DOI: 10.5455/bcp.20130308015536

Personality Traits of Schizophrenic Patients in Remission and Their First-Degree Relatives: A Dopaminergic and Glutamatergic Gene Polymorphism Study

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ÖZET:

Remisyondaki şizofreni hastalarında ve birinci derece yakınlarında kişilik özellikleri: dopaminerjik ve glutamaterjik gen polimorfizmi çalışması

Amaç: Dopaminerjik ve glutamaterjik sistem, şizofreninin ve şizofreni ile ilişkili olduğu öngörülen kişilik özellikleri gibi endofenotiplerin etyolojisinde önemli ilgi alanları arasında yer almaktadır. Bu çalışmada katekol-o-metil transferaz (COMT) geni P2 promoter rs2075507 ve Val/Met (rs4680) polimorfizmleri, dopamin transporter geni (DAT1) VNTR ve glutamat transporter geni (SLC1A2) promoter 181A/C polimorfizmlerinin kişilik özelliklerinin yanı sıra şizofreninin semptomatik özellikleri ile ilişkisinin araştırılması amaçlanmıştır.

Yöntem: Çalışmaya 112 sağlıklı kontrol, en az 6 aydır remisyonda olan 51 şizofreni hastası ve 45 birinci derece hasta yakını alınmıştır. Denekler COMT P2 promoter rs2075507, val/met, DAT1 VNTR ve SLC1A2 promoter -181A/C polimorfizmleri yönünden genotiplendirilmiş ve Karakter ve Mizaç Envanteri ile değerlendirilmiştir. Şizofreni hastaları ayrıca PANSS ve Psikotik Hastalık için Operasyonel Kriterler Kontrol Listesi'nden (Operational Criteria Checklist for Psychotic Illness/OPCRIT) elde edilen beş faktör skalası (negatif semptomlar, delüzyonlar, halusinasyonlar, mani ve depresyon) ile değerlendirilmiştir

Bulgular: Çalışmamız şizofreni hastalarının remisyon sonrasında bile sağlıklı kontrollerden farklı bir kişilik paternine; zarardan kaçınmada ve kendini aşmada daha yüksek skorlara; yenilik arayışı, sebatkarlık, kendini yönetme ve işbirliği yapmada daha düşük skorlara sahip olduklarını göstermiştir. Şizofreni hastalarının birinci derece yakınları ise hastalardan orta düzeyde zarardan kaçınma ve daha yüksek işbirliği yapma skorları ile ayrışmışlardır. Genotipler ve kişiliğin ilişkisi incelendiğinde, COMT val/met polimorfizminin hastalarda veya sağlıklı kontrollerde kişilikle ilişkisi saptanmamıştır. COMT geninde diğer bir foksiyonel polimorfizm olan P2 promoter rs2075507 G aleli, şizofreni hastalarında istatistiksel anlamlı olarak A alelinden daha yüksek yenilik arayışı skorlarıyla ilişkiliydi. DAT1VNTR polimorfizmi uzun alelleri (10 ve 11 tekrar) hastalarda ve sağlıklı kontrollerde kısa allerden (3, 7, 8 veya 9 tekrar) daha yüksek kendini aşma skorları gösterme eğilimindeydi. SLC1A2 promoter -181A/C polimorfizmi C aleli sağlıklı kontrollerde A alelinden istatistiksel anlamlı olarak daha yüksek kendini aşma puanları ile ilişkiliydi. DAT1VNTR, SLC1A2 promoter -181A/C ve COMT val/met polimorfizmleri ile hastaların psikotik semptom boyutları arasında anlamlı ilişki saptanmadı, fakat COMT P2 promoter rs2075507 polimorfizmi delüzyon ve mani skorları ile ilişkiliydi.

Sonuç: Şizofreni sağlıklı bireylerden farklı bir kişilik paternine sahip olabilir ve kişiliğin bazı boyutları psikotik semptomların görünümü ile ilişkili olabilir. Şizofrenide hastalık gelişiminden ve kişilik yapısından, en azından hastaların bir grubunda benzer genler sorumlu olabilir.

Anahtar sözcükler: Şizofreni, kişilik, genetik polimorfizmler

Klinik Psikofarmakoloji Bülteni 2013;23(2):138-48

ABSTRACT:

Personality traits of schizophrenic patients in remission and their first-degree relatives: a dopaminergic and glutamatergic gene polymorphism study

Objective: The dopaminergic and glutamatergic systems are of major interest in the etiology of schizophrenia and supposed endophenotypes such as personality traits. In the present study, we investigated the association between the catechol-O-methyltransferase (COMT) gene P2 promoter rs2075507, Val/Met (rs4680), the dopamine transporter gene (DAT1) VNTR and the glutamate transporter gene (SLC1A2) promoter -181A/C polymorphisms, and personality traits as well as symptomatic features in schizophrenia.

