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ORIGINAL PAPER

Is 5-HTTLPR linked to the response of selective serotonin reuptake inhibitors in MDD?

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Abstract The role of a functional polymorphism in the transcriptional control region of serotonin transporter gene (5-HTTLPR, SERTPR) has been studied intensively in major depression and in the response to selective serotonin inhibitors (SSRIs) in major depression. The findings have been contradictory, although majority of the studies indicate that the short allele is associated with poor response to SSRIs in major depression. In the present study, we evaluated the association of 5-HTTLPR with treatment response to SSRI medication in Finnish Caucasian MDD patients. A secondary purpose was to study the possible association of this particular polymorphism with major depressive disorder. The aim of the study was to replicate the previous findings in this area. Primary outcomes of the treatment were remission, defined by an exit score of seven or less, and response, defined by a reduction of at least 50% on the MADRS. We had also a control population of 375 healthy blood donors, as a secondary objective was to evaluate the possible association of this particular polymorphism with major depressive disorder. Twenty-nine of the 85 (34.1%) patients reached the remission and 58.8% achieved the predefined response criteria. The l/l genotype of 5-HTTLPR was presented in 51.7% of those patients who achieved remission vs. 25.0% in the non-remitters ($P = 0.03$). The result remained statistically significant after adjusting for age, gender, medication and MADRS points at the study entry. However, the small sample size limits the reliability of this result.

Keywords Serotonin transporter · 5-HTTLPR · MDD · SSRI · Drug response

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Introduction

The brain serotonin transporter (5-HTT, SERT) regulates the serotonergic system by uptaking serotonin into the presynaptic neuron. 5-HTT is thus the site of action of reuptake-inhibiting antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs).

A single human 5-HTT gene (SLC6A4) encodes the human 5-HTT. The 5-HTT gene is located on chromosome 17q11.2-12. A functional polymorphism (5-HTTLPR, SERTPR) in the transcriptional control region of SLC6A4 has been identified. 5-HTTLPR alleles are most commonly either 484 base pairs (short or s allele) or 528 base pairs (long or l allele). The long allele has been associated with more efficient transcription, resulting in greater serotonin uptake activity when compared with the short variant [27, 28]. 5-HTTLPR has been intensively investigated with regard to its role in the response to SSRIs in major depressive disorder (MDD). The original finding by Smeraldi et al. [1] pointed to that both homozygotes for the long variant (l/l) and heterozygotes (l/s) showed a better response to fluvoxamine than homozygotes for the short variant (s/s). Since then, several studies have obtained similar results, but there are also contrasting and contradictory findings (see Table 1 [1–20, 25, 26]). Kim et al. [4] found an opposite association in the Asian population, as in their sample the l/l genotype showed a poor response both to fluvoxamine and to paroxetine. However, most of the studies especially in Caucasian population but also in Asian population have shown that the s/s genotype and/or s allele is associated with a poor response and the l/l genotype and/or l allele is associated with a better response to SSRIs in major depressive disorder (MDD). A meta-analysis by Serretti et al. [21] also confirmed this, and the authors concluded that this effect is quite robust in spite of a significant heterogeneity is present in Asian samples. In a large clinical sample in the STAR*D study, however, the association was not replicated [19].

In the present study, the association of 5-HTTLPR for treatment response to SSRI medication in MDD in patients of Finnish Caucasian origin was evaluated. A secondary purpose was to study whether the patients with MDD differ from healthy controls concerning this functional polymorphism.

