

Genetic and Clinical Factors Affecting Plasma Clozapine Concentration

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ABSTRACT

Objective: To assess (1) the variance of plasma clozapine levels; (2) the relative importance of sex, smoking habits, weight, age, and specific genetic variants of cytochrome P450 1A2 (*CYP1A2*), uridine diphosphate glucuronosyltransferase 1A4 (*UGT1A4*), and multidrug resistance protein 1 (*MDR1*) on plasma levels of clozapine; and (3) the relation between plasma clozapine levels, fasting glucose levels, and waist circumference.

Method: There were 113 patients on clozapine treatment recruited from psychosis outpatient clinics in Stockholm County, Sweden. Patients had genotype testing for single nucleotide polymorphisms: 2 in *MDR1*, 3 in *CYP1A2*, and 1 in *UGT1A4*. Multiple and logistic regression were used to analyze the relations.

Results: There was a wide variation in plasma concentrations of clozapine (mean = 1,615 nmol/L, SD = 1,354 nmol/L), with 37% of the samples within therapeutic range (1,100–2,100 nmol/L). Smokers had significantly lower plasma clozapine concentrations than nonsmokers ($P \leq .03$). There was a significant association between the rs762551 A allele of *CYP1A2* and lower plasma clozapine concentration ($P \leq .05$). Increased fasting glucose level was 3.7-fold more frequent in CC and CA genotypes than AA genotype (odds ratio = 0.27; 95% confidence interval, 0.10–0.72). There was no significant relation between higher fasting glucose levels, larger waist circumference, and higher clozapine levels.

Conclusions: It is difficult to predict plasma clozapine concentration, even when known individual and genetic factors are considered. Therefore, therapeutic drug monitoring is recommended in patients who are treated with clozapine.

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Clozapine is an antipsychotic drug that is clinically effective and has limited extrapyramidal adverse events.^{1,2} Clozapine is effective in patients who have schizophrenia that is resistant to other treatment.³ However, there are adverse events that are more frequent with clozapine than other neuroleptics including weight gain, increased fasting glucose, electroencephalographic changes, and seizures.² In contrast with other second-generation antipsychotic drugs, clozapine has a dose-response relation between plasma concentration and risk of these adverse events.^{4–6}

Clozapine has wide intraindividual and interindividual variation in plasma concentration with a given dose. Many factors may affect clozapine plasma levels including genetic variants of drug-metabolizing enzymes and transporting proteins, smoking habits, sex, age, concurrent use of other drugs, and food.^{7–9} It is unknown whether plasma concentration may be predicted from these factors.

The objectives of this study were to assess (1) the variance of plasma clozapine levels; (2) the relative importance of sex, smoking status, weight, age, and specific genetic variants of cytochrome P450 1A2 (*CYP1A2*), uridine diphosphate glucuronosyltransferase 1A4 (*UGT1A4*), and multidrug resistance protein 1 (*MDR1*) on plasma levels of clozapine; and (3) the relation between plasma clozapine level, fasting glucose level, and waist circumference.

METHOD

Study Subjects

All patients who had regular clinical treatment in specialized psychosis clinics were asked to participate in the Swedish Study of Metabolic Risks in Psychosis, performed mainly in Stockholm County, Sweden. These clinics provided treatment for all outpatients in the clinic catchment area who had long-term psychotic disorders. Patients for the current study were recruited to the Swedish Study of Metabolic Risks in Psychosis from 2005 to 2010. Clinical diagnoses were confirmed according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*).¹⁰ Of 731 patients, 113 patients were prescribed clozapine (15%) including 74 patients who were prescribed clozapine as monotherapy. Genetic analysis was performed in 95 of the 113 patients (84%) who took clozapine. Information about dosage of antipsychotic drugs, time between dose and venous blood sampling, concomitant medications, waist circumference, fasting plasma glucose level, body weight, sex, and smoking habits was included in the study database. Daily clozapine dose was recorded for each patient, and concurrent drugs known to alter the activity of *CYP1A2* or *CYP2D6* were identified to assess potential effects on clozapine blood level. Patients were given written instructions to fast overnight and not to take their prescribed morning dose of clozapine before venous blood sampling. All participants gave informed consent to participate. Ethical approval was given by the Stockholm Regional Ethical Review Committee.

