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# Serotonin transporter polymorphisms and clinical response to sertraline across ethnicities

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**Abstract**

The aim of this pilot study was to examine the relationship between clinical response, adverse effects, sertraline (SERT) plasma concentrations and the genetic polymorphism of the serotonin transporter gene-linked polymorphic region (5HTTLPR) in 2 ethnic patient groups. The study involved 45 patients in a clinical trial who received a fixed dose regimen of 50 mg SERT for one week, then a variable-dose regimen for a further 6 weeks for major depressive disorder. At weeks 1 and 6, the following assessments were completed: Hamilton Depression Rating Scale (HDRS), Clinical Global Impression (CGI), drug adverse reaction scale and measurement of plasma SERT levels. Genomic analysis for the long and short allele variants of the 5HTTLPR polymorphism was also carried out. Caucasian subjects had a higher rate of *l*/*l* genotype while Chinese subjects had higher frequencies of *l*/*s* and *s*/*s* genotypes. Comparison of the subjects with the 5HTTLPR *s*/*s* genotype and those with the *l*/*l* and *l*/*s* genotypes found no significant differences in the HDRS scores, CGI scores, response rates, adverse effects and SERT plasma concentrations at week 6.
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*Keywords:* Adverse effects; 5-HTT polymorphisms; Plasma concentrations; Sertraline

## 1. Introduction

In spite of current advances in the pharmacotherapy of mood disorders, there remains substantial inter-individual and inter-ethnic variability in antidepressant response. Although the determinants of such variations are not completely understood, genetic factors are thought to play a large role. The serotonin transporter (5HTT) is a prime target of action of selective serotonin reuptake inhibitors (SSRIs). Drug transporter systems are subject to functional polymorphisms, which may affect both drug availability and response to medication. The rate of polymorphism of the long and short allele of the serotonin transporter gene (5HTTLPR) located on chromosome 17, varies between ethnic groups. Long (*l*) and short (*s*) allele frequencies in Caucasians are 57% and 43%, respectively (Lesch et al., 1996), while in Koreans the frequencies are 14% and 86% (Lee et al., 2004).

A number of studies have shown a relationship between the functional polymorphisms of the 5HTTLPR and treatment response to SSRIs (Smeraldi et al., 1998; Pollock et al., 2000; Zanardi et al., 2000, 2001; Arias et al., 2003). These studies in general found that depressed patients with the long allele genotypes (*l*/*l* and *l*/*s*) showed a greater response to SSRIs than those with the short allele (*s*/*s*) (Smits et al., 2004). However, divergent results have been found in recent studies in Korean and Japanese depressed subjects (Kim et al., 2000; Yoshida et al., 2002). This may be due to ethnic differences in the 5HTTLPR polymorphism and/or pharmacogenetics of drug targets (Ng et al., 2004).

*Abbreviations:* CGI, Clinical Global Impression; HDRS, Hamilton Depression Rating Scale; 5HTT, serotonin transporter; 5HTTLPR, serotonin transporter-linked polymorphic region; *l*/*l* and *l*/*s*, long allele genotypes; LUNSERS, Liverpool University Neuroleptic Side Effect Rating Scale; MAOIs, monoamine oxidase inhibitors; *s*, short allelic variant; SERT, sertraline; *s*/*s*, short allele genotype; SSRIs, selective serotonin reuptake inhibitors; *l*, long allelic variant; STin2, polymorphism in the *5HTT* gene occurring in intron 2.

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Cross-ethnic studies of the 5HTT genotype and response are needed to further elucidate the impact of genotype on antidepressant response patterns, and to examine if these are applicable to diverse population subgroups. This prospective pilot study aimed to test if differences exist in the response to sertraline (SERT) in relation to 5HTTLPR polymorphism when conducted across two ethnic groups where distinct inter-ethnic profiles of the allelic variations have previously been found. It is hypothesized that the functional polymorphisms of the 5HTTLPR gene influence the response to SERT but may be subject to the genotype–ethnicity interaction in Chinese and Caucasian patients.

