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Influence of *CYP2D6* polymorphisms on symptomatology and side-effects of patients with schizophrenia in Malaysia

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Abstract

Background: Our objective was to investigate the association of *CYP2D6* polymorphisms with symptoms and side-effects of patients with schizophrenia.

Methods: The subjects were 156 patients with schizophrenia undergoing antipsychotic treatment at a psychiatric clinic. Patients with co-morbid diagnoses of substance abuse or mental retardation were excluded from the study. Psychopathology was evaluated using the Positive and Negative Symptoms Scale (PANSS). Extrapyramidal side-effects and akathisia were assessed with the Simpson Angus Scale (SAS) and the Barnes Akathisia Rating Scale (BARS), respectively. DNA was extracted from blood and subjected to PCR-genotyping.

Results: We found that *CYP2D6* polymorphisms were significantly associated with a subtotal negative PANSS score. In addition, *CYP2D6* is not related to side-effects of antipsychotic therapy, or SAS and BARS scores. The results suggest that *CYP2D6* polymorphisms may have implications in treatment response.

Conclusions: Therefore, *CYP2D6* may be a predictor for treatment outcomes of patients with schizophrenia. However, further investigation is required to confirm these findings in a larger sample.

Keywords: Cytochrome P450 CYP2D6, schizophrenia, treatment outcomes, neurosciences

Introduction

Schizophrenia is a highly heritable condition, as demonstrated in family, twin and adoption studies (1). Such studies have also shown that environmental factors combined with genetic predisposition contribute to the development of schizophrenia (1,2). Despite extensive research, no mutations or disease-predisposing DNA sequence variations have been identified. The mode of inheritance of schizophrenia is likely to be polygenic or multifactorial (1,2).

Pharmacological treatment of schizophrenia involves antipsychotic therapy. The variation in individual clinical responses to antipsychotic therapy remains a critical problem in the management of patients with schizophrenia despite considerable progress in delineating different domains of this illness. These range from positive and negative symptoms to cognitive dysfunction and psychosocial vulnerabilities. Although a minority of patients experience complete symptom remission, a large proportion of patients continue to experience significant psychiatric symptoms (3,4). Moreover, there is a subset of patients who develop drug-induced side-effects such as extrapyramidal side-effects (EPS) including acute dystonic reactions, neuroleptic-induced parkinsonism and akathisia, later-onset movement disorders such as tardive dyskinesia or dystonia and life threatening

Table 1: Demographic and clinical characteristics of 156 patients with schizophrenia

Variable	n	(%)
Positive family history [a]		
No	113	(72.4)
Yes	43	(27.6)
Family support		
Good	149	(95.5)
Poor	7	(4.5)
Education level		
Primary	8	(5.1)
Secondary	123	(78.8)
Tertiary	24	(15.4)
Others	1	(0.6)
	Mean	**(SD)**
Age (year)	34.1	(10.01)
	Median	**(IQR)**
Age at first onset (year)[b]	23.2	(10.15)
Duration of illness (year)	8.8	(8.98)
Number of admission	1.0	(3.00)

[a]A positive family history was defined as the presence of at least one first- or second-degree relative with schizophrenia. [b]The age at first onset was defined as the age at which the subject presented schizophrenic symptoms noticeable to family members, or the age when the illness started as noted in medical records. The definition was chosen because the definition was equal for all patients by evaluating the medical records.

side-effects such as agranulocytosis and neuroleptic malignant syndrome, which require significant medical intervention (5). Genetic factors may be considered as one of the causes of this phenomenon. Psychopharmacogenetic studies have focused on three major phenotypes that are the clinical efficacy of antipsychotic drugs, the efficacy of antidepressant medications and the development of side-effects associated with treatment (6).

Debrisoquine 4-hydroxylase (*CYP2D6*) is a polymorphic enzyme involved in the metabolism of many centrally acting drugs. A study by Seigle et al. (7) clearly demonstrated that *CYP2D6* mRNA and protein are expressed within different regions of normal human brains. Although the total amount of *CYP2D6* in the brain is rather low, they identified specific cell types in certain areas of the brain expressing significant *CYP2D6* levels, indicating a mechanism of local drug metabolism.

