CYP1A2 genetic polymorphisms are associated with treatment response to the antidepressant paroxetine

Aim: Paroxetine is a drug of choice in the treatment of major depressive disorder (MDD). Its metabolism has recently been reported to be mediated through the CYP enzymes 1A2 and 2D6. In our current study, we tested whether genetic polymorphisms in *CYP1A2* are associated with the treatment efficacy and side effects of paroxetine. **Materials & methods:** A total of 241 MDD patients who had taken paroxetine continually for 8 weeks were recruited, and their steady state paroxetine concentrations were measured at weeks 2, 4 and 8. The genotypes of these patients were then assessed for the presence of nine SNPs, which were selected from either the HapMap Chinese ethnic group, the literature report or through their functional role in the *CYP1A2* gene. **Results:** The allele types for SNPs rs4646425 (permutation p = 0.03), rs2472304 (permutation p = 0.01) and rs2470890 (permutation p = 0.004) demonstrated significant associations with paroxetine treatment remission at week 8. Response rates in the Hamilton Rating Scale for Depression (HAM-D) and for The Hamilton Rating Scale for Anxiety (HAM-A) were significantly associated with the SNPs rs4646425 (p = 0.0126 and 0.0088 for HAM-D and HAM-A, respectively) and rs4646427 (p = 0.0067 and 0.0196 for HAM-D and HAM-A, respectively). The inducible SNP rs762551 had a significant association with paroxetine dose at week 4 (permutation p = 0.012). We did not find an association between these SNPs and the side effects or serum concentrations of paroxetine. **Conclusion:** Genetic variants in the *CYP1A2* region may be indicators of treatment response in MDD patients to paroxetine.

KEYWORDS: ***CYP1A2*** ■ **depression** ■ **HAM-A** ■ **HAM-D** ■ **paroxetine** ■ **SNP**

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Major depressive disorder (MDD; also known as major depression) has multiple characteristics [1] including low mood, low self esteem and a loss of joy in daily living [2]. The prevalence and incidence of MDD is increasing in Taiwan [3] and effective antidepressants with low side effects are essential in the treatment of affected patients [4]. Although the current pharmacogenetic information remains insufficient for use as a guide in the proper antidepressant treatments of MDD [5], SNPs have shown promise as markers of effective treatment response and avoidance of side effects and future relapse [6].

Paroxetine is a selective serotonin reuptake inhibitor that has gained clinical approval for the treatment of adults with MDD, obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, post-traumatic stress disorder and social phobia [7]. This drug is metabolized by oxidation, methylation and conjugation processes [8]. Differences in the levels of any of these metabolic pathways could therefore lead to wide interindividual variation in the elimination of paroxetine [9]. The most well described metabolic processing of paroxetine is through the liver CYP enzyme 2D6 [10], which demethylates paroxetine to paroxetine catechol. This is then further metabolized by catechol-*O*-methyl transferase into the metabolites (-)trans 4-(4-fluorophenyl)-3-(hydroxymethyl) piperidine-hydrochloride (BRL-36583A) and (-)trans 4-(4-fluorophenyl)-3-(4-hydroxy-3-methoxyphenoxymethyl) piperidine-hydrochloride (BRL-36610A) [11,12]. As paroxetine has been reported to interact with other drugs [13,14], a complete knowledge of the enzymes involved in its metabolic processing will be of great importance in preventing its inappropriate use with other agents [15]. In addition to the metabolic enzymatic considerations, genetic differences also cause great variation in metabolic capacity [16]. It is therefore important to examine both factors in long-term treatments with antidepressants such as paroxetine.

CYP1A2 was recently identified as a metabolic enzyme that targets paroxetine and could influence treatment outcome [8]. The genetic locus of *CYP1A2* is 15q24.1, and this gene contains seven exons. Genetic polymorphisms in *CYP1A2* have been reported to influence the serum concentrations of the antipsychotic drug olanzapine and its treatment outcomes [17]. To test whether genetic variations in *CYP1A2* are related to the

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response to paroxetine, we investigated the association of specific SNPs at this gene locus with the serum concentration of paroxetine, the severity of depression, the treatment response and the side effects in MDD patients receiving this drug.