Materials and methods

Subjects and study protocol

We recruited 106 outpatients of Finnish origin, aged 18–72 years, who met the criteria for major depression of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV. The patients were recruited from a larger sample in primary and secondary outpatient services as well as through newspaper advertisements. All patients were diagnosed and interviewed by a psychiatrist, and the severity of their depression was evaluated using the Montgomery–Åsberg Depression Rating Scale (MADRS). Patients with a baseline MADRS score of 20 or more were eligible for the study. Patients with severe somatic diseases or medication affecting their mood, bipolar mood disorder, schizophrenia and other psychotic disorders, or severe personality disorders or alcohol or substance dependency were excluded. Altogether, 85 patients completed the entire study according to the study protocol (all visit data and genotype data available) and were included in the analysis of the primary outcomes. Control DNA samples ($n = 375$) were obtained from healthy Finnish blood donors. The distribution for 5-HTTLPR genotypes among the whole sample set was in the Hardy–Weinberg equilibrium ($P = 0.93$). The control population consisted of 375 healthy Finnish blood donors. The blood donors complete a health questionnaire including information on their mental health and are also interviewed by a nurse about their medications, chronic illnesses every time they donate blood. Blood donors are not paid in Finland.

At the first study visit, citalopram, fluoxetine or paroxetine was initiated at the investigators' discretion. Anxiolytics and sedative hypnotics as adjuvant treatment and other medication for concomitant general medical conditions were allowed. Of the patients, 23.7% used adjuvant benzodiazepines (diazepam, oxazepam, lorazepam, clonazepam). Hypnotics used were as follows: 14 patients, zopiclone; eight patients, temazepam; six patients, zolpidem; and one patient, nitrazepam. One patient used levomepromazine, and one patient a combination of chlordiazepoxide/amitriptyline. Patients were seen again after using the study medication at 3 and 6 weeks. The mean doses (SD) of the three SSRIs were citalopram 23.5 mg (7.8), fluoxetine 21.1 (4.8) and paroxetine 22.0 (4.2). Compliance was evaluated by a medication diary kept by the patient. Treatment was deemed eligible if the patient had taken the medication on at least 80% of days of the study period. However, it has to be recognized that the medication diary is not as reliable measurement of compliance as is plasma drug measurements. After 6 weeks' treatment, the response was checked using the MADRS. Primary outcomes of the treatment were remission, defined by an exit score of 7 or less and response, defined by a reduction of at least 50% on the MADRS.

All patients gave written informed consent to participate in the clinical study. The study was performed according to the code of ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the local ethics committees. The local ethics committees reviewed and approved the study protocol.

Table 1 Characteristics of studies investigating the association between SSRI treatment and 5-HTTLPR in major depression

Authors (year)	Ethnicity	*N* (male/female)	Mean age (years)	Drugs and doses (mg/day)	Inclusion criteria	Instruments for assessing diagnosis and response	Time of response evaluation; remission; drug plasma level	Results
Smeraldi et al. [1]	Italian	53 (16/37)	49.0	Fluvoxamine (100–300)	Inpatients with MD including psychotic features; HAM-D >21	DSM-IV criteria; HAM-D-21	6w; not reported; plasma level at 3w	*s/s* = poor response
Pollock et al. [2]	Caucasian	51 (not reported)	72.0 (whole group)	Paroxetine (20–30)	Geriatric out- and inpatients with MD, not psychotic, bipolar or schizoaffective; HAM-D >14; MMSE >17	DSM-IV (SCID-IV), HAM-D-17	1–12w; not reported; plasma level weekly	*s/s* + *s/l* = slower response
Zanardi et al. [3]	Italian	58 (15/43)	47.7	Paroxetine (40)	Inpatients with MD and without psychotic features; HAM-D >20	DSM-IV, HAM-D-21	4w; 4w; plasma level at 4w	*s/s* = poor/slow response
Kim et al. [4]	Korean	120 (78/42)	54.2	Fluoxetine (20–50), or paroxetine 20–60)	Outpatients with MD or bipolar depressive episode or dysthymia; HAM-D >16, MMSE >24, age 25–65	DSM-IIIR (DIS), HAM-D-17, interview with significant other	6w; not reported; plasma level not reported	l/l = poor response
Zanardi et al. [5]	Italian	88 (25/63)	52.0	Fluvoxamine (100–300)	Inpatients with MD (with or without psychotic features) or with non-psychotic bipolar depressive episode	DSM-IV, HAM-D-21	6w; 6w; plasma level once	*s/s* > *s/l* > *l/l* for poor response
Rausch et al. [6]	United States, no other information reported	51 (not reported)	Not reported	Fluoxetine (1.25–40)	Outpatients and inpatients with MD HAM-D >17, age 18–65	DSM-IV (SCID), HAM-D-24	6w, 12w, 18w; not reported; plasma level not reported	*s* = poor response
Yoshida et al. [7]	Japanese	54 (22/32)	51.2	Fluvoxamine (50–200)	Outpatients and inpatients with MD, MADRS >20	DSM-IV, MADRS	1w, 2w, 4w, 6w; not reported; plasma level at 4w	*s* = better response
Yu et al. [8]	Chinese	121 (70/51)	44.7	Fluoxetine (20–60)	Outpatients with MD, HAM-D >17	DSM-IV, HAM-D-21	4w; 4w; plasma level not reported	*s/s* + *s/l* = poor response
Arias et al. [9]	Spanish	131 (31/100)	40.0	Citalopram (20–40)	Outpatients with MD	DSM-IV (SCID), HAM-D-21	4w, 8w, 12w; 12w; plasma level at 6w	*s/s* = non-remission