The gene encoding *CYP2D6* is highly polymorphic. The *CYP2D6* allele nomenclature is available at http://www.cypalleles.ki.se/cyp2d6. htm. The *CYP2D6* allele subgroups are associated with absent, decreased, normal or increased enzyme activity (8). Currently, more than 50 mutations and 90 alleles for *CYP2D6* have been discovered (9,10). Many different polymorphisms that impact *CYP2D6* activity have been reported in all parts of the world (11). These mutations include genetic alterations that lead to over expression (gene duplication), absence of an active protein product (null allele or non-functional alleles) or production of a mutant protein with diminished catalytic capacity (inactivating allele).

Patients who express dysfunctional or inactive enzyme molecules are considered PM. For example, patients with two null alleles are considered as a poor metabolisers (PM) (12,13,14,15). There are also alleles (inactivating alleles) that lead to the production of an enzyme with diminished or reduced catalytic capacity, but these changes do not lead to PM status. Patients with one non-functional allele (null allele) and those carrying two alleles that code for an enzyme with reduced activity are considered intermediate metabolisers (IMs). Patients with two functional alleles (wild-type allele, *CYP2D6*1*) and those carrying one allele coding for an enzyme with reduced activity are considered extensive metabolisers (EMs) (15,16). As a general rule, the number of functional *CYP2D6* genes present in an individual dictates the drug metabolism phenotype (13,16,17). In addition, the ultrarapid metaboliser (UM) phenotype results from a gene duplication that results in multiple functional copies of a single *CYP2D6* gene. When elimination of a drug is highly dependent on *CYP2D6*, lower clearance is seen in PMs compared to EMs. At the same dosage, PMs achieve higher steady state plasma drug levels than EMs due to their reduced metabolic capacity and are therefore more prone to develop side-effects (18,19). On the other hand, UMs are susceptible to treatment-refractoriness to antipsychotics. In the present study, our objective was to investigate the association of *CYP2D6* polymorphisms with symptomatology and side-effects of patients with schizophrenia.

Materials and Methods

Patient enrolment and assessment

This was a cross-sectional study. One hundred and fifty-six patients with schizophrenia according to the DSM-IV criteria attending the Psychiatric Clinic, Hospital Universiti Sains Malaysia undergoing antipsychotic treatment or treated with antipsychotics in the past were recruited for the study. Patients with co-morbid diagnoses such as substance abuse or mental retardation were excluded from the study. Written informed consent was obtained after explaining a complete

Table 2: Association of items of PANSS scale and *CYP2D6* polymorphisms

Items of PANSS Scale	*CYP2D6* Polymorphisms		
	Allele	Genotype	Phenotype
	P value[a]	*P* value[a]	*P* value[a]
Positive symptom			
1. Delusions	0.330	0.815	0.868
2. Conceptual disorganization	0.966	0.854	0.796
3. Hallucinatory behaviour	0.576	0.747	0.536
4. Excitement	0.004	0.017	0.005
5. Grandiosity	0.326	0.076	0.005
6. Suspiciousness	0.547	0.299	0.906
7. Hostility	0.071	0.238	0.090
Negative symptom			
1. Blunted effect	0.021	0.035	0.014
2. Emotional withdrawal	< 0.001	0.018	0.001
3. Poor rapport	< 0.001	0.003	< 0.001
4. Passive/apathetic social withdrawal	< 0.001	0.018	0.001
5. Difficulty in abstract thinking	0.987	0.919	0.771
6. Lack of spontaneity and flow of conversation	0.446	< 0.001	0.011
7. Stereotyped thinking	ND	ND	ND
General symptom	0.406	0.348	0.091
1. Somatic concern	0.062	0.276	0.211
2. Anxiety	0.210	0.489	0.498
3. Guilt feeling	0.164	0.362	0.392
4. Tension	ND	ND	ND
5. Mannerism and posturing	0.263	0.456	0.055
6. Depression	0.586	0.011	0.170
7. Motor retardation	< 0.001	< 0.001	< 0.001
8. Uncooperativeness	ND	ND	ND
9. Unusual thought content	ND	ND	ND
10. Disorientation	0.081	0.181	0.172
11. Poor attention	0.614	0.033	0.006
12. Lack of judgement and insight	0.586	0.023	0.003
13. Disturbance of volition	0.003	< 0.001	< 0.001
14. Poor impulse control	< 0.001	< 0.001	< 0.001
15. Preoccupation	0.004	0.034	0.006
16. Active social avoidance			

[a]Analysis of variance (ANOVA). ND indicates that no statistics are computed because the values are constant.

description of the study. The patients were then called for interviews to obtain detailed histories of present illness, past treatments, side-effects during the past two years, current medications, socio-demographic variables and family histories. Psychopathology was rated using the Positive and Negative Syndrome Scale (PANSS). EPS were assessed with the Simpson Angus Scale (SAS) and akathisia with the Barnes Akathisia Rating Scale (BARS). The accuracy of the information given by patients was counter-checked against their medical records. The protocols for the study were approved by the Research and Ethical Committee at Universiti Sains Malaysia.