Methods: There were 112 healthy subjects, 51 schizophrenic patients in remission for at least six months and 45 first-degree relatives of the patients enrolled in the study. The samples were genotyped for the COMT P2 promoter rs2075507, Val/Met, DAT1 VNTR and SLC1A2 promoter -181A/C polymorphisms and assessed with the Temperament and Character Inventory (TCI). Schizophrenia patients were also evaluated using the Operational Criteria Checklist for Psychotic Illness (OPCRIT) for each of the five factor-derived scales (negative symptoms, delusions, hallucinations, mania, and depression) and The Positive and Negative Symptom Scale.

Results: Our findings demonstrate that schizophrenic patients, even after remission, had a different personality pattern from controls, showing higher scores in harm avoidance and self-transcendence and lower scores in novelty seeking, persistence, self-directedness and cooperativeness. First-degree relatives of patients also had profiles distinguishable from those of the patients only by intermediate levels of harm-avoidance and higher levels of cooperativeness. In the association of genotypes and personality, COMT Val/Met polymorphism was not associated with personality in patients or in healthy subjects. Another functional polymorphism in the COMT gene the P2 promoter rs2075507 G allele was associated with significantly higher novelty seeking scores in patients than was the A allele. DAT1 VNTR long alleles (10 or 11 repeats) were demonstrated to show a non-significant trend to association with higher self-transcendence scores than in those with the short alleles (3, 7, 8 or 9 repeats) in control samples and patients. In SLC1A2 promoter -181A/C polymorphism, the C allele was significantly associated with higher self-transcendence scores than in those with the A allele in healthy subjects. We did not find any associations between the psychotic symptom dimensions of patients and DAT1 VNTR, SLC1A2 promoter -181A/C and COMT Val/Met polymorphism; however, COMT P2 promoter rs2075507 polymorphism showed an association with the delusion and mania factor scores.

Conclusions: Schizophrenia may be associated with different personality patterns from controls and some personality dimensions may be associated with the appearance of psychotic symptoms. The same genes may be responsible for the development of the disease, with personality patterns seen in at least one group of patients.

Key words: Schizophrenia, personality, genetic polymorphisms

Bulletin of Clinical Psychopharmacology 2013;23(2):138-48

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Gönderme tarihi / Date of submission: 8 Ekim 2012 / October 8, 2012

Kabul tarihi / Date of acceptance: 8 Mart 2013 / March 8, 2013

Bağıntı beyanı:
V.A., A.G.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:
V.A., A.G.: The authors reported no conflict of interest related to this article.

INTRODUCTION

The psychobiological model of personality suggests that approximately 30-60% of the variance in an individual's temperament and possibly also dimensions of character are due to inherited factors (1). Personality may also be considered as an endophenotype of schizophrenia, if common traits can be found both in schizophrenic patients and their first-degree relatives (2). Different personality patterns in schizophrenia have been associated with the onset, course and symptom dimensions of the disorder (3), but the possible relationships between personality dimensions and psychopathology have not been clearly explained to date. According to the Cloninger et al. (4) personality model, each temperament dimension is postulated to be associated with a specific neurotransmitter; novelty seeking (NS) is hypothesized as being related to dopaminergic activity, harm avoidance (HA) to serotonergic activity and reward dependence (RD) to noradrenergic activity. Additionally, it has recently been demonstrated that glutamate plays an important role in personality traits (5). A negative correlation between glutamate levels in the anterior cingulate cortex and the sensation-seeking personality trait in healthy subjects has been shown using magnetic resonance spectroscopy (5).

The concentration of dopamine in the synaptic cleft is regulated via the dopamine transporter (DAT) in the presynaptic membrane and via catechol-O-methyltransferase (COMT) enzyme-soluble and membrane-bound forms (6). COMT catalyzes the transfer of a methyl group to catecholamines, including the neurotransmitters dopamine, adrenaline and noradrenaline. The gene encoding COMT is located on chromosome 22q11 (7). Several functional variants affecting gene activity in the COMT gene are rs4680 the Val(108/158)Met amino acid exchange and rs2075507 (previously rs2097603) linked upstream in the P2 promoter (8,9). Meyer-Lindenberg et al. (10) demonstrated haplotypes of rs2075507 and Val158Met that were highly significantly associated with PFC efficiency. However, the association of these functional SNP's (rs2075507, Val158Met) with schizophrenia, symptom dimensions of schizophrenia or personality traits in psychotic or normal individuals remains unclear (11-15). Previous studies of the relationship between the COMT gene and personality traits have mainly been conducted on rs4680 (Val158Met) polymorphism and have produced inconsistent results that have associated this polymorphism with a variety of personality traits such as novelty seeking (12), harm avoidance/neuroticism (13), persistence and cooperativeness (14), and schizotypal traits (15), but not in all studies (16,17).

