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PHARMACOGENETICS

Further evidence for the association between 5-HT_{2C} receptor gene polymorphisms and extrapyramidal side effects in male schizophrenic patients

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Abstract
Rationale Antipsychotic-induced extrapyramidal side effects (EPS) are still a major problem in the treatment of schizophrenia. Serotonin 2C receptors (5-HT_{2C}) have regulatory effects on dopaminergic pathways in brain regions involved with EPS. Polymorphisms in the 5-HT_{2C} gene (*HTR2C*) have been suggested to be associated with the risk of developing EPS.
Objective Our purpose was to evaluate the impact of polymorphisms in the *HTR2C* gene on the occurrence of EPS in male schizophrenic patients.
Methods Ninety-nine male Caucasian chronic schizophrenic patients on long-term treatment with classical antipsychotics were genotyped for the −997 G/A, −759 C/T, −697 G/C and Cys23Ser polymorphisms of *HTR2C*. EPS (dystonia, parkinsonism, tardive dyskinesia) were assessed by the Simpson-Angus Scale and the Abnormal Involuntary Movement Scale. Fifty-one patients had current or previous history of EPS, whereas 48 patients had no symptoms or history of EPS. To rule out a possible association between *HTR2C* polymorphisms and schizophrenia, 112 healthy male volunteers were also genotyped.
Results Allele frequencies of −997A, −759T and −697C did not differ between the groups, whereas patients with EPS had a significantly (p=0.025) higher frequency of the 23Ser allele (0.29) than did patients without EPS (0.15) or healthy volunteers (0.13). A similar trend was observed for a haplotype including the −997G, −759C, −697C and 23Ser alleles (p=0.04).
Conclusions Results confirm previously reported associations between the *HTR2C* 23Ser allele and EPS occurrence and suggest the novel finding of an *HTR2C* haplotype association with EPS in male chronic schizophrenic patients.

Keywords Extrapyramidal side effects · 5-HT_{2C} · Serotonin · Polymorphism · Antipsychotics

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Background

Dopaminergic and serotoninergic pathways are involved in the mechanisms of therapeutic and adverse effects of drugs used in the treatment of schizophrenia. The main disadvantage of classical antipsychotics is the occurrence of extrapyramidal side effects (EPS). Based on the time of onset, EPS are generally categorised into acute (akathisia, dystonia, parkinsonism) and delayed (tardive dyskinesia, chorea, tics) syndromes. Acute EPS may occur within days or weeks of treatment initiation, with a frequency of up to 90%, whereas delayed EPS syndromes have been reported to develop in about 20% of patients after months or years [1, 2]. Age, gender, treatment duration, dosage and previous EPS history are known to influence the risk of developing EPS [1, 2]. More recently, genetic factors have also been considered. Several studies have reported significant associations between polymorphisms in the genes coding for

serotonin and dopamine receptors and the risk of developing EPS [3–6]. However, the results have not always been confirmed [7].

Different mechanisms have been hypothesised for the different types of EPS. Blockade of nigrostriatal dopamine receptors has been suggested to cause acute EPS, whereas compensatory dopamine receptor supersensitisation in basal ganglia has been hypothesised as the underlying mechanism for tardive dyskinesia [8, 9]. However, as patients who have experienced acute EPS show a predisposition to develop tardive dyskinesia [2, 10], a common or related pathophysiology for both acute and tardive EPS could be expected.

The lower propensity of atypical antipsychotics to induce EPS compared with classical antipsychotics is attributed to their higher affinity for serotonin type 2 receptors than for dopamine D2 receptors [11]. Serotonin 2C receptors (5-HT_{2C}) are expressed in rat basal ganglia (substantia nigra pars reticulata, striatum and subthalamic nucleus), known to be involved in movement disorders [12, 13] and exert an inhibitory control on dopaminergic pathways [14, 15]. Both peripheral and local subthalamic administration of 5-HT_{2C} agonists has been reported to induce orofacial dyskinesia, which was blocked by 5-HT_{2C} antagonists in rats [16, 17]. Furthermore, intracerebral infusion of a specific 5-HT_{2C} antagonist, SB 206553, into substantia nigra pars reticulata showed an antiparkinsonian effect in a 6-hydroxydopamine-lesioned rat model of Parkinson's disease [18]. Therefore, 5-HT_{2C} receptor antagonism has been suggested as a protective mechanism against EPS for atypical antipsychotics [19].