Genotyping Methods

Genomic DNA was obtained from peripheral leukocytes extracted from ten millilitres of blood withdrawn from the patients using previously described methods (20). Samples were screened for *CYP2D6*3, *4, *5, *6, *9, *10, *14, *17* and gene duplication. PCR was performed on a Perkin Elmer GeneAmp PCR System 9700® (Applied Biosystems, Foster City, CA, USA) according to previously described procedures with slight modifications (21).

The prediction of a patient's *CYP2D6* phenotype was based on their genotype. Patients with two non-functional alleles were classified PMs. Patients with one non-functional allele and

Table 3: Association of *CYP2D6* alleles and PANSS scores

	Subtotal Positive[a]		Subtotal Negative[a]		Subtotal General[a]		Total PANSS[a]	
*CYP2D6*1*	9.7	(3.52)	8.9	(3.86)	20.2	(4.46)	38.7	(10.11)
*CYP2D6*4*	9.8	(2.75)	7.3	(0.50)	22.3	(5.32)	39.3	(8.42)
*CYP2D6*5*	10.9	(2.78)	9.2	(3.74)	22.5	(6.26)	42.6	(11.13)
*CYP2D6*10*	9.4	(2.63)	8.8	(3.77)	20.6	(4.27)	38.9	(8.96)
Duplication	11.2	(5.01)	14.1	(7.67)	24.5	(8.76)	49.8	(19.31)
F statistic (*df*)	1.29	(4, 289)	4.44	(4, 289)	2.67	(4, 289)	3.22	(4, 289)
P value[b]	0.276		0.002		0.033		0.013	
NA	8.1	(2.19)	7.2	(0.65)	18.8	(2.90)	34.1	(4.86)
Total	9.6	(3.12)	8.9	(3.97)	20.5	(4.65)	39.1	(10.02)

[a]Mean (SD), [b]Analysis of variance (ANOVA). NA represents samples that were amplifiable during first PCR, but genotypes were not determined during the second PCR. Samples were screened for *CYP2D6*3, *4, *5, *6, *9, *10, *14, *17* and duplication gene.

those carrying two alleles coding for an enzyme with reduced activity were classified as IM. Patients with two functional alleles and those carrying one allele coding for enzyme with reduced activity were classified as EMs. A patient was classified as a UM if duplication of a functional gene was detected.

Statistical analysis

Comparisons of clinical features between genotypic groups were evaluated using an Independent t-test, analysis of variance (ANOVA), or non-parametric tests (Mann-Whitney U-test and Kruskal-Wallis test), Chi-square test or Fisher's Exact test when appropriate.

PANSS total and subscales scores were used to measure the current psychopathology. We tested if the potential factors which affect drug response factors such as gender, positive family history, educational level, age, age of onset, duration of illness and number of admission influenced the treatment response using either Independent t-test, ANOVA or simple linear regression analyses. The relationship of different genotypes, predicted phenotypes and alleles with the severity of symptoms of schizophrenia was analyzed using ANOVA. The associations of the distribution of the *CYP2D6* polymorphisms between patients who experienced side-effects with antipsychotics treatment and patients without side-effects in the past two years were studied using the Chi-square test. Data analyses were done after all genotyping of the patients was completed. The statistical analysis was carried out using SPSS/Win software (Version 11.0, SPSS, Inc., Chicago, IL). The limit of significance was set to 0.05.

Results

One hundred and fifty-six patients with schizophrenia (female, *n* = 76, 48.7%) were recruited. Their age ranged from 18 to 62 years. One hundred and fifty-three were Malays (98.1%) and the other three were Chinese (1.9%). Table 1 shows the demographic and clinical characteristics of the patients.