Table 1 continued

Authors (year)	Ethnicity	*N* (male/female)	Mean age (years)	Drugs and doses (mg/day)	Inclusion criteria	Instruments for assessing diagnosis and response	Time of response evaluation; remission; drug plasma level	Results
Joyce et al. [10]	New Zealand, 95% of European origin	86 (not reported)	Not reported	Fluoxetine (10–80)	Major depressive episode	MADRS HAM-D	6w; not reported; plasma level not reported	*s*/*s* = poor response in patients ≥25 years old
Durham et al. [11]	United States, Caucasian majority	106 (47/59)	69.7	Sertraline (50–100)	Elderly outpatients with MD and no psychotic features, HAM-D >17, MMSE >23	DSM-IV, HAM-D-17, CGI, MMSE	1w (only CGI-I), 2w, 4w, 6w, 8w; not reported; plasma level not reported	*l*/*l* = early response
Murphy et al. [12]	United States, Caucasian majority	122 (57/64)	72.2	Paroxetine (20–40)	Outpatients with MD, age >64, HAM-D >17, MMSE ≥ the age-adjusted 25th percentile	DSM-IV, HAM-D-17, geriatric depression scale	1w, 2w, 3w, 4w, 6w, 8w; not reported; plasma level at 4w	No association with efficacy; major effect on the tolerability of the drug
Peters et al. [13]	United States, Caucasian majority	96 (47/49)	37.1	Fluoxetine (10–60)	MD, age 18–65	DSM-IV (SCID-I), CGI	12w; not reported; plasma level not reported	No association
Kato et al. [14]	Japanese	80 (44/36)	44.0	Fluvoxamine (50–150) or paroxetine (20–40)	Recurrent MD, not bipolar.	DSM-IV (SCID-I); HAM-D-21	2w, 4w, 6w; 6w; plasma level at 4w	*l* carriers = better response
Kraft et al. [15]	United States, caucasian majority	96 (47/49)	37.1	Fluoxetine (not reported)	MD, a history of past or current non-response to an adequate SSRI trial was exclusion criteria	DSM-IV (SCID), HAM-D-17, CGI	12w; not reported; plasma level not reported	No association
Hong et al. [16]	Chinese	224 (93/131)	44.0	Fluoxetine (20–40)	MD, HAM-D >17	DSM-IV, HAM-D-21, interview with family members, clinical records	4w; not reported; plasma level not reported	*l* carriers = better response
Kim et al. [17]	Korean	119 (33/86)	59.9	Fluoxetine (20–50), or sertraline (50–100)	MD; HAM-D >14, age >17	DSM-IV; HAM-D-17; interview with significant other	2w, 4w, 6w; 6w; plasma level at 4w	*s*/*s* = better response
Ng et al. [18]	Caucasian (15), Chinese (30)	35 (18/17)	41.6	Sertraline (50–200)	MD; HAM-D >17; age >17	DSM-IV; HAM-D-17; CGI	6w; not reported; plasma level at 1w and 6w	No association