The dopamine transporter gene (DAT1; SLC6A3) is located on chromosome 5p15.3 (18) and displays several polymorphisms. A 40-bp polymorphic variable number tandem repeat (VNTR) is present in the 3' untranslated region of the gene and can vary from 3 to 12 repeats (19) and suggests that 3'-UTR VNTR is associated with a main effect of DAT expression (20). Association of DAT1 VNTR polymorphisms and schizophrenia remain controversial (21,22) but it has been shown that the putamen dopamine transporter density correlates with detached personality and social desirability scores (23). However, association studies between DAT1 polymorphisms and personality traits have produced inconsistent results (24,25).

Glutamate is the most abundant excitatory neurotransmitter in the human central nervous system (26). Glutamate is terminated from the synaptic cleft into neurons and glial cells by uptake with high affinity excitatory amino acid transporter (EAAT) and five subtypes of EAAT (1-5) have been identified (26), with EAAT2 (SLC1A2) responsible for more than 90% of the total glutamate uptake (27). The human SLC1A2 gene is located on 11p13-12 (28). Mallolas et al. (29) have found a –181 A/C functional polymorphism in the transcription start site of the SLC1A2 gene, where the C allele induces a 30% reduction in promoter activity compared with the A allele. An association study of the SLC1A2 with schizophrenia has been reported (30) but not confirmed (31). The SLC1A2–181 A/C polymorphism has been shown to affect reward dependence in healthy subjects (32).

In the present study, our aim was to evaluate the association of COMT locus (rs2075507, rs4680), DAT1 VNTR and SLC1A2 gene promoter –181 A/C polymorphisms with personality traits in healthy subjects selected from the general population and a sample of remitted schizophrenic patients and their first-degree relatives. In addition, we investigated the association of personality and manifestations of illness in schizophrenic patients. To the best of our knowledge, this is the first study to investigate the association between rs2075507, DAT1 VNTR and SLC1A2 -181A/C polymorphisms and personality traits and symptom dimensions in remitted schizophrenic patients and their relatives.

MATERIALS AND METHODS

Study Sample

One hundred and twelve healthy subjects, fifty one schizophrenic patients in remission and forty-five first-degree relatives of these patients participated in the study. The group of patients with a diagnosis of schizophrenia according to DSM-IV criteria was formed from outpatients of the Psychiatry Department in Adnan Menderes University Medical Faculty, Research Hospital in Aydin, Turkey. Patients were clinically diagnosed by their treating psychiatrists according to DSM-IV criteria using the Structured Clinical Interview for DSM-IV (SCID-I) (Turkish version) (33) and were included in the study if they were in a period of at least 6 months of remission according to the Andreasen criteria (34). Mean Positive and Negative Symptom Scale (PANSS) positive subscale 7.62±1.19 (7-11), mean PANSS negative subscale 10.88±3.22 (7-21), mean PANSS general psychopathology 21.31±4.11 (13-32), mean PANSS total 39.41±5.54 (30-58) scores were obtained from patients. Mean duration of illness of the patients was 12.07±8.34 years (1-33), mean age at onset of illness was 23.28±6.76 years (13-46) and there were no statistical differences in mean age at onset of schizophrenia between men and women ($p>0.05$). All individuals with schizophrenia were currently taking atypical antipsychotic medications. To configure the relative samples, we selected siblings, parents and lastly children and these relatives were interviewed by a team member to rule out the existence of a current or earlier history of psychiatric pathologies using the SCID-I. Lastly, a control group of 112 healthy subjects with no personal or family psychiatric antecedents was selected and recruited from the general population. Control subjects were assessed by the SCID-I for a current or earlier history of psychiatric pathologies. Exclusion criteria for all participants were neurological or medical disease, mental retardation, substance abuse, toxic psychosis, cognitive damage, or an education level of less than 5 years. The project was approved by the Adnan Menderes University Clinical Research Ethics Committee. All participants gave their written informed consent for the study.

Evaluation Instruments

All participants were given a demographic information form and the Turkish version of the Temperament and Character Inventory (TCI) (35,36). The TCI is a self-reported measure with 240 true/false items measuring four domains of temperament (novelty seeking (NS), harm avoidance (HA), reward dependence (RD), persistence (PS)) and three domains of character (self-directedness (SD), cooperativeness (C), self-transcendence (ST)). The TCI questionnaire was administered to patients only after a remission phase of at least 6 months.