Plasma Clozapine Concentration

Plasma concentrations of clozapine and its major metabolite norclozapine were measured in 98 patients (87%) with reversed phase high-performance liquid chromatography (HPLC) coupled with ultraviolet detection. Plasma

- Routine therapeutic drug monitoring is advised when clozapine is used.
- It is difficult to predict plasma clozapine concentration, even when known factors are considered.
- The risk of increased fasting glucose may be dependent on plasma clozapine concentration.

samples (500 μ L) were prepared by a 2-step liquid-liquid extraction, starting with extraction to an organic phase followed by back extraction to an acidic water phase, from which an aliquot was injected into the HPLC system. Quantification range was 0.1 to 10 μ M for both analytes, and total coefficient of variation was 4.1%–8.3%. Plasma concentrations of clozapine were corrected for daily dose (ratio of concentration to dose [C/D]) based on the linear relation between given dose and achieved plasma concentration as previously reported.¹⁰ Therapeutic plasma interval for clozapine was 1,100 to 2,100 nmol/L (360–690 ng/mL; conversion: [ng/mL] = [nmol/L] \div 3.06); this was the interval used clinically by the Division of Clinical Pharmacology at the Karolinska University Hospital, Stockholm, Sweden.^{11–17}

Genotyping

The DNA was extracted from venous blood samples (5 mL per sample) using a conventional sodium dodecyl sulfate-urea buffer and quantified with spectrophotometry. Genotyping of the *UGT1A4* L48 V allele, with the Valine-encoding G allele expected to cause lower enzyme activity, was performed according to previously published polymerase chain reaction–restriction fragment length polymorphism analyses.¹⁸ The primer sequences, rs number, fragment length, and reaction conditions were previously described (Supplementary Table 1).¹⁸ Genotyping of the *CYP1A2* *1F (increased enzyme activity), *1D (unknown effect on enzyme activity), *1K (decreased enzyme activity), and *MDR1* –3435C>T alleles (associated with altered expression of the transport protein) was performed using single-nucleotide polymorphism genotype assays (TaqMan, Life Technologies, Carlsbad, California) (7900HT instrument, Applied Biosystems, Foster City, California) as described previously with specific sequences of interest, rs numbers, and reaction conditions (Supplementary Table 2).¹⁹ Genotype determination of the *MDR1* –2677G>T allele (associated with altered expression of the transport protein) was performed using pyrosequencing with specific rs numbers, primers (forward, reverse, and sequencing primers), and reaction conditions (Supplementary Table 3).^{20,21}

Statistical Methods

All variables were summarized with descriptive statistics (mean, standard deviation, and frequency). Differences in mean plasma C/D ratio for clozapine, unadjusted and

adjusted for differences in time to most recent dose taken, were analyzed with Mann-Whitney test for differences between patients with different sex (men, women), age (<44 y, \geq 44 y), smoking status (current smoker, nonsmoker), body weight (<90 kg, \geq 90 kg), and genetic variants. The genotypes of the different single-nucleotide polymorphisms were coded under a dominant or recessive model as dichotomous variables.