Materials & methods

Subjects

This study was performed in accordance with the Declaration of Helsinki regarding human experimentation by the World Medical Association, and was approved by the institutional review board of the National Health Research Institutes (London, UK) and participating hospitals. Written informed consent was obtained from all patients. This study was also registered as a clinical trial with the US NIH [101]. We recruited 241 Han Chinese patients with MDD from the outpatient psychiatric clinics of five hospitals in or around Taipei, Taiwan (Chang Gung Memorial Hospital, Mackay Memorial Hospital, Far Eastern Memorial Hospital, TMU-Wan Fang Hospital, Songde branch of the Taipei City Hospital). Clinical interviews were performed by trained research nurses and MDD was diagnosed via the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria using the Structured Clinical Interview for DSM-IV-TR Axis-I Disorders (SCID) [18]. For enrollment, patients, needed at baseline, to have a moderate depressive episode of at least 14 points on the 21-item Hamilton Rating Scale for Depression (HAM-D) assessment tool [19,20]. Participants could not have been previously refractory or intolerant to paroxetine treatment, and must have completed a 7-day washout period from any earlier antidepressant treatment. Individuals with a primary or comorbid diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, alcohol or substance dependence, dementia or other significant medical conditions were excluded. Patients received paroxetine at an average dose of 20 mg/day for the first 4 weeks, followed by dosages of 10–40 mg/day for another 4 weeks as determined by the clinical response. Additional psychotropic drugs were prohibited during the study except for hypnotics (zolpidem 10 mg taken per night as needed, but not exceeding four nights per week) and anxiolytics (lorazepam 1–2 mg per day) for severe anxiety. Blood samples (collected 12–20 h after the most recent dose) were taken at weeks 2, 4 and 8, analyzed for paroxetine and its metabolites and genotyped in a central facility. Sampling times, drug dosages and patient compliance were documented in accordance with the protocol.

Depression symptoms rating scales

Medication efficacy was assessed using the 21-item HAM-D [21], Hamilton Rating Scale for Anxiety (HAM-A) [19], the Clinical Global Impression for severity of illness (CGI-S) and the Clinical Global Improvement (CGI) scales [22]. The HAM-D items were further subgrouped into core (items 1, 2, 7, 8, 10 and 13), sleep (items 4, 5 and 6), activity (items 7 and 8), psychic anxiety (items 9 and 10), somatic anxiety (items 11, 12 and 13) and delusion (items 2, 15 and 20) [23]. The combination scores of these items further enabled evaluation of subgroup improvement after paroxetine treatment. Patients were evaluated at baseline and later at weeks 1, 2, 4, 6 and 8 of continuous treatment. All research nurses who carried out the SCID, HAM-D and HAM-A ratings received the same training module [24,25]. All independent rating scores were compared with the Cohen's κ value [26,27]. Training proceeded until the inter-rater reliability (κ value) of each assessment between the nurses reached 0.8. The κ coefficients were examined every 2 months to ensure that all clinical assessments used in this study were reliable. Side effects were assessed using the Treatment Emergent Signs and Symptoms (TESS) scale and the Arizona Sexual Experiences Scale [28], which is a five item rating scale quantifying sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm and satisfaction from orgasm.

CYP1A2 SNP selection & genotyping

Patient DNA was extracted from 8 ml of whole blood lymphocyte pellets using a Puregene® kit (Gentra Systems, MN, USA). We selected the *CYP1A2* SNPs from the literature [29,30], from HapMap tagSNPs [102] with a minor allele frequency above 0.1 and a r^2 cutoff of 0.8, and from functional SNPs predicted by FastSNP [31]. Genotyping was performed by 12-plex PCR (384-well plate), using the GenomeLab™ SNPstream® genotyping platform (Beckman Coulter, CA, USA) and its accompanying SNPstream software suite (Beckman Coulter). The PCR reactions were carried out in a total volume of 5 µl, with 5 ng of template DNA using the cycling conditions recommended by the manufacturer. The amplified DNA fragments were cleaned up using exonuclease I and shrimp alkaline phosphatase (USB Corporation, OH, USA). Tagged extensions of these products were then performed using 12 site-specific SNP primers. The primers were extended with single TAMRA- or bodipy-fluorescein-labeled nucleotides and then

spatially resolved by hybridization to complementary oligonucleotides arrayed on the 384-well SNPware® Tag array (Beckman Coulter). The Tag array plates were imaged with a two-laser, two-color charged couple device-based imager (GenomeLab SNPstream array imager, Beckman Coulter). The nine individual SNPs tested in the experiments were identified by their position and fluorescent color in each well based on the tagged oligonucleotide positions.

