hardy–Weinberg equilibrium ($P < 0.001$), and all SNPs belonging to the X chromosome were removed prior to the analyses. Identity by state (IBS), a phenomenon where two or more than two individuals share similar nucleotide sequences was measured using GenABEL package in R software [27]. Patients were excluded from the analyses if they had too high IBS (≥0.95).

Overlapping gene selection

Genetic polymorphisms in DMET genes were analyzed for the association with two outcomes which are hyperprolactinemia (case–control) and serum prolactin level (continuous data) by their significance levels ($P < 0.05$) as shown in Supplementary Table 1 and 2, respectively. Significant genes can be then combined and selected if they are overlapping between two data set analyses (Table 2).

TaqMan SNP genotyping assay

With the aim of testing the accuracy of the results produced by DMET Plus array, we chose a random subset of 59 samples and selected four SNPs from the DMET marker panel that passed QC for genotype concordance using PCR-based TaqMan allele discrimination method (Applied Biosystems, CA, USA) [28]. The four SNPs included two SNPs from *CYP2D6* (rs3892097 and rs28371725) and two SNPs from *ABCB1* (rs1045642 and rs2032582). A genotype concordance of greater than or equal 98% for each variant between DMET assay and TaqMan SNP assay was considered acceptable performance [29].

Statistical analysis

Descriptive data analyses were performed by the statistical program PASW statistics 18 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk normality test was applied to the data; $P < 0.05$ indicated that the data (serum prolactin level, age, risperidone dose and risperidone duration) were not in normal distribution. Statistical analysis was performed by two-tailed χ^2 or Fisher's exact test. To describe clinical characteristics, we presented them as median and interquartile range (Q1–Q3). To test the association between dependent variable (continuous data; serum prolactin level, age, risperidone dose, and risperidone duration) and two categorical groups (hyperprolactinemia vs non-hyperprolactinemia), we chose the Mann–Whitney *U* test. Significance was set at P-value < 0.05.

Allelic association analysis was performed using the GenABEL package in R software (Version 3.1.2), by computing the Cochran-Armitage trend test and obtaining the *P* value for each SNP. The results of potential interest were limited to those SNPs which showed a *P* value <0.01. Pairwise linkage disequilibrium (D′) was estimated using Haploview 4.2. SNPs with D′ values >0.9 were considered as a surrogate marker for each other.

Table 1 Demographic and clinical characteristics of the ASD patients ($n = 84$)

Characteristic	Total ($n = 84$)	Non-hyperprolactinemia ($n = 51$)	Hyperprolactinemia ($n = 33$)	*P*-value*
Age, years; median; Q1–Q3	8.96; 7.44–10.98	8.75; 7.58–10.92	9.75; 6.46–11.50	0.851[a]
Sex				
Male, *n* (%)	73 (86.90)	43 (58.90)	30 (41.10)	0.515[b]
Female, *n* (%)	11 (13.10)	8 (72.73)	3 (27.27)	
Risperidone treatment				
Risperidone dose, mg/day; median; Q1–Q3	0.55; 0.50–1.00	0.70; 0.50–1.00	0.50; 0.50–1.00	0.955[a]
Risperidone duration, months; median;Q1–Q3	43.57; 21.19–68.95	44.40; 29.67–69.20	33.67; 16.19–68.30	0.114[a]
Risperidone single medication, *n* (%)	54 (64.29)	33 (61.11)	21 (38.89)	0.920[c]
Concomitant treatments, n *(%)*	30 (35.71)	18 (60.00)	12 (40.00)	
Methylphenidate, *n* (%)	14 (46.67)	9 (64.29)	5 (35.71)	
Valproic acid, *n* (%)	13 (43.33)	8 (61.54)	5 (38.46)	
Methylphenidate +valproic acid, *n* (%)	3 (10.00)	1 (33.33)	2 (66.67)	
Serum prolactin levels, ng/ml; median; Q1–Q3	15.90; 10.43–22.40	11.90 (8.06–16.30)	23.70 (17.95–41.65)	<0.001[a]

ASD autism spectrum disorder, *Q1–Q3* quartile 1–3

*$P < 0.05$ was considered statistically significant.

[a]*p*-value reported by Mann–Whitney *U* test

[b]*p*-value reported by Fischer exact test

[c]*p*-value reported by χ^2 test

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of all participants, which were separated in non-hyperprolactinemia and hyperprolactinemia patients are summarized in Table 1. The majority of patients were male (86.90%) and with a median age of 8.75 years among the non-hyperprolactinemia and 9.75 years among the hyperprolactinemia group. Age, sex, risperidone dose, or risperidone treatment duration was not significantly different between the normal prolactin group and the hyperprolactinemia group. The number of patients taking risperidone as single medication and using concomitant medications in both groups was not significantly different. The median prolactin level was significantly higher (23.7 ng/ml vs. 11.9 ng/ml, $P < 0.001$) in the hyperprolactinemia group compared to the normal prolactin group.