Multiple regression analysis (stepwise forward) was used to study the combined effect of sex (men, women), smoking status (currently smoking, not smoking), age (<44 y, \geq 44 y), weight (continuous), and the different dichotomized genotypes on C/D ratio for clozapine or norclozapine as dependent variable. There were 3 additional regression models created: (1) a logistic regression model (stepwise forward) was created to study the combined effect of genotypes with an association to C/D ratio for clozapine, sex, age, and smoking status on increased fasting plasma glucose level; (2) The same independent variables were entered into a logistic regression model (stepwise forward) with increased waist circumference as dependent variable; the dependent variables “increased fasting plasma glucose” and “increased waist circumference” were dichotomized (increased plasma glucose level defined as >5.6 mmol/L or use of antidiabetic treatment, and increased waist circumference defined as >102 cm for men and >88 cm for women) based on the global definition of the metabolic syndrome²²; and (3) A logistic regression model (stepwise forward) also was used to investigate the relation between plasma clozapine levels, fasting glucose levels, and waist circumference. Statistical significance was defined by $P \leq .05$.

RESULTS

Daily Dose of Clozapine and Interacting Drugs

Information about daily clozapine dose was available for all 113 patients (Table 1). In 93 patients who provided information about drugs taken concurrently with clozapine, 7 patients were taking medication possibly affecting CYP1A2 or CYP2D6 activity (Table 1). No patients took drugs that may have inhibited CYP1A2 such as fluvoxamine (Table 1).

Plasma Clozapine and Norclozapine Concentration

There was a wide variation in clozapine and norclozapine plasma levels (Table 1). There were only 34 patients (37%) who had plasma clozapine levels within the suggested therapeutic range (1,100–2,100 nmol/L), and 22 patients (24%) had plasma levels below the suggested lower limit (<750 nmol/L) at 12 hours after the most recent dose taken (Figure 1).²³ After exclusion of patients who took \geq 2 antipsychotic drugs, there were 20 patients (22%) who had a clozapine level <750 nmol/L. There were 9 patients (10%) who had a plasma clozapine level >3,000 nmol/L and may have required dose reduction, including 2 outliers in the sample who had exceptionally high plasma clozapine levels (8,070 and 7,136 nmol/L).⁸

Table 1. Clinical Characteristics of Patients Who Had Clozapine Treatment^a

Characteristic	Patients
Diagnosis, n (%)	
Schizophrenia	93 (82)
Schizoaffective disorder	8 (7)
Psychosis not otherwise specified	5 (4)
Other diagnoses	4 (4)
Not done	3 (3)
Sex, men, n (%)	73 (65)
Age, mean \pm SD (range, minimum–maximum), y	44 \pm 11 (13–73)
Current smoker, n (%)	54 (48)
Body weight, mean \pm SD (range, minimum–maximum), kg	90 \pm 19 (48–166)
Increased waist circumference, n (%) ^b	74 (68)
> 102 cm (men)	47 (66)
> 88 cm (women)	27 (71)
Fasting glucose > 5.6 mmol/L, n (%) ^b	55 (52)
Men	39 (60)
Women	16 (40)
Antidiabetic medication, n (%)	7 (6)
Clozapine daily dose, mean \pm SD (range, minimum–maximum), mg	324 \pm 160 (50–875)
Concurrent drugs, n (%) ^c	
Carbamazepine	3 (3)
Omeprazole	3 (3)
Metoprolol	3 (3)
Propranolol	2 (2)
Paroxetine	2 (2)
Fluvoxamine	0 (0)
Plasma drug levels, mean \pm SD (range, minimum–maximum), nmol/L	
Clozapine	1,615 \pm 1,354 (143–8,070)
Norclozapine	787 \pm 528 (100–3,110)

^aN = 113 patients (but N for different variables was varied because of sporadic missing information).

^bIncreased waist circumference and raised fasting glucose according to the global definition of the metabolic syndrome.²³

^cInformation available about drugs used concurrently with clozapine in 93 patients (82%).

Genotype, Patient Characteristics, and Clozapine Concentration

Genotyping was performed on samples from 95 patients. Among the minor alleles of single-nucleotide polymorphisms in *CYP1A2* studied, the most common alleles were the C allele of rs762551 (44 patients, allele frequency 28%) and the deletion allele of rs35694136 (9 patients, allele frequency 6%). The T allele of rs12720461 was not detected in any patient. In *MDR1*, the most common allele was the C allele of rs1045642 (63 patients, allele frequency 41%). In *UGT1A4*, the Val allele of rs2011425 was present in 11 patients (allele frequency 6%). Genotype frequencies of *CYP1A2*, *UGT1A4*, and *MDR1* with corresponding mean C/D ratios of clozapine were varied (Supplementary Table 4).