Measurement of serum paroxetine & its metabolites

We measured the serum concentrations of paroxetine and its metabolites BRL-36583A and BRL-36610A using HPLC [11]. The analytical column was a reverse-phase C8 column (Sphere-Image®, 5 µm, 100 × 3 mm) with a C18 guard column (Phenomenex, CA, USA, 4 × 3 mm). We set the column oven at 35°C. The mobile phase was composed of 35% acetonitrile, 65% potassium phosphate buffer (10 mM), and triethylamine (1 ml/l of mobile phase), with a final pH of 3.2.

Patient sera samples were obtained from whole blood centrifuged at 3000 rpm (1710 × g) for 15 min. Serum levels of paroxetine, BRL-36583A, BRL-36610A and 62.5 ng supplement imipramine (internal standard) were extracted with a C18-E 100 mg/ml capacity STRATA column. After conditioning the column with a Waters (MA, USA) vacuum manifold with 1 ml each of methanol, water and 45 mM potassium phosphate buffer (pH 4.5), 800 µl of a serum sample and imipramine were added. The column was then washed with 1 ml each of water and a 50% methanol-water solution and vacuum dried for 1 min. The retained paroxetine, BRL-36583A, BRL-36610A and internal standard were eluted using 1 ml of ammonium acetate/methanol (1 g/100 ml) and the collected eluent was evaporated in a water bath at 55°C under a stream of air for 17 min. The remaining residue was dissolved in 100 µl of mobile phase and 50 µl of each sample was subjected to HPLC.

Paroxetine was a gift from Research and Education Institute for Texas Health Resources (TX, USA). BRL-36583A and BRL-36610A were gifts from GlaxoSmithKline (Brentford, UK). Using 1.95 ng each of paroxetine, BRL-36583A and BRL-36610A as standards for reproducibility analyses, the intra-day and inter-day coefficients of variation were calculated as 0.64 and 3.40% for paroxetine, 0.80 and 3.80% for BRL-36583A and 0.74 and 2.64% for BRL-36610A, respectively. The recovery rates for paroxetine, BRL-36583A and BRL-36610A were 129.7 ± 9.3, 125.4 ± 24.2 and 113.9 ± 7.7%, respectively. The lower detection limit was 0.2 ng/ml for all three compounds.

Statistics

All statistical analyses were performed using SAS software, Version 9.1 (SAS Institute, Inc., NC, USA) unless otherwise specified. The SNP Hardy–Weinberg equilibrium test was performed using HAPLOVIEW version 4.1 [32]. One-way analysis of variance (ANOVA) was used to assess the associations between genotypes and the side effect rating scales from each week. Frequencies were compared using the χ^2-square test. Survival analysis for the association between rs4646425, rs4646427, and the HAM-D and HAM-A response rates was performed using GraphPad Prism 5 (CA, USA). Permutation tests using the MULTTEST procedure of the SAS software were used to adjust the p-values for multiple testing. Generalized Estimating Equation (GEE) Models adjusted for treatment dose, plasma paroxetine concentrations, age and gender were used for repeated measures when analyzing improvements of the HAM-D and TESS scores. Power calculations for comparison of the repeated measurement HAM-D scores during the 8-week experimental period were computed using the PROC MIXED procedure, and for the ANOVA model were computed using the PROC POWER procedure of the SAS software. The dropout data were either corrected with the last observation carried forward or not corrected. The rate of smoking was adjusted as a covariate using a general linear model procedure for significant results. The significance level was set at 0.05 after hypotheses testing.