A total of 84 ASD patients, including 51 with normal prolactin level and 33 with hyperprolactinemia, were retained for analyses from the 87 recruited ASD patients. Two patients were excluded because of a genotype call rate of <95%. One patient was excluded because of too high IBS. A multidimensional scaling plot did not show any clearly discrete clusters both hyperprolactinemia and non-hyperprolactinemia, and quantile−quantile (Q–Q) plot presented λ not more than 1.04 ($\lambda = 0.939$) indicating an absence of population stratification in our study samples (Supplementary Figure 1).

DMET assay genotyping quality results

The average genotype call rate for the samples was 96.5%. When 1936 DMET markers were tested based on the quality criteria setup, 144 SNPs were removed owing to a genotype call rate <95% and 1233 SNPs were removed owing to a MAF <0.05. As a result, the final analysis included 508 DMET SNPs.

Associations of DMET variants with hyperprolactinemia

Of the 508 SNPs, top three SNPs in two different genes showed a suggestive association with hyperprolactinemia ($P < 0.01$, Supplementary Table 1). The best SNP was rs11678615 in the *AOX1* exon ($P = 0.0055$). Two other SNPs on *UGT2B11* (rs72551395, $P = 0.0062$; rs72551394,

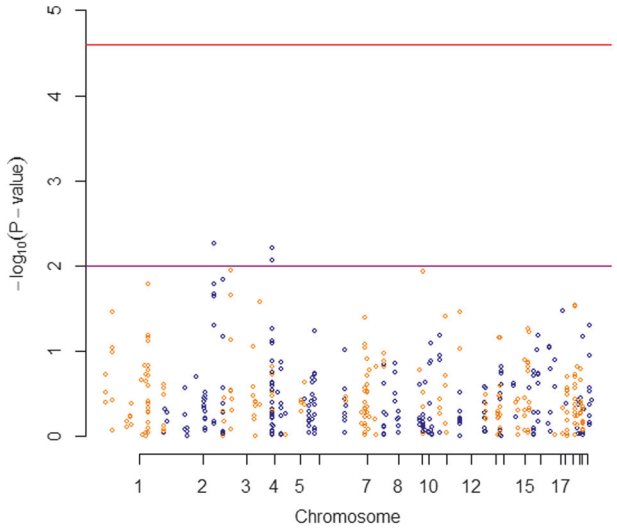

Fig. 1 Manhattan plot of association of drug metabolizing enzymes and transporters (DMET) variants with serum prolactin level. The horizontal *x*-axis represents the chromosomal positions; the vertical *y*-axis represents $-\log_{10}$ *P*-values from the linear regression. The red horizontal line represents the significance level of $P = 2.5 \times 10^{-5}$ after Bonferroni correction. The magenta horizontal line represents the *P*-value of 0.01

$P = 0.0085$) also showed associations with hyperprolactinemia. The SNP set for the DMET variants with $P < 0.05$ associated with hyperprolactinemia are presented in Supplementary Table 1.

Associations of DMET variants with serum prolactin level

The top three significant findings of DMET SNPs associated with serum concentrations of prolactin are shown in Fig. 1 and Supplementary Table 2 ($P < 0.01$). Analysis showed that *CYP2D6* 2850 C > T (rs16947), *SLC22A8* c.723 T > A (rs2276299), and *CA5P* C > T (rs11150564) had significant associations. The SNP set for the DMET variants with $P < 0.05$ associated with prolactin concentration are presented in Supplementary Table 2.

Suggestive associations of DMET variants with overlap of hyperprolactinemia and serum prolactin level

To evaluate the risk associated with risperidone-induced prolactin response, an overlapping genes between hyperprolactinemia and serum prolactin levels were conducted. Of all the DMET SNPs, five SNPs of three genes (*UGT1A1**80; c.-364C > T (rs887829), *93; c.-3156G > A (rs10929302), and c.-2950A > G (rs111741722), *SLC22A8* c.723 T > A (rs2276299), and *TYMS* c.381 A > G (rs3786362) were found to be associated with the risperidone-induced prolactin response (Table 2, Fig. 2). The frequency of genotypes and alleles of the polymorphisms associated with the hyperprolactinemia and the non-hyperprolactinemia group are presented in Table 3. Among the *UGT1A1* variants, the frequency of the heterozygous allele of the polymorphic variant rs887829, rs10929302 and rs111741722 of *UGT1A1* was significantly higher in the hyperprolactinemia group as compared to the non-hyperprolactinemia group (61.90% vs. 38.10%; $P = 0.014$). While this was not the case for rs2276299 and rs3786362. Pairwise measure of linkage disequilibrium calculated by Haploview showed complete linkage disequilibrium (D′ value of 1) between the three *UGT1A1* SNPs, rs887829, rs10929302, and rs111741722 as presented in Fig. 3.