## 2. Methods

### 2.1. Patient population

Patients with major depressive disorder were recruited from The Melbourne Clinic in Australia and Hospital Kuala Lumpur in Malaysia. Two groups comprising of 15 Caucasian patients (all Australian) and 30 Chinese patients (17 living in Australia and 13 from Malaysia) were matched according to age, sex and severity of depression. All patients were at least 18 years of age and had a diagnosis of major depressive disorder according to the DSM-IV criteria (American Psychiatric Association, 1994) with a minimum Hamilton Depression Rating Scale 17-items (HDRS) score at a baseline of 18. They were not previously refractory or intolerant to SERT, and had completed appropriate washout period for any previous antidepressant treatment (3 days for all SSRIs and venlafaxine except fluoxetine, 7 days for mirtazepine and tricyclics, 14 days for irreversible MAOIs, 28 days for fluoxetine) and had no electroconvulsive therapy treatment (ECT) in the previous 6 months. Patients with primary or comorbid diagnosis of schizophrenia, schizoaffective disorder, rapid cycling bipolar disorder, alcohol or substance dependence, dementia or significant medical condition were excluded from the study. The ethnicity of each group was specifically defined as either Caucasian or Chinese (for at least 3 generations).

### 2.2. Drug administration

SERT was administered initially at a fixed-dose regimen of 50 mg for one week, followed by dosages ranging from 25–200 mg/day according to clinical response over the 6 weeks treatment duration. Psychotropic drugs were not allowed except for hypnotics (e.g. zopiclone 7.5–15 mg) or anxiolytics (e.g. lorazepam 1–3 mg) for severe anxiety. Prior approval from the relevant institutional research and ethics committees and written consent were obtained before the commencement of the study.

### 2.3. Clinical measures

Efficacy was assessed using the 17-item HDRS and Clinical Global Impression for severity of illness and global improvement (CGI) (Guy, 1976). These evaluations were done at baseline and at weeks 1 and 6 of treatment. All raters for the HDRS at the Australian and Malaysian study sites received the same training module for investigators. The inter-rater reliability coefficient for all raters was consistently good (alpha value > 0.9). A validated translated Chinese version of the HDRS (Zheng et al., 1988) was used when necessary. Responders were defined as those subjects with a decrease in HDRS by ≥ 50% from the baseline to week 6. Side effects were assessed using a modified version of the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) (Day et al., 1995) which included the addition of three items: feeling anxious, increased appetite and loss of appetite. A translated Chinese version of the LUNSERS was also available for use. In addition, a subscale of serotonergic side effects was separated out from the main scale to include SSRI-specific adverse effects only.

### 2.4. Plasma concentration measurements

Blood samples (12 to 20 h after the last dose) were collected by venepuncture at baseline and weeks 1 and 6. Plasma was stored at −20 °C then sent to the same biochemical laboratory to standardise the assay methodology for plasma SERT. The sampling time and dosage of medication were documented. SERT concentrations in the plasma samples were analysed by Gas Chromatography–Mass Spectrometry using a standard method (details available from the authors or reference).

### 2.5. DNA genotyping for 5HTTLPR polymorphism

Plasma samples originally collected for SERT assay were sent to a common genetics laboratory. DNA was extracted from 400 μl plasma from each sample using a QIAamp DNA Mini Kit (QIAGEN Inc.). The genomic DNA was amplified with a Genomiphi DNA Amplification Kit (Amersham) according to the Amersham protocol with 30 to 100 ng of DNA used for each polymerase chain reaction (PCR). The primers employed were stpr5 (5′ GGC GTT GCC GCT CTG AAT GC 3′) and stpr3 (5′ GAG GGA CTG AGC TGG ACA ACC AC 3′). PCR reactions mixture consisted of 20 μl volume, using 2 μl of DNA, 2 μl of 10× PCR buffer, 2 μl of 2 mM dNTPs, 0.8 μl of 25 mM $MgCl_2$, 0.5 μl of 10 μM of each primer, Taq DNA polymerase and ddH2O to make a total volume of 20 μl. The PCR condition was a cycle of pre-denaturation at 95 °C for 3 min, 35 cycles of denaturation at 95 °C for 30 s denaturing, annealing at 61 °C for 30 s and extension at 72 °C for 1 min. The final cycles PCR reaction were at 72 °C for 7 min and 25 °C for 5 min. With electrophoresis, the amplified products were run at 130 V for 2.5 h, resolved on 2.5% agarose gel and visualized with ethidium bromide. Alleles were designated as short (484 bp) and long (528 bp) against a DNA marker in genotyping for the 5HTTLPR polymorphism.

### 2.6. Statistical data analysis

In the analysis of the 5HTTLPR genotype, the rates of the long (*l*) and short alleles (*s*) were compared between the ethnic groups. Those with homozygous 5HTTLPR *s*/*s* genotype were

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