The outcome criteria of MDD remitters were defined by a HAM-D score of 7 or less [33]. For HAM-A the remitters were defined by a score of 17 or less and for CGI-S of 2 or less. The responder rating was based upon a score greater than 50% reduction from the baseline. Sexual dysfunction was defined by a total Arizona Sexual Experiences Scale score for the first five items of 19 or more. The TESS scores and bodyweights were also recorded. The higher TESS scores indicated more severe side effects of the treatment.

Results

Demographics

A total of 241 patients with MDD were recruited in this study (with an average age of 41 years and an average age of onset of 36 years). The patient

cohort was 85% female, with 40% of the cases reporting a recurrent episode and 60% reporting a first episode of depression. Patient bodyweights (GEE model, p = 0.67) and sexual functions (GEE model, p = 0.41) were unchanged during the 8 week paroxetine treatment period.

The total HAM-D scores and most of the clustered depressive symptoms rated by HAM-D were significantly improved by week 8 (GEE model, p < 0.0001 for the sum of the HAM-D, core, activity, psychic and somatic scores and p = 0.0013 for sleep). However, the patients showed no obvious improvement in the HAM-D delusion symptoms subgroup (GEE model, p = 0.0877). The HAM-A and CGI-S scales showed statistically significant improvements at week 8 (GEE model, p < 0.0001 for both).

The average HAM-D scores were 22.43 at baseline, 14.18 at week 2, 12.90 at week 4 and 10.31 at week 8. The actual remitter rates were 25% at week 2, 39% at week 4 and 40% at week 8. The patient dropout rate was about 29% at week 8. The drug side effects evaluated by TESS increased during weeks 1 and 2, and then significantly decreased (GEE model, p < 0.0001) after the 8-week treatment. The average compliance rate based on the pill count from each week was approximately 80%.

Single locus & haplotype structure of *CYP1A2*

All nine SNPs of *CYP1A2* were found to be in Hardy–Weinberg equilibrium (Table 1). In terms of association analysis, no significant associations were found between the SNPs and the plasma concentrations of paroxetine and its metabolites. A single haplotype block composed of the trinucleotide rs2069526–rs762551–rs4646425 (intron 1–intron 1–intron 2) (Figure 1) was created using the default algorithm [34] of HAPLOVIEW [32].

CYP1A2 association with the paroxetine treatment responses

Three SNPs (rs4646425, rs2472304 and rs2470890) of *CYP1A2* demonstrated significant associations with MDD remission after paroxetine treatment at week 8 (Table 2). The minor T allele carrier in rs4646425 demonstrated more nonremitters than remitters. However, the minor allele carriers in rs2472304 (A allele) and rs2470890 (T allele) demonstrated more remitters than nonremitters after paroxetine treatment. Comparing the major allele of the homozygous genotype with other genotypes revealed that the rs4646425 (CC genotype) and rs4646427 (TT genotype) SNPs were associated with a slower response than other genotypes of both SNPs in both the depression rating by HAM-D and anxiety rating by HAM-A (Figure 2).

The haplotype G–A–T of rs2069526–rs762551–rs4646425 showed a significantly lower HAM-D and HAM-A score than other haplotypes at week 8 (permutation p = 0.0069, power = 0.77 for HAM-D and permutation p = 0.0002, power = 0.96 for HAM-A, respectively).

CYP1A2 association with paroxetine dose & side effects

The rs762551 SNP (*CYP1A2*1F*) genotype and allele type (intron 1 of *CYP1A2*) demonstrated a significant association with the treatment dose of paroxetine at week 4 (permutation p = 0.012

Table 1. The validated SNPs of the *CYP1A2* gene analyzed in this study.

SNP_ID†	Chromosome‡	Function§	Allele¶	Role	MAF	HW test p-value	n
rs2069526	72828394	*CYP1A2*1E* (-739T>G)	T/G	Intron 1	0.097	0.58	208
rs762551	72828970	*CYP1A2*1F* (-163C>A), tagSNP	A/C	Intron 1	0.35	1	204
rs35407132	72829354	Sense/synonymous, splicing regulation	C/T	Exon 2	0.007	1	210
rs4646425	72830334	TagSNP	C/T	Intron 2	0.096	0.57	210
rs35796837	72830646	Missense (conservative), splicing regulation	G/A	Exon 3	0.002	1	210
rs2472304	72831291	TagSNP	G/A	Intron 4	0.13	1	206
rs3743484	72831453	TagSNP	G/C	Intron 4	0.13	1	198
rs4646427	72832745	Intronic enhancer	T/C	Intron 6	0.087	0.37	208
rs2470890	72834479	*CYP1A2*15* (5347T>C)	C/T	Exon 7	0.14	0.94	208