The 5-HT_{2C} receptor coding gene, *HTR2C*, is located on the long arm of the X chromosome [20]. A polymorphism in the coding region of *HTR2C*, leading to a cysteine substitution by a serine at codon 23 (Cys23Ser), was described with a 23Ser allele frequency of 13% in male Caucasians [21]. The 23Ser allele has been reported to be associated with better response to clozapine [22], higher cerebrospinal fluid concentrations of the noradrenaline metabolite 3-methoxy-4-hydroxyphenylglycol [23], bipolar disorder [24] and tardive dyskinesia in chronic schizophrenia [3]. Moreover, higher constitutive activity of 5-HT_{2C} receptor was found in vitro in cells expressing the 23Ser allele compared with the 23Cys variant [25]. The 5-HT_{2C} mRNA undergoes extensive RNA editing, generating multiple isoforms. The alteration in constitutive activity caused by the Cys23Ser polymorphism could not be reproduced when evaluated in mammalian cells expressing these alleles in the nonedited (INI) or edited (VSV) isoforms [26]. Other polymorphisms in the promoter region of *HTR2C* (-997 G/A, −759 C/T and −697 G/C) have been described [27]. A 60% lower transcriptional activity of the −759C allele compared with the −759T variant was reported in human cell lines [28]. Recently, haplotypes containing the −697C allele were shown to have lower promoter activity compared with haplotypes with −697G [29]. Additionally, the −697 G/C polymorphism has been found to be associated with persistent tardive dyskinesia in male Chinese schizophrenic patients, the −697C allele being more frequent among patients with tardive dyskinesia than among patients without [6].

Based on the findings from animal studies and reported associations, it could be expected that polymorphisms in the *HTR2C* gene, possibly altering the function or expression of the 5-HT2C receptor, may influence the risk to develop EPS during antipsychotic therapy. Therefore, we aimed to evaluate the impact of polymorphisms and haplotypes of the *HTR2C* gene on the occurrence of EPS in male patients treated with classical antipsychotics.

Materials and methods

Subjects

Ninety-nine Italian male chronic schizophrenic patients (aged 25–75 years) resident in a long-term psychiatric unit in Messina, Italy, and diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders Fourth Revision* (DSM IV) criteria were included. Patients had participated in previous studies evaluating the relationship between EPS and other genetic factors such as the *CYP2D6* genotype [30, 31]. All patients had been treated with classical antipsychotic drugs (haloperidol, perphenazine, levomepromazine, fluphenazine, chlorpromazine, thioridazine or zuclopenthixol) for at least 5 and up to 25 years [mean±standard deviation (SD); 17±5 years] (Table 1). All subjects were of Caucasian origin. Patients receiving atypical antipsychotics or with organic disorders were not included. At the time patients were included in the original study [30], the occurrence of parkinsonism was rated by the Simpson-Angus Scale (SAS score of 3 or more) and tardive dyskinesia by the Abnormal Involuntary Movement Scale (AIMS score of 4 or more). Additionally, their medical records were reviewed to recognise the occurrence of acute dystonic reactions. Fifty-one patients were classified as having EPS, whereas 48 had neither current symptoms nor history of movement disorders. Of the 51 patients who had current or documented history of EPS, 22 had parkinsonism, 13 dystonia, six tardive dyskinesia, five parkinsonism and dystonia, and five parkinsonism and tardive dyskinesia. The mean antipsychotic daily dose, expressed in chlorpromazine equivalents, did not differ between patients with EPS and without EPS (Table 1). Among patients who had EPS, 29 received anticholinergic drugs (biperiden or orphenadrine), whereas none of the patients without EPS were treated with anticholinergic drugs.