Table 1 continued

Authors (year)	Ethnicity	*N* (male/female)	Mean age (years)	Drugs and doses (mg/day)	Inclusion criteria	Instruments for assessing diagnosis and response	Time of response evaluation; remission; drug plasma level	Results
Kraft et al. [19]	United States, Caucasian majority (78.4%)	1914 (38.2%/61.8%, whole group)	42.6	Citalopram (20–60)	Outpatients from primary care or psychiatric clinics with major depressive episode, and neither an inadequate response nor intolerance to an adequate trial of the protocol treatments during the current episode	PDSQ, QIDS-SR-16	6w; 12w; plasma level not reported	No association
Smits et al. [20]	Dutch	50 (18/32) and 164 (47/117) referents	43.1 and 50.1	Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	Primary care patients with MD, age 18–64, only caucasian, used an SSRI for at least 6 weeks without a satisfactory clinical response assessed by a psychiatrist	DSM-IV,	Not assessed; not assessed; plasma level not reported	Women and younger patients with s allele had a less favorable response to SSRI treatment
Maron et al. [25]	Estonian (96%)	135 (43/92)	31.1	Escitalopram 10–20 mg	Outpatients with MD, MADRS $\geq$ 22	DSM-IV, HAM-D, CGI	Biweekly in 12 weeks; biweekly in 12 weeks; not reported	No association
Huezo-Diaz et al. [26]	White Europeans	450 (172/278)		Escitalopram 10–30 mg	MD, at least moderate severity	MADRS, HAMD-17, BDI	Weekly in 12 weeks; –; plasma level at 8 weeks	SS = worse outcome in men

SSRI selective serotonin reuptake inhibitor, *5-HTTLPR* serotonin-transporter-linked polymorphic region, *N* number of subjects, *MD* major depression, *HAM-D-(n)* Hamilton rating scale for depression-(number of items), *DSM-IV* diagnostic and statistical manual of mental disorders, 4th version, *SCID* structured clinical interview for DSM-IV, *DIS* diagnostic interview schedule, *MMSE* the mini-mental state examination, *MADRS* Montgomery Åsberg depression rating scale, *CGI* clinical global impression for severity of illness and global improvement, *PDSQ* psychiatric diagnostic screening questionnaire, *QIDS-SR* 16-item quick inventory of depressive symptomatology self-report version, *s* short allele of 5-HTTLPR, *l* long allele of 5-HTTLPR

DNA extraction and genotyping

For the DNA extraction, 9.0 ml EDTA-whole blood was taken from the participants and stored in a freezer at −70°C. Genomic DNA was extracted from 200 µl of whole blood using QIAamp®DNA Blood Minikit and automated biorobot M48 extraction (Qiagen, Hilden, Germany). The primer sequences for genotyping by fragment analysis were as follows: 5′ FAM-GGCGTTGCCGCTCTGAATGC-3′ and 5′-GTGGTTGTCCAGCTCAGTCCCTC-3′. (DNA Technology, Denmark). PCR amplification was carried out in a final volume of 15 µl with 1× GeneAmp PCR Buffer II (Applied Biosystems), 200 µM deoxyribonucleotides (GE Healthcare) and dGTP/7 deaza-dGTP 1/1 (Roche), 0.1 µM of each primer, 1 mM MgCl2 (Applied Biosystems), 5% dimethylsulfoxid (Sigma), 0.5 U AmpliTaq Gold polymerase (Applied Biosystems) and approximately 50 ng of genomic DNA. PCR was as follows: 95°C 12 min, 35 cycles at 94°C 30 s, 61°C 30 s, 72°C 30 s and a final elongation at 72°C for 10 min. Fragment sizes were analyzed with ABI 3730 sequencer and the program GeneMapper 3.7 (Applied Biosystems). Random samples were sequenced to determine the ins/del length and position.