There was a significant difference in mean plasma concentration of clozapine (C/D) between the genotypes of rs762551 in *CYP1A2*, with lower values for AA genotype (4.2) than AC and CC (6.3; $P \leq .05$). The genotypes of the other single nucleotide polymorphisms showed no significant difference in mean C/D (unadjusted for covariates). We found no significant association between mean C/D for clozapine and smoking status, sex, age, or weight (unadjusted for covariates).

Factors Affecting Plasma Clozapine Concentration

There was a significant association between the AA genotype in rs762551 (*CYP1A2*) and lower plasma clozapine concentration (Table 2). There was a significant association between the GG genotype in rs2032582 (*MDR1*) and lower plasma clozapine concentration (Table 2). Smoking was associated with lower plasma clozapine concentration (Table 2). The variance of clozapine concentration in the sample was explained by the factors in the regression model only to a limited extent (R^2 linear = 0.162).

Factors Affecting Plasma Glucose and Waist Circumference

Odds ratios from the logistic regression (stepwise forward) were used to study the combined effect of genotype in rs762551, rs2032582, and the potential independent variables sex, age, and smoking status on the risk of increased fasting glucose level and increased waist circumference. Increased fasting glucose level was less common among AA genotype in rs762551, but rs2032582 showed no significant association. Increased fasting glucose level was more common in men than women and in older than younger patients (Table 3). Smoking did not affect fasting glucose level in the model, and there was no effect of the different genotypes, sex, age, or smoking status on waist circumference.

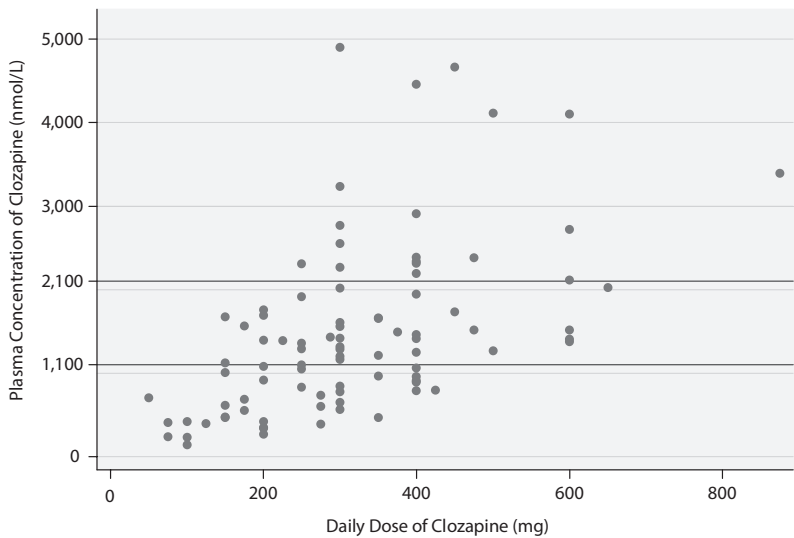
DISCUSSION

The present results showed wide variation in plasma clozapine concentration, and few patients had clozapine levels within the therapeutic range (Figure 1). Many patients had plasma clozapine concentrations below the therapeutic range. With specific dose such as 300 mg/d, plasma concentrations may be below, within, or above therapeutic range. The variation in drug levels could be explained only to a limited extent (16%) by genetic variants assessed in this study and smoking habits.