Table 1 Characteristics of patients with (EPS+) and without (EPS-) extrapyramidal side effects

	EPS+	EPS-
N	51	48
Age	48±12	51±12
Duration of antipsychotic exposure (years)	17±5	17±6
Pharmacotherapy N (%)		
High potency antipsychotics	26 (51)	19 (40)
Medium potency antipsychotics	6 (12)	6 (12)
Low potency antipsychotics	10 (19)	20 (42)
Combination therapy	9 (18)	3 (6)
Anticholinergic N (%)	29 (57)	0
Daily dose (mg) in chlorpromazine equivalents	237±94	215±88

Age, duration of antipsychotic exposure and daily dose in chlorpromazine equivalents are in mean±standard deviation. High-potency antipsychotics: haloperidol, fluphenazine, perphenazine. Medium-potency antipsychotics: zuclopenthixol. Low-potency antipsychotics: thioridazine, levomepromazine, chlorpromazine. All subjects were male

To compare distributions of *HTR2C* polymorphisms among a healthy Italian population and schizophrenic patients, male subjects aged 25 years or older, from the same geographical area as patients, were recruited from a pool of unrelated healthy volunteers. A total of 112 volunteers (aged 25–50 years) were included. The study protocol was approved by the ethics committee at Azienda Sanitaria Locale 5, Messina, Italy, and written informed consent was obtained from patients or their relatives, as well as from the volunteers, before inclusion.

Genotyping methods

Genomic DNA was isolated from peripheral leukocytes with Qiagen Blood and Cell Culture Kit (Qiagen, Hilden, Germany). The −997 G/A (rs3813928), −759 C/T (rs3813929), −697 C/G (rs518147) and Cys23Ser (rs6318) polymorphisms of the *HTR2C* gene were analysed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis according to the methods previously described [21, 27], with minor modifications.

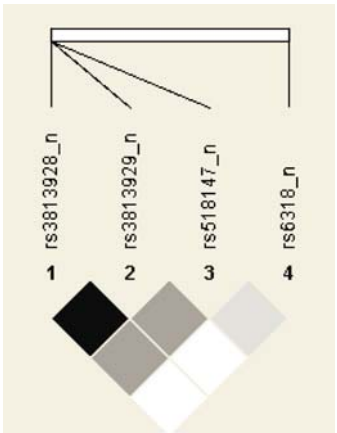
Statistical analysis

Kruskal–Wallis and Mann–Whitney *U* tests were used for comparisons of group characteristics (age, chlorpromazine equivalent doses, duration of antipsychotic treatment) using GraphPad Prism 4 Software (San Diego, CA, USA). Chi-square test was used for comparisons of allele frequencies, and multiple model analyses were performed using Statistical Analyses Software (SAS), version 9.1. Statistical significance was defined as $p<0.05$.

Results

There was complete linkage disequilibrium between the −997 G/A and −759 C/T polymorphisms (Fig. 1). No difference was observed in the −997A and −759T allele frequencies between overall patients (0.17) and healthy volunteers (0.18) or between patients with (0.16) and without (0.19) EPS (Fig. 2). Also, the frequency of the −697C variant did not differ significantly between patients (0.39) and healthy volunteers (0.31). Although the frequency of the −697C variant tended to be higher among patients with EPS compared with patients without EPS and healthy volunteers (0.43, 0.38 and 0.31, respectively), the differences were not statistically significant (Fig. 2).