Statistical analysis

Summary descriptive statistics were computed, including frequencies, medians, means and SDs. Differences in nominal variables between the 5-HTTLPR genotypes were tested with the Pearson χ^2 test. Statistical tests were 2-sided, and $P \leq 0.05$ was considered statistically significant. Statistical analyses were carried out by SPSS version 14.0 (SPSS Inc., Chicago, IL).

Results

Twenty-nine of the 85 (34.1%) patients reached the remission and 58.8% achieved the predefined response criteria. The MADRS score at the study entry was slightly higher in the non-remission group than in the remission group, and the mean age was higher in the non-responders than in responders. See Table 2 for details for the selected clinical data. The l/l genotype of 5-HTTLPR was presented in 51.7% in the patients who reached remission vs. 25.0% in the non-remitters ($P = 0.03$, Table 3). The result remained statistically significant after adjusting for age, gender, medication and MADRS points at the study entry ($P = 0.04$). The genotype frequencies did not differ between patients and controls ($P = 0.60$, Table 3).

Table 2 Selected clinical data of the study population

	Remission $N = 29$	Non-remission $N = 56$	Responders $N = 50$	Non-responders $N = 35$
Mean age (SD)	40.9 (14.3)	41.8 (14.7)	38.5 (14.4)**	45.7 (13.7)**
Sex				
Male (%)	15 (51.7)	21 (37.5)	23 (46.0)	13 (37.1)
Female (%)	14 (48.3)	35 (62.5)	27 (54.0)	22 (62.9)
MADRS starting points mean (SD)	25.2 (4.7)*	28.4 (5.7)*	26.4 (5.0)	28.3 (6.2)
Dose of SSRI mean (SD)				
Weeks 1–3	19.5 (2.0)	19.7 (2.9)	19.7 (1.9)	19.6 (3.5)
Weeks 4–6	22.4 (6.5)	22.7 (6.5)	21.9 (5.3)	23.7 (7.8)
SSRI used				
Citalopram (%)	12 (41.4)	31 (55.4)	24 (48.0)	19 (54.3)
Fluoxetine (%)	13 (44.8)	19 (33.9)	21 (42.0)	11 (31.4)
Paroxetine (%)	4 (13.8)	6 (10.7)	5 (10.0)	5 (11.8)

* $P = 0.01$ (*t*-test)

** $P = 0.02$ (*t*-test)

Table 3 Distribution of the 5-HTTLPR genotype

	All *N*	*l/l N* (%)	*s/l N* (%)	*s/s N* (%)	*P* value
Responders	50	19 (38.0)	26 (52.0)	5 (10.0)	
Non-responders	35	10 (28.6)	19 (54.3)	6 (17.1)	0.50
Remission	29	15 (51.7)	10 (34.5)	4 (13.8)	
Non-remission	56	14 (25.0)	35 (62.5)	7 (12.5)	0.03
All patients with MDD[a]	97	36 (37.1)	48 (49.5)	13 (13.4)	
Controls	375	129 (34.4)	180 (48.0)	66 (17.6)	0.60

[a] All patients with genotyping data available (including the dropouts)

Discussion

Psychopharmacologic drug response is extremely variable, and although the role of genetic factors is obviously crucial, so far it has proved to be very difficult to obtain consistent, reliable and replicable findings in this area. Probably, the most studied and the most promising results in this field are from the studies evaluating the role of 5-HTTLPR in the antidepressant response to SSRIs in MDD. However, the findings on 5-HTTLPR are also inconsistent and even contradictory across the different studies. Most likely, the contribution of a single gene is modest or even minimal, and thus a single nucleotide polymorphism (SNP)-based investigations are vulnerable to spurious findings [22–24]. However, the importance of adjusting the medication individually to different patients

has a huge impact on clinical patient work, and therefore despite the difficulties, pharmacogenetic studies are important [22–24]. Interactions between several different genes could result in a dramatic change in drug response, when additive, non-additive or synergistic effects of single genes are counted [24].