The Positive and Negative Symptom Scale (PANSS) and the Operational Criteria Checklist for Psychotic Illness (OPCRIT) were also administered to the patients. The OPCRIT checklist is designed for use in a best-estimate procedure, in which psychosis symptoms and course features are coded by an experienced clinician. For patients the OPCRIT was completed by a review of detailed hospital records and personal interviews. These ratings reflected both the severity of the symptoms as well as their chronicity. OPCRIT items were entered into factor analysis, carried out as described by Fanous et al (37). Five factors were extracted, and 56 of the OPCRIT items were used to generate corresponding factor-derived scales: negative symptoms, delusions, hallucinations, mania, and depression.

DNA Isolation and Genotyping

Ten ml of venous blood were obtained from every subject by peripheral venous aspiration. DNA was isolated by a commercially available DNA-isolation kit (Quiagen Corp., Germany). A polymerase chain reaction (PCR) was performed as described elsewhere with slight modifications (38-42). The PCR reaction was carried out in a 25 µl volume containing 150 ng genomic DNA, 10 pM of each primer (Fermantes, Italy), 200 µM each dNTP (Promega, USA), 1× PCR reaction buffer that contained 40 mM KCl, 10 mM Tris-HCl (pH 8.3) 1.5 mM MgCl2, and 1 U of Taq Hot-start Polymerase (DNA Helix, South Korea). Primers (Fermantes, Italy) used in the PCR were 5'-CTC TGG CGG AAA GGA AT-3' and 5'-TCG GCA TCA AAA GGA GGA AAA AG-3 for COMT rs2075507; F:5-TCG TGG ACG CCG TGA TTC AGG-3 R:5-AGG TCT GAC AAC GGG TCA GGC-3 for rs4680; 5'-TGA AAC CAG CTC AGG CTA CTG-3' and 5'-AAA GCC ATT CGC AAA CAT AAA-3' for DAT VNTR polymorphism, and 5'-GAG CGG CGG GGC CTC TTT TC- 3' and 5'-TGC AGC CGC TGC CAC CTG TG-3' for SCL1A2 promoter 181A/C. The PCR was conducted after an initial step of 5 min at 95°C, 35 cycles of amplification (30 s at 95°C, 30 s at 54-65°C depending on primers Tm, 30 s at 72°C) and a final extension step of 10 min at

Table 1: Sociodemographic characteristics, COMT rs2075507, rs4880 (Val158Met), DAT1 VNTR and SLC1A2 –181 A/C polymorphisms genotypes and alleles frequency of samples

	Controls (n=112)	Patients (n=51)	Relatives (n=45)	
Gender(Female/Male) n(%)	64(57.1)/48(42.9)	25 (49)/26(51)	27(60)/18(40)	χ^2=1.354, df=2, p=0.508
Age (N±SD)	39.27±12.96	35.69±9.21	41.44±11.07	F=3.018, df=2, p=0.051
Education (year) (N±SD)	11.49±3.58	10.12±3.47	7.69±3.07	F=19.602, df=2, p<0.0001
COMT rs4680 (val/met) (n,%)				
Val/Val	37 (33.9)	13 (28.9)	13 (34.2)	χ^2=1.289, df=4, p=0.863
Val/Met	53 (48.6)	22 (48.9)	16 (42.1)	
Met/Met	19 (17.4)	10 (22.2)	9 (23.7)	
Val	129 (52.9)	48 (53.3)	43 (56.6)	χ^2=0.908, df=2, p=0.635
Met	89 (40.8)	42 (46.7)	33 (43.4)	
COMT rs2075507 (n,%)				
AA	46 (42.2)	19 (42.2)	17 (44.7)	χ^2=0.304, df=4, p=0.990
AG	48 (44)	19 (42.2)	15 (39.5)	
GG	15 (13.8)	7 (15.6)	6 (15.8)	
A	140 (64.2)	57 (63.3)	49 (64.5)	χ^2=0.029, df=2, p=0.986
G	78 (35.8)	33 (36.7)	27 (35.5)	
DAT1 VNTR genotypes (n,%)				
520/480	3 (2.8)	1 (2.2)	0	χ^2=20.925, df=16, p=0.181
520/440	0	0	1 (2.6)	
480/480	52 (47.7)	16 (35.6)	21 (55.3)	
480/440	41 (37.6)	24 (53.3)	10 (26.3)	
480/400	1 (0.9)	0	0	
440/440	11 (10.1)	3 (6.7)	3 (7.9)	
440/400	0	0	1 (2.6)	
360/360	1 (0.9)	1 (2.2)	1 (2.6)	
200/200	0	0	1 (2.6)	
DAT1 VNTR alleles (n,%)				
520 (allele 11)	3 (1.4)	1 (1.1)	1 (1.3)	χ^2=15.174, df=10, p=0.126
480 (allele 10)	149 (68.3)	55 (61.1)	52 (68.4)	
440 (allele 9)	63 (28.9)	29 (32.2)	18 (23.7)	
400 (allele 8)	1 (0.5)	3 (3.3)	1 (1.3)	
360 (allele 7)	2 (0.9)	2 (2.2)	2 (2.6)	
200 (allele 3)	0	0	2 (2.6)	
SLC1A2-181A/C (n,%)				
AA	33 (29.7)	11 (24.4)	8 (21.1)	χ^2=1.482, df=4, p=0.830
AC	47 (42.3)	22 (48.9)	18 (47.4)	
CC	31 (27.9)	12 (26.7)	12 (31.6)	
A	113 (50.9)	44 (48.9)	34 (44.7)	χ^2=0.866, df=2, p=0.649
C	109 (49.1)	46 (51.1)	42 (55.3)	