A strength of this study was the inclusion of a population-based clinical sample of patients who were receiving continuous treatment with clozapine. The sample was representative of patients who typically are prescribed clozapine because most patients had schizophrenia (82%), and the distribution of sex and smoking status in the sample was consistent with patient groups in other studies.²⁴ Limitations of the study may include bias because 32% of patients used clozapine in combination with another antipsychotic drug. Another potential limitation of the study was the absence of data about the effect of clozapine treatment. Previous studies showed that intraindividual variability of plasma clozapine concentration may be 32% for heavy smokers and 19% for nonheavy smokers.²⁵ The patients in the present study were informed of blood sampling to study plasma concentrations of clozapine, and this might have affected compliance with drug intake before sampling.

Several factors may affect plasma levels of clozapine. The present results showed that the A allele of the rs762551 polymorphism in *CYP1A2* was associated with increased metabolism and lower plasma concentrations of clozapine.

Figure 1. Relation Between Plasma Clozapine Level and Daily Dose: Measured Clozapine Concentrations at 12 Hours After Most Recent Dose Plotted Against Daily Dose in 92 Patients Who Had Continuous Treatment^{a,b}



^aDaily doses of clozapine were available for 92 patients.
^bThe 2 outliers, 7,136 and 8,070 nmol/L, are not plotted in the graph.

Table 2. Relation Between Independent Variables and Dose-Corrected Plasma Clozapine Concentration^{a,b}

Independent Variable ^c	β	Standard Error	$P \leq$	95% Confidence Interval	
				Lower	Upper
CYP1A2 rs762551 AA genotype	-2.0	0.75	.008	-3.54	-0.55
Currently smoking	-1.8	0.76	.03	-3.31	-0.28
MDR1 rs2032582 GG genotype	-1.7	0.85	.05	-3.45	-0.05
Constant	11.4	1.69	.001	8.02	14.72

^aMultiple regression analysis (stepwise forward).
^b $R^2 = 0.16$.
^crs762551 AA genotype (no = 0, yes = 1), smoking status (no = 0, yes = 1), rs2032582 GG genotype (no = 0, yes = 1).
Abbreviations: CYP=cytochrome P450, MDR1=multidrug resistance protein 1.

In patients who were homozygous for the rs762551 A allele, the strength of the relation was similar to that of smoking status, which may markedly reduce plasma clozapine levels. Patients homozygous for the rs762551 A allele of CYP1A2 also had a lower risk of developing increased fasting glucose level, but this may be a chance finding because of multiple statistical analyses. Among the genetic factors, the strongest association was observed between the AA genotype in rs762551 and low plasma clozapine concentration, consistent with previous findings that suggested a major function of CYP1A2 in the metabolism of clozapine.²⁶

Smoking, a potent inducer of CYP1A2 activity,^{7,10,27} was associated with lower clozapine C/D ratios in the present study. The induction of CYP1A2 activity is caused by the polycyclic aromatic hydrocarbons in cigarette smoke and not by nicotine.²⁸ Female sex previously had been associated with markedly (40%) increased clozapine concentrations.^{29,30} In contrast, the present study showed no significant association between sex and clozapine

Table 3. Relation Between Independent Variables Related to Raised Fasting Plasma Glucose (> 5.6 mmol/L) or Antidiabetic Treatment^a

Independent Variable ^b	Odds Ratio	Standard Error	$P \leq$	95% Confidence Interval	
				Lower	Upper
Sex	5.28	2.79	.002	1.88	14.89
rs762551 AA genotype	0.27	0.13	.009	0.10	0.72
Age, y	1.08	0.03	.001	1.03	1.13

^aLogistic regression analysis (stepwise forward).
^bSex (women = 0, men = 1), rs762551 AA genotype (no = 0, yes = 1).

C/D ratios, consistent with another study.³¹ Studies about CYP1A2 activity usually have shown lower activity in women than men, and CYP1A2 activity is decreased by oral contraceptives. The sex difference in CYP1A2 activity may be specific to ethnicity, and people of European ancestry have shown no sex difference, in contrast with Asians or Africans.³² Some studies have shown increased plasma clozapine levels with increased age,^{7,30,33} but this was not observed in the present and other previous studies.^{31,34} These differences may be attributed to shorter age ranges between different studies.