†*As according to the dbSNP database.*
‡*The SNP locations are based upon NCBI Human Genome Build 36.*
§*Estimated by FastSNP.*
¶*The allele under the slash is the minor allele.*
HW: Hardy–Weinberg; MAF: Minor allele frequency.

and 0.0028, power = 0.77 and 0.84, respectively). The A allele carrier required a higher dose of paroxetine than the C allele carrier at week 4. The allele type significant level was increased after adjustment for smoking (from a permutation p-value of 0.0028 to 0.0003). The same SNP genotype also showed a significant association with fatigue side effects (ANOVA p = 0.0055, power = 0.78, permutation p = 0.27) at week 1. These results are all summarized in Figure 3.

Discussion

To our knowledge, our present study is the first report on the possible association of genetic polymorphisms in the metabolic enzyme CYP1A2 with the treatment efficacy, side effects and metabolic plasma concentrations of the antidepressant paroxetine in patients with MDD. The *CYP1A2* enzyme has been reported to have a lower capacity (V_{max}) to metabolize paroxetine than the well-characterized paroxetine metabolic enzyme CYP2D6 [35]. Similar results have been reported in a recent finding, which suggests that CYP1A2 is important for paroxetine metabolism [8]. We therefore tested the hypothesis that the *CYP1A2* genetic polymorphisms have an influence on the serum levels of paroxetine and affect treatment response to this drug.

In pharmacogenetic association analyses, none of the *CYP1A2* SNPs showed an association with the steady state serum concentrations of paroxetine and its metabolites in MDD patients. A possible reason for this is that the minor allele frequency (MAF) in the exon regions of rs35407132 (MAF = 0.007 at exon 2) and rs35796837 (MAF = 0.002 at exon 3) is too low to detect its association with paroxetine serum concentrations from a sample size of 241 patients. As a consequence, we cannot yet exclude the possible effects of a rare SNP on the paroxetine plasma concentration. Another possibility is that the paroxetine metabolic capacity of CYP1A2 is lower than that of CYP2D6. The SNPs in *CYP2D6* may also have a stronger influence on the paroxetine serum concentration than *CYP1A2*. Similar analyses of the genetic variants in *CYP2D6* should thus be considered in future studies.

Our analyses of the association between *CYP1A2* SNPs and the paroxetine treatment response in MDD patients yielded the most significant results in this study. In both the allelic remission and genotype response analyses depicted in Figure 2, the rs4646425 (intron 2), rs2472304 (intron 4), rs4646427 (intron 6) and rs2470890 (exon 7) *CYP1A2* SNPs were demonstrated to be potential predictors of the treatment