A statistically significant difference in the 23Ser allele frequency was observed between groups of patients with EPS (0.29), without EPS (0.15) and healthy volunteers (0.13) ($p=0.025$) (Fig. 2). However, the difference in 23Ser allele frequency between patients with and without EPS did not reach statistical significance [$p=0.076$, odds ratio (OR) 2.4 with a 95% confidence interval (CI) of 0.9–6.7]. In multiple model analyses, including the 23Ser allele frequency, *CYP2D6* genotype (data from the previous study [30]), age and chlorpromazine equivalent dose as covariants, the 23Ser allele frequency was the closest to



L1	L2	r^2
(-997 G/A) rs3813928	(-759 C/T) rs3813929	1.0
(-997 G/A) rs3813928	(-697G/C) rs518147	0.386
(-997 G/A) rs3813928	(Cys23Ser) rs6318	0.044
(-759 C/T) rs3813929	(-697G/C) rs518147	0.386
(-759 C/T) rs3813929	(Cys23Ser) rs6318	0.044
(-697 G/C) rs518147	(Cys23Ser) rs6318	0.23

Fig. 1 Linkage disequilibrium analyses of the *HTR2C* −997 G/A (rs3813928), −759 C/T (rs3813929), −697 C/G (rs518147) and Cys23Ser (rs6318) polymorphisms

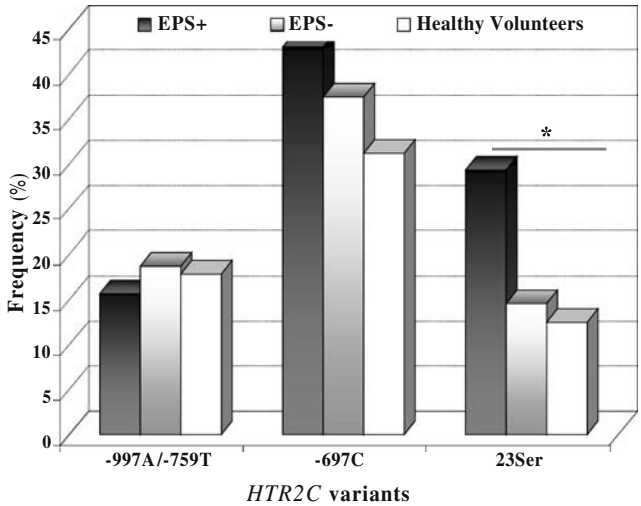


Fig. 2 Frequencies of the *HTR2C* −997A/−759T, −697C and 23Ser variant alleles in patients with (EPS+) and without extrapyramidal symptoms (EPS-) and healthy volunteers (* p=0.025)

significance (p=0.09) compared with other covariants, with an OR of 2.5 (95% CI 0.9-7.1). No significant influence of *CYP2D6* genotype, age and chlorpromazine equivalent dose was observed (p values 0.21–0.97).

There was no strong linkage disequilibrium between the −697 G/C and Cys23Ser polymorphisms in our study population (r^2=0.23, Fig. 1). A haplotype, including the −997G, −759C, −697C and 23Ser alleles, was observed with a total frequency of 0.15 (Table 2). The frequency of this haplotype did not differ significantly between patients and healthy volunteers (0.18 vs. 0.12, p>0.05). However, a statistically significant difference (p=0.04) was found between patients with EPS (0.26), patients without EPS (0.10) and healthy volunteers (0.12). When comparing the frequency of this haplotype between patients with and without EPS, a p value of 0.05 and an OR of 2.9 (95% CI 0.96–9.01) was obtained. The multiple model analysis, including this haplotype, *CYP2D6* genotype, age and chlorpromazine equivalent dose as covariants, indicated the haplotype as the covariant closest to a significant association with EPS (p=0.057, OR 3.2, 95% CI 0.97–10.4), whereas none of the other covariants showed this tendency.