The low proportion of patients (37%) who had plasma clozapine concentration within therapeutic range suggests that treatment was not optimized for adverse events or antipsychotic effects. This result is consistent with results of a recent study of clozapine blood levels in 778 subjects that showed only one-third of patients within the target range and another one-third of patients above or below the target range.³⁵ Therapeutic drug monitoring of clozapine has been recommended internationally but is not performed routinely in Sweden.

Both outliers who had high plasma clozapine concentration were males who were treated with moderate to high daily doses of clozapine (300 mg and 500 mg), were nonsmokers, had no interacting drugs, and carried genotypes in rs762551 and rs2032582 associated with high plasma concentrations of clozapine. Furthermore, both patients had increased fasting glucose, and 1 patient had increased waist circumference.

According to the Swedish Prescribed Drug Register of the National Board of Health and Welfare,³⁶ 5,777 patients were prescribed clozapine during 2012, and 551 patients were prescribed clozapine for the first time. Future studies are warranted to investigate whether genotype evaluation may affect clinical outcomes such as time to efficacy and adverse events.

The AA variant of rs762551 in *CYP1A2* may be associated with nonresponders to clozapine.³⁷ Many patients in the current sample (54%) were homozygous for the rs762551 A allele. In this study, the AA genotype was associated with lower plasma clozapine concentrations and normal plasma glucose levels (≤ 5.6 mmol/L). Further studies may compare genotypes in *CYP1A2* and metabolic measurements in responders and nonresponders to clozapine. There is an association between metabolic changes and clinical effect for olanzapine and risperidone,³⁸ but it is unknown whether this is true for clozapine.

The difficulty to predict plasma clozapine concentration, even when known interacting factors and genetic variants are considered, suggests that therapeutic drug monitoring should be implemented whenever clozapine is used. Individual dosage guided by plasma concentration, antipsychotic effect, and adverse events may optimize treatment and may minimize risk of increased fasting glucose, weight gain, and seizures.

Drug names: carbamazepine (Carbatrol, Equetro, and others), clozapine (Clozaril, FazaClo, and others), fluvoxamine (Luvox and others), metoprolol (Toprol, Lopressor, and others), olanzapine (Zyprexa), omeprazole (Prilosec and others), paroxetine (Paxil, Pexeva, and others), propranolol (Inderal, InnoPran, and others), risperidone (Risperdal and others).

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.



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Supplementary Material

Article Title: Genetic and Clinical Factors Affecting Plasma Clozapine Concentration

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Supplementary Table 1. Primer Sequences for Amplification of Polymerase Chain Reaction Fragments That Contained the Polymorphism, Polymerase Chain Reaction Fragment Size, and Restriction Endonucleases Used in Polymerase Chain Reaction-Restriction Fragment Length Polymorphism*

Gene and Single Nucleotide Polymorphism	Primer (5'-3')	Fragment Length (bp)	Restriction Enzyme	Reference
UGT1A4 -142T>G rs2011425	fo-GTTGGGCCCATAACGAAAGGCAGTT re-GCTCCACACACAACACCTATGAAG	576	FastDigest StuI (Eco1471)	[18]

*DNA fragments spanning the single nucleotide polymorphism were amplified in individual reactions by polymerase chain reaction (10 ng DNA/reaction) containing the forward and reverse primers. The temperature program was 95°C for 5 min, followed by 50 cycles of 95°C for 30 s, 55.5°C for 1 min, and 72°C for 1 min. The amplified 576-bp fragment was digested (FastDigest StuI, Eco1471, Fischer Scientific, Stockholm, Sweden) for 10 min at 37°C and analyzed on 1% agarose gels. The wild type allele, and not the mutant allele, was cut into 324- and 252-bp fragments.