Patients were currently on typical antipsychotics such as haloperidol (10.5%), chlorpromazine (12.5%), trifluperazine (5.0%), perphenazine (2.5%), fluphenazine (8.0%), flupentixol (14.0%), sulpiride (4.0%) and zuclopenthixol (0.5%). Of the atypical antipsychotics, risperidone (26.5%), olanzapine (9.0%), clozapine (6.5%) and quetiapine (1.0%) were prescribed to the patients. About 47.4% of patients treated with antipsychotics were given anticholinergic drugs such as benzhexol to counteract extrapyramidal side-effects (EPS). This was standard practice among some psychiatrists at the clinic to prescribe anti-parkinson drugs (anticholinergic drugs) routinely if their patients were treated with haloperidol.

The results showed that *CYP2D6* polymorphisms have no association with clinical features including positive family history, age, age at first onset, duration of illness, number of admission, educational level and current medication profiles. The associations between *CYP2D6* polymorphisms and PANSS items are shown in Table 2. PANSS total and subscales scores were used to measure the current psychopathology. Possible stratification effects, such as gender, positive family history, educational level, age, age of onset, duration of illness and number of admission were considered.

Table 4: Association of *CYP2D6* genotypes and predicted phenotypes and PANSS scores

Variable	Subtotal Positive [a]		Subtotal Negative [a]		Subtotal General [a]		Total PANSS [a]	
Genotype								
*1/*1XN	11.8	(5.85)	12.5	(6.40)	24.0	(10.17)	48.3	(22.07)
*1/*10XN	9.0	(2.83)	20.5	(13.44)	26.5	(7.78)	56.0	(18.39)
*1/*1	9.8	(3.94)	8.6	(3.57)	19.8	(4.48)	38.1	(10.32)
*1/*10	9.7	(2.97)	9.3	(4.39)	20.8	(4.56)	39.7	(10.18)
*1/*5	10.0	(2.83)	8.5	(2.12)	19.5	(3.54)	38.0	(8.49)
*10/*10	9.2	(2.49)	8.3	(2.49)	20.3	(3.89)	37.8	(7.53)
*4/*10	9.8	(2.75)	7.3	(0.50)	22.3	(5.32)	39.3	(8.42)
*5/*10	10.1	(2.30)	9.4	(4.60)	20.9	(5.33)	40.4	(11.02)
*5/*5	15.0	(0.00)	9.0	(0.00)	32.0	(0.00)	56.0	(0.00)
F statistic (*df*)	0.72	(8, 138)	2.97	(8, 138)	1.68	(8, 138)	1.64	(8, 138)
P value [b]	0.678		0.004		0.107		0.119	
Predicted phenotype								
UM	10.8	(4.92)	15.2	(8.82)	24.8	(8.70)	50.8	(19.39)
EM	9.7	(3.37)	9.0	(4.01)	20.3	(4.49)	39.0	(10.13)
IM	9.4	(2.46)	8.4	(2.80)	20.5	(4.16)	38.3	(8.05)
PM	15.0	(0.00)	9.0	(0.00)	32.0	(0.00)	56.0	(0.00)
F statistic (*df*)	1.40	(3, 143)	5.45	(3, 143)	3.88	(3, 143)	3.86	(3, 143)
P value [b]	0.246		0.001		0.011		0.011	
NA	8.4	(2.51)	7.3	(0.76)	18.9	(3.13)	34.6	(5.50)
Total	9.6	(3.12)	9.0	(4.05)	20.6	(4.70)	39.3	(10.16)

[a]Mean (SD), [b]Analysis of variance (ANOVA). NA represents samples that were amplifiable during first PCR but genotypes were not determined during the second PCR. Individuals carrying two null alleles (*CYP2D6*3, *4, *5, *6* and *14*) are PMs, while those carrying two alleles conferring decreased enzyme activity (*CYP2D6*9, *10* and *17*), or one null allele and one decreased allele are IMs and those with one or two functional alleles (*CYP2D6*1*) are EMs. Subjects with duplicated gene are classified as UMs.

However, the result did not reveal any significant effects on PANSS scores.

Patients with *CYP2D6* gene duplications had a tendency to have higher mean values of PANSS scores than patients with other *CYP2D6* alleles (Table 3).

Table 4 shows the PANSS scores of patients according to their genotypes and predicted phenotypes for *CYP2D6* polymorphisms. ANOVA revealed that mean subtotal negative scores were significantly different among *CYP2D6* genotypes. However, no significant differences were found between genotypes in relation to other PANSS scores such as subtotal positive, subtotal general scores and total PANSS scores. In terms of *CYP2D6* predicted phenotype, it was associated with subtotal negative, subtotal general scores and total PANSS scores. However, the *CYP2D6* predicted phenotype was not associated with subtotal positive scores.