Genotyping accuracy

All of the four selected SNPs had genotype concordance >98% between two platforms. Two *CYP2D6* SNPs (rs3892097 and rs28371725) were 100% concordant and the remaining two *ABCB1* SNPs had a concordance of 98.3%. The overall concordance was 99.2% across both platforms.

Discussion

In the present study, we identified a suggestive DMET variant of *UGT1A1* associated with the prolactin response. Patients carrying the heterozygous mutant allele of this variant were predisposed to hyperprolactinemia upon treatment with risperidone. None of these SNPs reached significance level after the Bonferroni correction *P* value of 2.5×10^{-5}. The results of this study did not find any significant influence of age, sex, risperidone dose, and duration of risperidone treatment on the prolactin level in both the normal prolactin and the hyperprolactinemia group.

The uridine diphosphate glucuronosyltransferase (UGT) enzymes are a superfamily of conjugating enzymes which conjugates phase I metabolites, other intermediates, or the parent compound for renal or biliary excretion [30]. UGT is located in the endoplasmic reticulum of hepatic and extrahepatic tissue (particularly skin, lung, small intestine, and kidney) [31]. These enzymes transfer the glucuronyl group from uridine-5k-diphosphoglucuronate to many compounds having nucleophilic functional groups of oxygen, nitrogen, sulfur, or carbon. The resulting glucuronide is more water-soluble, less toxic, and more easily excreted than the parent compound. UGTs have evolved to catalyze the glucuronidation of both endogenous compounds (bilirubin, thyroid hormones, sexual hormones, and serotonin) and xenobiotics [31].

Table 2 List of overlapping gene between hyperprolactinemia and serum prolactin levels

Common name	rs ID	Amino acid change	Chromosome	Minor allele frequency
UGT1A1*80_c.-364C > T	rs887829	3′UTR	2	0.125
UGT1A1*93_c.-3156G > A	rs10929302	Promoter	2	0.125
UGT1A1_c.-2950A > G	rs111741722	3′UTR	2	0.125
SLC22A8_c.723 T > A	rs2276299	T241T	11	0.292
TYMS_c.381 A > G	rs3786362	E127E	18	0.179

SNPs single-nucleotide polymorphisms, *UTR* untranslated region

Table 3 Genotype and allele frequencies of the polymorphisms associated with non-hyperprolactinemia and hyperprolactinemia

Gene	rs ID	Genotypes	Non-hyperprolactinemia ($n = 51$); *n* (%)	Hyperprolactinemia ($N = 33$), *n* (%)	*P*-value
UGT1A1*80; c.-364C > T	rs887829	CC ($n = 63$)	43 (68.25)	20 (31.75)	0.014
		CT ($n = 21$)	8 (38.10)	13 (61.90)	
		TT	0	0	
UGT1A1*93; c.-3156G > A	rs10929302	GG ($n = 63$)	43 (68.25)	20 (31.75)	0.014
		GA ($n = 21$)	8 (38.10)	13 (61.90)	
		AA	0	0	
UGT1A1; c.-2950A > G	rs111741722	AA ($n = 63$)	43 (68.25)	20 (31.75)	0.014
		AG ($n = 21$)	8 (38.10)	13 (61.90)	
		GG	0	0	
SLC22A8; c.723T > A	rs2276299	TT ($n = 41$)	29 (70.73)	12 (29.27)	0.117
		TA ($n = 37$)	20 (54.05)	17 (45.95)	
		AA ($n = 6$)	2 (33.33)	4 (66.67)	
TYMS; c.381A > G	rs3786362	AA ($n = 55$)	29 (52.73)	26 (47.27)	0.105
		AG ($n = 28$)	21 (75.00)	7 (25.00)	
		GG ($n = 1$)	1 (100.00)	0 (0.00)	

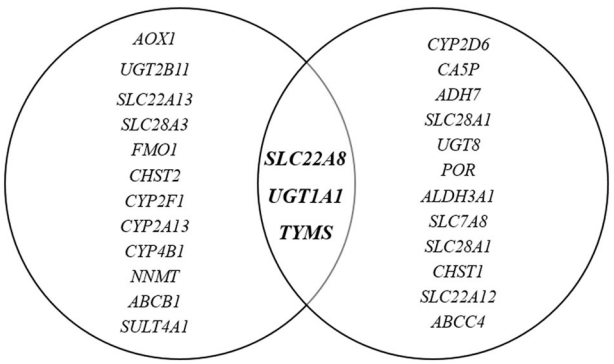

Fig. 2 Significantly genetic polymorphisms with overlapping between hyperprolactinemia and serum prolactin levels