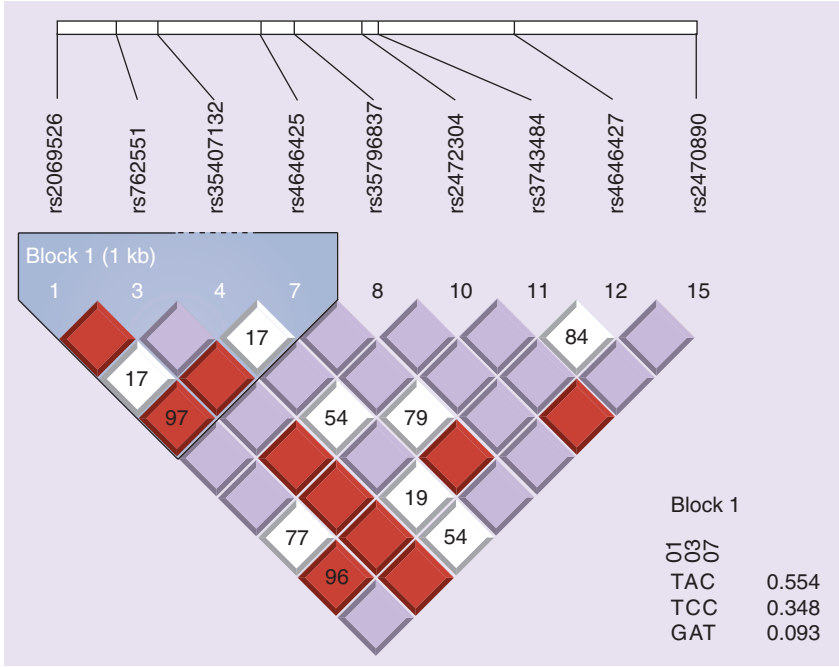

Figure 1. Haploview linkage disequilibrium (D') for a haplotype block within the nine *CYP1A2* SNP markers. Each marker is numbered by primer ID according to the physical length of each SNP. The number in each square is D' × 100 between two SNPs. D' = 0.97 in Block 1 (rs2069526–rs762551–rs4646425). The log of the odds (LOD) was 43.05 in Block 1. The rs35407132 SNP was not included in the block (dashed line). The red shades indicate a LOD ≥2 and white and purple indicate LOD <2.

Table 2. Associations of the indicated *CYP1A2* SNPs with paroxetine treatment remission at week 8.

SNP ID	Remitters		Nonremitters		Remission association				
					Allele type				Genotype p-value
	n	*MAF*	*n*	*MAF*	*p-value*	*p-value*†	*Odds ratio*	*95% CI*	
rs4646425	69	0.07	102	0.14	0.03	0.044	2.30	1.12–4.73	0.002
rs2472304	69	0.17	102	0.07	0.01	0.017	0.39	0.19–0.82	0.024
rs2470890	68	0.17	102	0.07	0.004	0.0071	0.34	0.16–0.74	0.015

p-value: calculated from permutation test based on 10,000 permutations.
Remitter: Hamilton rating scale for Depression ≤7.
†p-value: calculated from last observation carried forward for dropout data correction.
MAF: Minor allele frequency.

response to paroxetine in MDD patients. The rs4646425 SNP however is the only one that could possibly be an indicator in terms of both the allele type and the genotype. This result is inconsistent with a previous report claiming no association between *CYP1A2* and the antidepressant remission rate in MDD [36]. However, this earlier study tested many antidepressants but only used a cohort size of 41 patients for the treatment with paroxetine. In our previous escitalopram study, a significant association between remission at week 8 and *CYP1A2* genetic polymorphisms was also found for the rs2472304 and rs2472890 SNPs. We thus consider that the results of our present study are reproducible. The rs2472304 and rs2472890 *CYP1A2* SNPs may therefore be common predictors of both the escitalopram and paroxetine treatment responses.

In our *CYP1A2* SNP and paroxetine treatment dose association analysis, rs762551 showed a significant association with the paroxetine dose at week 4 only. If the dropouts were corrected using last observation carried forward, the association between rs762551 and the paroxetine dose at week 4 was still significant ($p = 0.02$). This SNP was previously reported to be a highly inducible locus for the genetic expression of *CYP1A2* [37]. Our current findings therefore suggest that rs762551 may be an indicator for paroxetine treatment dose and consequently be of great importance in continuous dose adjustment. The same SNP demonstrated a significant association with fatigue symptom side effects in our current experiments and has previously been reported to be associated with the side effects of tardive dyskinesia