We could not analyse the SAS and the BARS because the majority of patients (94.2%) had zero scores for the both scales. Only nine patients were found to have experienced side-effects during the interview. Side-effects were effectively treated since

the beginning of therapy, and thus, the assessment of the antipsychotics side-effects was invalid.

There were no significant differences in terms of side-effects of antipsychotics between the genotypic subgroups and alleles of *CYP2D6* polymorphisms. From the treatment history, we found that one third of the patients experienced side-effects during the past two years. We compared side-effects during past two years between different genotype and predicted phenotype subgroups. However, there were no significant differences between the groups (Table 5).

Among those who experience side-effects during past two years, the most common genotype was *CYP2D6*1/*10* followed by *CYP2D6*10/*10*, which is the same as the overall patients (Table 5).

Discussion

Pharmacogenetics data are largely unavailable in Malaysia, especially for psychiatric patient populations. To the best of our knowledge, this is the first pharmacogenetic study conducted with patients with schizophrenia in Malaysia.

Table 5: Association of *CYP2D6* genotypes and predicted phenotypes and experience of side-effects during past two years

| Variables | n | Experience of Side-effects | | | | X^2 (df) | P value |
| | | No | | Yes | | | |
		n	(%)	n	(%)		
Genotype							
*1/*1XN	4	2	(50.0)	2	(50.0)	10.42	0.237[a]
*1/*10XN	2	2	(100.0)	0	(0.0)	(8)	
*1/*1	36	27	(75.0)	9	(25.0)		
*1/*10	48	28	(58.30	20	(41.7)		
*1/*5	2	0	(0.0)	2	(100.0)		
*10/*10	42	31	(73.8)	11	(26.2)		
*4/*10	4	2	(50.0)	2	(50.0)		
*5/*10	8	6	(75.0)	2	(25.0)		
*5/*5	1	1	(100.0)	0	(0.0)		
Predicted phenotype							
UM	6	4	(66.7)	2	(33.3)	1.52	0.678[a]
EM	86	55	(64.0)	31	(36.0)	(3)	
IM	54	39	(72.2)	15	(27.8)		
PM	1	1	(100.0)	0	(0.0)		
NA	9	7	(77.8)	2	(22.2)		
Total	156	106	(67.9)	50	(32.1)		

[a]Chi-square test. NA represents samples that were amplifiable during first PCR but genotypes were not determined during the second PCR.

The *CYP2D6* allelic frequencies showed a unique distribution in Malaysian patients with schizophrenia. Compared with Malaysian healthy volunteers (21), patients reported slightly higher duplication alleles (3.2%, 95% CI 1.3–5.2% versus 0.9%, 95% CI 0.0–2.2%), but a lower frequency of *CYP2D6*4* (1.3%, 95% CI 0.0–2.5% versus 2.8%, 95% CI 0.6-5.0%) and *CYP2D6*9* (0.0% versus 3.3%, 95% CI 0.9–5.7%) polymorphisms. The most commonly occurring *CYP2D6* genotype among the patients was *CYP2D6*1/*10* (30.8%), followed by *CYP2D6*10/*10* (26.9%), which are similar to findings among healthy Malay volunteers (21). The genotypes that predicted an EM phenotype was found (55.1%, 95% CI 47.3–62.9%) to be similar to those found among healthy Malay volunteers, 62.0% (95% CI 52.5–70.9%) (21). The frequency of predicted PM phenotype was 0.6% (95% CI 0.0–1.9%) which is at the lower end of the range reported for healthy volunteers at 1.8% (95% CI 0.0–4.4%) (21).

An important finding of this study is that *CYP2D6* polymorphisms are significantly associated with a subtotal negative PANSS score. Patients who were UMs had more pronounced or severe negative symptoms of schizophrenia. This observation is in contrast with other reports that found no association between polymorphic *CYP2D6* alleles and schizophrenia or with its symptoms (19,22,23). Hamelin et al. (22) investigated whether a relationship exists between *CYP2D6 *1, *3, *4, *5, *6* and *7* polymorphisms and schizophrenia. They found no differences among different genotypes in disease symptom severity, number and severity of adverse drug effects, or attitudes toward drug treatment at baseline and at the end of the study. They concluded that common *CYP2D6* alleles were not associated with schizophrenia or with disease symptoms, antipsychotic-related adverse effects, or attitudes toward treatment. Jaanson et al. (19) studied 52 patients with schizophrenia and schizoaffective disorder who received zuclopenthixol decanoate monotherapy for eight weeks. They found that the duration of illness and BPRS score did not differ significantly between *CYP2D6* genotypes (*CYP2D6*3/*4*) (PMs), *CYP2D6*1/*4* (heterozygous EMs) and *CYP2D6*1/*1* (homozygous EMs). A recent study in Sweden found no correlation between the number of active *CYP2D6* alleles and PANSS, and Extrapyramidal Symptoms Rating Scale (ESRS) scores in 26 outpatients with schizophrenia