Risperidone is metabolized primarily by CYP2D6 in the liver, giving way through hydroxylation to the active metabolite 9-hydroxyrisperidone [32]. While paliperidone (9-hydroxyrisperidone) is not metabolized extensively in the liver, and renal excretion is the major route of elimination. This active metabolite is largely devoid of phase I oxidation metabolism, undergoing primarily phase II conjugation reactions, which accounts for ~60% of the dose excreted unchanged in the urine [32, 33]. While a small amount is excreted via the UGT enzyme [34]. UGT is presumably a minor pathway of 9-hydroxyrisperidone excretion. Our previous study[8] revealed that a high level of 9-hydroxyrisperidone in ASD patients during risperidone treatment was significantly correlated with high serum prolactin levels. *UGT1A1* variants *UGT1A1**80, *UGT1A1**93, and *UGT1A1* c.-2950, predicted to cause low enzyme activity, seem to be associated with a higher accumulation of plasma 9-hydroxyrisperidone concentrations and an increased risk of developing hyperprolactinemia. However, the relationship of UGT1A1 with prolactin has not been clearly stated in the studies conducted till date. Although genetic association with risperidone-induced hyperprolactinemia have been reported in pharmacodynamic variants within genes including *DRD2* and *HTRC* [10, 18, 35, 36].

The 22 SNPs, reported in Supplementary Table 1 and the 20 SNPs, reported in Supplementary Table 2, both with $P < 0.05$ might offer further possible relevance and deeper understanding of risperidone-induced hyperprolactinemia and

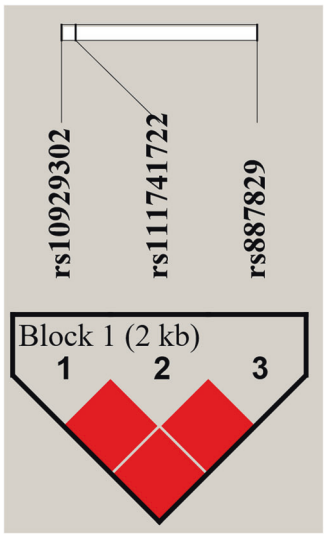

Fig. 3 Haploview linkage disequilibrium map of SNPs across *UGT1A1* genes. Pairwise linkage disequilibrium (D′) values are given in blocks for each SNP combination. Dark red shading denotes D′-values >0.9, and empty dark red blocks indicate D′ values of 1.0

serum prolactin level, respectively, if they are validated in another study cohort.

Regarding the effect of non-genetic variables on hyperprolactinemia, higher doses of risperidone were found to correlate with hyperprolactinemia in Thai children and adolescents with ASD [7]. In addition, a significant association of plasma concentrations of 9-hydroxyrisperidone with hyperprolactinemia was reported by the same group of authors in Thai ASD patients [8]. In the present study, none of the clinical variables showed a significant relationship with hyperprolactinemia. These findings support that the genetic polymorphisms in DMET are important in predicting the risk of risperidone-induced hyperprolactinemia.

The limitations of our study were the lack of validation of the variants and the small sample size. Also, the SNPs with a suggestive association in this study are not shown to play a major role in the metabolism of risperidone. Evidences of pathway linkup must be established in future studies. The three SNPs associated with hyperprolactinemia in our study are all synonymous codons. It is uncertain how these SNPs will bring change in the response to the drugs. The Affymetrix DMET Plus GeneChip microarray platform appears to be a valid approach in finding new genetic variants involved in risperidone-induced hyperprolactinemia. It should be noted that several genome-wide association studies have identified the link between polymorphisms in phase I and phase II drug-metabolizing enzymes and altered drug response, but it is difficult to establish the relationship between the polymorphisms identified and their functional role and molecular mechanism of action in the drug response [37]. Also, the utility of microarray-based SNP genotyping systems in association studies is complicated by the issue of SNP panel selection for association with disease or treatment outcome. This issue has prompted researchers to select candidate gene approach studies which are based on the association between genetic variations within prespecified genes of interest [38].

Despite our study limitations, the findings from our study can be utilized to design a pharmacogenomic study in future to better understand the role of genetics in the metabolism of risperidone. In this study, we analyzed population stratification and did not find significant different origins among the participants, thus reducing the risk of false-positive findings. Further, we excluded close relatives based on the genotyping profile and avoided the bias of genotype within families being over-represented.

Conclusion

We conducted a genetic association study of DMET markers with risperidone-induced prolactin response assessed by both hyperprolactinemia and prolactin level in Thai ASD patients using a microarray platform and found the suggestive association of *UGT1A1* variants with prolactin response that may lay the basis for future pharmacogenomic studies in different set of populations. We suggest further validation of these findings using standard sequencing methods in a different cohort. In addition, inclusion of a drug-naïve population in the pharmacogenomic study will make clinical translation of the results more relevant.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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