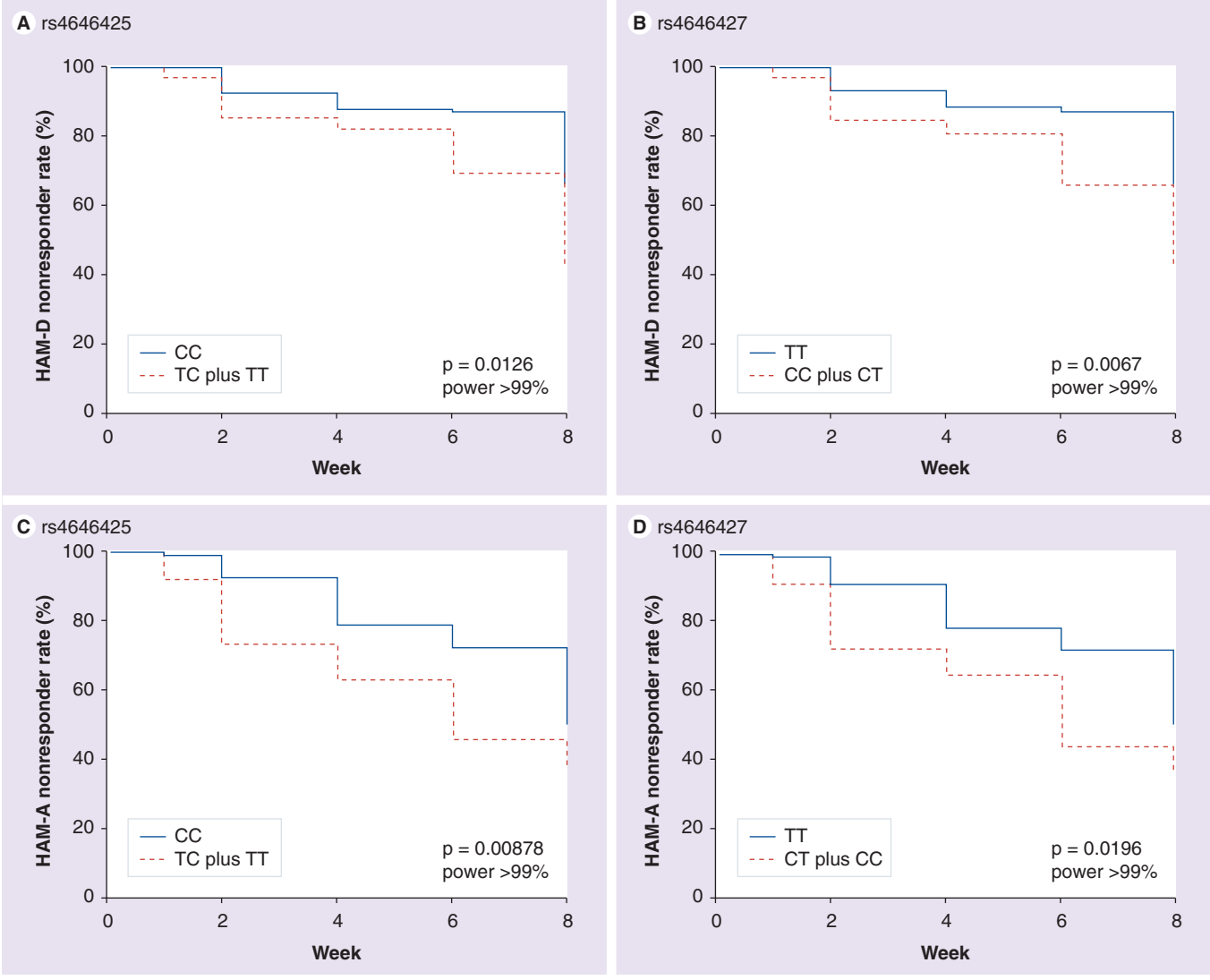

Figure 2. Cox regression analyses of the percentage of nonresponders carrying the *CYP21A2* SNPs rs4646425 and rs4646427, based on a 50% HAM-D or HAM-A score reduction from baseline.
HAM-A: The Hamilton Rating Scale for Anxiety; HAM-D: The Hamilton Rating Scale for Depression.

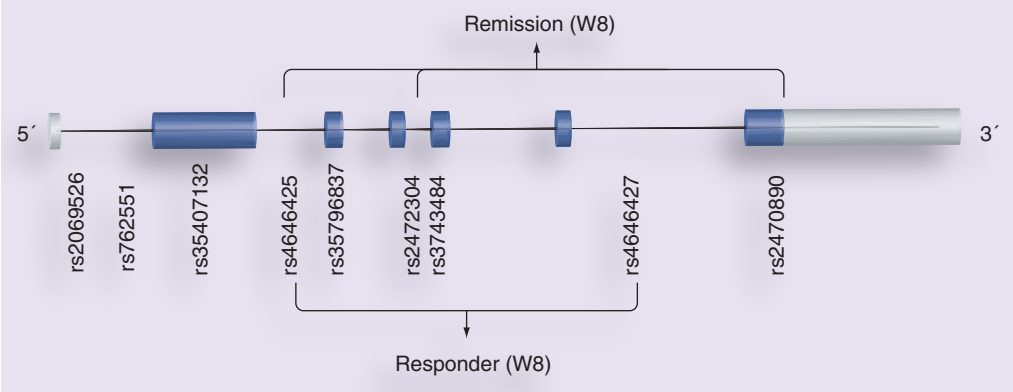

Figure 3. Significant associations between *CYP1A2* SNPs and major depressive disorder patient phenotypes after paroxetine treatment.