receiving depot haloperidol monotherapy. All patients were genotyped for *CYP2D6*3, *4, *5* and for gene duplications (23).

Unfortunately, published data originating from clinical studies regarding the impact of *CYP2D6* isoenzyme activity on the therapeutic effects of antipsychotics in schizophrenia are scarce, especially during long-term treatment (6,22). The results of our study are in agreement with a study conducted by Plesničar et al. (24). For example, we found significant differences in emotional withdrawal (P = 0.001), poor rapport (P < 0.001), passive social withdrawal (P = 0.001), lack of spontaneity and flow of conversation (P = 0.011) and uncooperativeness (P < 0.001) between *CYP2D6* phenotypes. These symptoms were also found to be significantly different between different *CYP2D6* genotypes.

It remains unclear whether some of the persistent negative symptoms are influenced by *CYP2D6* polymorphisms or reflect other antipsychotic-induced side-effects in patients receiving long-term antipsychotic treatment. However, we cannot speculate whether this was a phenomenological variation in the symptomatology of schizophrenia. Multiple genes, rather than just one, may play a role in complex phenotypes, including the clinical response to antipsychotics.

The present study found that *CYP2D6* alleles, genotypes and predicted phenotypes are not related to the incidence of side-effects from antipsychotic therapy and severity of SAS and BARS scores in our patients. We found that most patients were well controlled with regard to side-effects at the time of assessment. The results are in accordance with Hamelin et al. (22) who found no relationship between *CYP2D6* *1, *3, *4, *5, *6* and *7* genotypes and the number and severity of adverse drug effects. Panagiotidis et al. (23) also found no correlation between the number of *CYP2D6* alleles and side-effects. In addition, Plesničar et al. (24) also reported no statistically significant differences between PMs and patients having at least one functional *CYP2D6* allele (UMs/EMs/IMs) in relation to Abnormal Involuntary Movement Scale AIMS, SAS or BARS. In the Japanese population, Ohmori et al. (25) found no association between tardive dyskinesia TD and *CYP2D6*2*. In a recent study, Tiwari et al. (26) also showed no significant association between *CYP2D6*4* with TD (P = 0.935) in North Indian patients with chronic schizophrenia.

There was no over-representation of patients with genetically impaired drug metabolic capacities among patients experiencing side-effects during the past two years. In particular, there was no over-representation of PMs among patients with side-effects, which is in agreement with the results of previous studies (27,28,29) in which no over-representation of mutated *CYP2D6* alleles was reported in patients with side-effects during antipsychotic treatment.

The small number of subjects with null alleles may have influenced the apparent lack of an effect of *CYP2D6* genotypes on clinical outcomes. Individuals with these genotypes have been postulated to be more prone for side-effects during antipsychotics treatment. Prospective studies with a larger number of patients with null alleles and patients with multiple alleles are desirable, but the low frequency of these genotypes is an obstacle.

Some limitations must be pointed out in our study. First, our study has a selection bias caused by the exclusion of inpatients and the recruiting of outpatients who had given informed consent. This bias could not be eliminated because of ethical and social considerations. Second, we could not control variables such as type and dosage of antipsychotics that could affect treatment outcomes. In the future, it may be worthwhile to examine a subject group consisting entirely of first-episode patients and treated with the same type and dosage of antipsychotics. Lastly, we did not investigate the severity of symptoms of schizophrenia and side-effects prospectively, but evaluated at a single time-point only (cross-sectional assessment). A one-point assessment is not a proper assessment; it should include base line assessments to gauge the individual treatment response.

We conclude that *CYP2D6* activity may impact the treatment response and severity of schizophrenia. However, we would like to stress that our results are still preliminary because we do not understand the relationship between *CYP2D6* polymorphisms and psychopathology of the illness. Further work is required to confirm this.

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Author's contributions

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