Supplementary Table 2. Assay Identification and Sequences of Interest For Genotype Determination*

Gene and Single Nucleotide Polymorphism	Assay Identification	Sequence of Interest
CYP1A2 -729C>T rs12720461	C__30634146_10	GGCTAGGTGTAGGGGTCCTGAGTTC[C/T]GGGCTTTGCTACCCAGCTCTTGACT
CYP1A2 -163C>A rs762551	C__8881221_40	TGCTCAAAGGGTGAGCTCTGTGGGC[C/A]CAGGACGCATGGTAGATGGAGCTTA
CYP1A2 -2467delT rs35694136	C__60142977_10	TGCAGTGAGCCATGATTGTGGCACA[T/-]GAACCCCAACCTGGGTGACAGAGCA
MDR1 -3435C>T rs4005995	C__7586657_20	TGTTGGCCTCCTTTGCTGCCCTCAC[A/G]ATCTCTTCCTGTGACACCACCCGGC

*Primers and probes were obtained commercially (Life Technologies, Stockholm, Sweden). DNA fragments spanning the single nucleotide polymorphisms were amplified in individual reactions by polymerase chain reaction (10 ng DNA/reaction) containing forward primer, reverse primer, and probes for the single nucleotide polymorphisms. Polymerase chain reaction was performed in 96- or 384-well formats with 2 negative controls distributed per assay. The temperature program was 95°C for 10 min followed by 50 cycles of 92°C for 15 s and 60°C for 90 s.

Supplementary Table 3. Polymerase Chain Reaction Primers, Sequencing Primers, and Dispensing Order Used For MDR1 -2677G>T

Genotype Determination*

Gene and Single Nucleotide Polymorphism	Primer (5'-3')	Dispensing Order
MDR1 -142T>G	foB-CTGGACAAGCACTGAAAGATAAGA	GCAGCTAGCT
	re-TGGCTTTGCTACTTTCTGTAAGTT	
rs2032582	seq-TTAGTTTGACTCACCTTCC	

*Forward, reverse, and sequencing primers were obtained commercially (Fischer Scientific, Stockholm, Sweden). DNA fragments spanning the single nucleotide polymorphism were amplified in individual reactions by polymerase chain reaction (10 ng DNA/reaction) containing the forward and reverse primers for the single nucleotide polymorphism. The temperature program was 95°C for 10 min followed by 50 cycles of 92°C for 15 s and 58.5°C for 90 s. The amplified DNA fragments spanning the single nucleotide polymorphism were analyzed with a sequencer (PSQ96, QIAGEN Nordic, Solna, Sweden).

Supplementary Table 4. Genotype Frequencies With Corresponding Concentration-To-Dose Ratios of Clozapine*

Gene and Single Nucleotide Polymorphism	Genotype	No. of Patients (%)	Concentration-To-Dose Ratios
<i>CYP1A2</i>			
rs35694136	TT	86 (91)	5 ± 4
CYP1A2*1D -2467delT	T/del	7 (7)	5 ± 3
	del/del	2 (2)	2.7 ± 0.5
rs12720461	CC	95 (100)	5 ± 4
CYP1A2*K -729C>T	CT	0 (0)	
	TT	0 (0)	
rs762551	CC	9 (9)	4 ± 2
CYP1A2*F -163C>A	CA	35 (37)	6 ± 4
	AA	51 (54)	4 ± 2
<i>MDR1</i>			
rs1045642	TT	32 (34)	5 ± 3
-3435C>T	CT	49 (52)	5 ± 4
	CC	14 (15)	5 ± 4
rs2032582	TT	13 (14)	5 ± 3
-2677G>T	GT	51 (54)	6 ± 4
	GG	26 (27)	4 ± 2
	TA	2 (2)	4 ± 2
	GA	3 (3)	8 ± 8
	AA	0 (0)	
<i>UGT1A4</i>			
rs2011425	TT	84 (88)	5 ± 4
L48V -142T>G	TG	10 (11)	5 ± 3
	GG	1 (1)	4.1

*Data reported as mean ± SD.