in schizophrenia [38] and with the olanzepine concentrations [17]. However, this significance may not persist after multiple corrections. We suspect therefore, that in terms of its association with fatigue side effects, the rs762551 SNP may be a false positive.

CYP1A2 metabolizes paroxetine but only showed a significant association with its treatment response and not its concentration. This may be owing to some confounding genes or factors that were not detected in this study. This result is similar to our previous study of escitalopram [39] in which we found that the escitalopram metabolic enzyme CYP2D6 genetic dose model was associated with the treatment response, and that CYP2C19 was associated with serum escitalopram concentrations. More studies are needed to decipher the probable reasons for these observations.

No comorbidity or death occurred among our current patient group. The noteworthy limitations of our present study include the higher ratio of female participants (5.69-fold), although women have only twice the incidence rate of MDD [40], and the lack of a placebo arm. The unbalanced female:male ratio may make the SNPs to treatment response prediction more precise for women. A placebo arm could provide a cutoff for better estimation of the percentage of remissions and validate the association between the SNPs of *CYP1A2* and remission response. However, it is not indispensable, as in the future these SNP markers would only be applied to MDD patients to assist with the optimal paroxetine treatment approach. The major advantage of our present study was the 8-week treatment and monitoring period during which the sample size justified from the HAM-D reduction had a power above 99%. Our results indicating that the *CYP1A2* genotype is associated with the response to paroxetine in a Taiwanese population are therefore robust.

Conclusion

In summary, we demonstrate herein that CYP1A2 is an additional metabolic enzyme for paroxetine. We demonstrate that the *CYP1A2* SNPs rs4646425 (intron 2), rs2472304 (intron 4) and rs2470890 (exon 7) are associated with the treatment remission response to this antidepressant. The SNPs rs4646425 (intron 2 of the CC genotype) and rs4646427 (intron 6 of the TT genotype) were further found to be associated with a slower response to paroxetine treatment as rated by HAM-D and HAM-A. Moreover, the rs762551 *CYP1A2* SNP at intron 1 showed a significant association with the paroxetine treatment dose at week 4. We conclude from our data that the *CYP1A2* gene may be an indicator for the response of MDD patients to paroxetine.

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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

- The symptoms of depression (assessed by the Hamilton Rating Scale for Depression [HAM-D] and the clinical global Impression for severity of illness) and anxiety (assessed by Hamilton Rating Scale for Anxiety) were improved after 8 weeks of paroxetine treatment. However, the bodyweight, sexual function and the HAM-D delusion subgroup were unaffected by this drug.
- A trinucleotide haplotype block of rs2069526–rs762551–rs4646425 located between intron 1 and 2 of *CYP1A2* was found among the nine SNPs examined.
- The genotypes and allele types containing the rs4646425 (intron 2), rs2472304 (intron 4) and rs2470890 (exon 7) *CYP1A2* SNPs could be indicators of the remission response to paroxetine. The C allele carrier in rs4646425, the G allele in rs2472304 and the C allele in rs2470890 had more remitters than nonremitters at week 8 of the paroxetine treatment regimen.
- In the dominant model of genotype analyses, the CC genotype of rs4646425 (intron 2) and the TT genotype of rs4646427 (intron 6) responded more slowly to paroxetine than the other genotypes as determined by both the HAM-D and the Hamilton Rating Scale for Anxiety at week 8 of treatment.
- The A allele carrier of the rs762551 SNP (*CYP1A2*1F* at intron 1) may need a higher dose of paroxetine than the C allele carrier at week 4.

Bibliography

Papers of special note have been highlighted as:
- of interest

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