Table 2 *HTR2C* haplotype frequencies in the study population

-997G/A	−759C/T	−697G/C	Cys23Ser	Frequency
G	C	G	Cys	0.62
A	T	C	Cys	0.18
G	C	C	Ser	0.15
G	C	C	Cys	0.03
G	C	G	Ser	0.02

Discussion

Results of this study suggest an association between the Cys23Ser polymorphism of the *HTR2C* gene and the occurrence of EPS in male schizophrenic patients on long-term therapy with classical antipsychotics. This is in line with previous studies [3, 32]. Segman et al. [3] reported a significant association between the Cys23Ser polymorphism and tardive dyskinesia, with patients with dyskinesia having a higher frequency of the 23Ser allele. Recently, we observed a significant association between the −697G/C and Cys23Ser polymorphisms of the *HTR2C* gene and the risk of developing acute EPS in Estonian schizophrenic patients on short-term perphenazine monotherapy [32]. These studies were performed in populations of both male and female patients. Since the *HTR2C* gene is located on the X chromosome, the gender distribution influences the allele frequency calculations. In the study of Segman et al. [3], the higher 23Ser allele frequency among patients with compared with patients without tardive dyskinesia and healthy volunteers was actually attributed to the contribution of the difference found in female subjects. In order to avoid a possible gender bias, only male subjects were included in our study. The higher frequency of the 23Ser allele among patients with (0.29) compared with those without (0.15) EPS and healthy volunteers (0.13) (p=0.025) thus confirms this association also in males.

In our study, no association between the −697G/C polymorphism and EPS was found. This is in contrast to Zhang et al. [6], who reported that the −697C allele was more frequent among Chinese male schizophrenic patients with than among patients without persistent tardive dyskinesia. We also observed a significant association between the −697C allele of the *HTR2C* gene and the risk of developing acute EPS in Estonian schizophrenic patients on short-term perphenazine monotherapy [32]. On the other hand, the −697C allele was present with −997G, −759C and 23Ser alleles in the haplotype that was found to be more frequent (p=0.04) among patients with compared with patients without EPS and healthy volunteers in our study. To our knowledge, this is the first study evaluating the association between *HTR2C* haplotypes and EPS. Moreover, in multiple model analyses including this haplotype, *CYP2D6* genotype, age and chlorpromazine equivalent dose as covariants, only this haplotype contributed to a degree close to statistical significance (p=0.057, OR 3.2, 95% CI 0.97–10.4). Hill and Reynolds [29] reported that *HTR2C* haplotypes containing the −697C and −759T alleles lead to decreased promoter activity. This could be related to a decreased expression of the 5-HT_{2C} receptor and may thus alter the regulation of dopaminergic neurons in basal ganglia, providing a predisposition to the development of EPS.

The −997A/−759T, −697C and 23Ser allele frequencies among healthy volunteers evaluated in our study were similar to those previously reported in other Caucasian healthy populations [21, 24, 33]. Furthermore, we observed no significant difference in allele frequencies between the total patient group and healthy volunteers, ruling out a possible association between these polymorphisms and schizophrenia.

Most of the previous association studies have focused on tardive dyskinesia, whereas in this study, patients with either acute or tardive syndromes were included. The mechanisms behind acute and tardive EPS are still not fully understood. Previous reports point towards a predisposition for tardive dyskinesia in patients who have experienced acute EPS [2, 10]. Furthermore, the history of previous EPS has been reported as a potent predictor of future EPS [34]. According to the results of the European Schizophrenia Outpatient Health Outcomes study, a prospective analysis of 10,000 patients, 50% of patients who experienced tardive dyskinesia had previously experienced acute EPS [35].

EPS still constitute an important clinical problem, potentially influencing patient compliance to treatment. Recently, results of the Clinical Antipsychotic Trials of Intervention Effectiveness showed that whereas the classical antipsychotic perphenazine had similar treatment outcome rates as some of the newer, second-generation antipsychotics, there were more discontinuations due to EPS in the perphenazine group [36]. Therefore, risk factors for the occurrence of EPS are of clinical interest. In light of previous association studies and present findings, it can be suggested that *HTR2C* polymorphisms, in particular the 23Ser allele and the −997G/−759C/−697C/23Ser haplotype, are associated with EPS occurrence in male schizophrenic patients on long-term treatment with classical antipsychotics.

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