Although the 5-HTTLPR has been intensively investigated in a number of studies, ultimate consensus on its role in the response to SSRIs in MDD is still lacking or at least disputed. The reasons and difficulties in obtaining similar results across different studies are numerous: diagnostic reliability, different SSRIs in individual studies, different dosages of SSRIs, different ethnicities, disparate response criteria, age and gender differences, sample sizes, etc.

In our patient sample, the respective frequencies of s and l alleles were 39.4 and 61.6%, respectively. In the control population, the corresponding frequencies were 41.6 and 58.4%. These frequencies reflect those generally reported among Caucasians. In the Asian population, the frequencies of the s and l alleles differ markedly from Caucasians, the l allele is much more rare than its counterpart. This ethnic difference in the distribution of the alleles has been argued to partly explain the different results between Asian and Caucasian populations.

So far, although the results have been contradictory, most studies, however, do indicate that the s allele and/or s/s genotype is associated with a poor response to SSRIs while the l allele and/or l/l genotype show a better response. The strongest evidence against this argument comes from the study by Kraft et al. [19]. They studied the association of this polymorphism in response to citalopram in a large clinical sample of depressed patients and could not replicate the previous findings. There are, however, several possible explanations for this. First, in the evaluation of response the 16-item Quick Inventory of Depressive Symptomalogy Self-Report Version (QIDS-SR) was used. The inclusion criterion was $HRSD_{17} \geq 14$, suggesting that the sample may be less severely affected. In addition, no measure of adherence (i.e. serum level monitoring) was used. A potential limitation also arises from the fact that only a minority of the STAR*D patient population provided the DNA sample, and this limits the generalizability of the sample as a whole. However, there are several other studies also reporting a negative result or a result in the opposite direction [4, 7, 12, 15, 17, 18].

The findings of our study are in favor of the original findings by the Italian investigators [1, 3], which were subsequently replicated by many other investigators (see Table 1). In our sample, patients with the l/l genotype achieved remission more often than patients either with the l/s or s/s genotype ($P = 0.03$). In the comparison between l/l vs. l/s and s/s, $P = 0.01$. This result, although in the same direction, was not statistically significant between responders and non-responders. Our results may indicate that the strict remission criteria (MARDS ≤ 7) differentiates in more appropriately the true pharmacological response to treatment than the perhaps less valid response criteria (50% drop in the MADRS score). In addition, we possibly succeeded in excluding the milder forms of MDD, thereby somewhat reducing the placebo response.

The most critical weakness in our study is the rather limited sample size. Also, it is justified to mention that the mean MADRS score was somewhat higher in the non-remitters than in the remitters at the study entry. Drug plasma level monitoring was not used in our study. However, the medication diary was used, and the patients who took less than 80% of the medication according the diary were excluded because of non-adherence. Ethnic stratification is a common problem for pharmacogenetic studies. All our patients were of Finnish origin and geographically from a small area, which is thus a strength of our study.

In summary, it has been very difficult to obtain reliable, replicable findings in pharmacogenetic studies. This holds true also for the role of 5-HTTLPR in the antidepressant response to SSRIs in MDD. In our study, the patients of Finnish origin with the l/l genotype achieved remission more often than patients with the s/l or s/s genotype. Our study adds data that 5-HTTLPR is, in spite of the ongoing debate, associated with the response to SSRIs in MDD.

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