Table 2: TCI temperament scores (means±standard deviation) for patients (P), relatives (R) and healthy controls (C) with different COMT (rs2075507 and Val/Met,), DAT1 VNTR and SLC1A2-181A/C alleles

		COMT P2A n(C)=140 n(P)=57 n(R)=49	COMT P2 G n(C)=78 n(P)=33 n(R)=27	P[a,b]	COMT Val n(C)=127 n(P)=49 n(R)=42	COMT Met n(C)=91 n(P)=41 n(R)=34	P[a,b]	DAT L n(C)=155 n(P)=55 n(P)=52	DAT S n(C)=69 n(P)=35 n(P)=24	P[a,b]	Glut A n(c)=113 n(p)=44 n(r)=34	Glut C n(c)=109 n(p)=46 n(r)=42	P[a,b]
NS	[1]C	20.46±4.41	19.74±4.73	0.0001[a] **0.007[b]** 1>2,3	20.43±4.49	19.84±4.75	0.0001[a] 1>2,3	19.89±4.63	20.67±4.27	0.0001[a] 1>2,3	20.36±4.48	20.06±4.66	0.0001[a] 1>2,3
	[2]P	15.84±3.53	18.64±4.61		16.63±4.02	17.14±4.36		16.84±3.93	16.91±4.61		17.66±4.14	16.1±4.07	
	[3]R	15.45±4.62	15.15±2.51		15.09±4.38	15.64±3.98		15.35±4.10	15.30±3.81		15.38±4.05	15.38±3.98	
HA	[1]C	15.60±5.17	15.87±5.66	0.0001[a] 1<3<2	15.53±5.12	15.94±5.49	0.0001[a] 1<3<2	16.05±5.38	15.83±5.46	0.0001[a] 1<3<2	16.2±5.03	15.44±5.66	0.0001[a] 1<3<2
	[2]P	20.75±5.26	20.58±5.77		20.12±5.0	21.36±5.84		20.22±5.45	21.53±5.33		21.59±5.11	19.82±5.61	
	[3]R	18.08±6.24	16.67±4.22		18.57±6.08	16.35±4.79		17.58±5.99	17.57±4.79		17.35±5.96	17.76±5.39	
RD	[1]C	14.42±2.91	14.15±3.34	Non-sig.	14.43±3.27	14.36±2.91	Non-sig.	14.13±3.22	14.83±2.64	Non-sig.	14.69±3.08	14.06±3.1	Non-sig.
	[2]P	14.11±2.63	14.48±2.66		14.14±2.62	14.36±2.66		14.34±2.51	14.06±2.87		14.06±2.6	14.41±2.67	
	[3]R	14.73±2.37	14.74±1.93		14.5±2.38	15.02±1.97		14.98±2.34	14.17±1.80		14.76±2.27	14.71±2.18	
PS	[1]C	5.83±1.49	5.74±1.50	0.0001[a] 1>2,3	5.78±1.47	5.81±1.49	0.0001[a] 1>2,3	5.72±1.49	6.01±1.48	0.0001[a] 1>2,3	5.91±0.14	5.68±0.14	0.0001[a] 1>2,3
	[2]P	5.04±1.40	5.36±1.61		5.02±1.34	5.31±1.63		5.14±1.39	5.19±1.65		5.13±0.22	5.17±0.21	
	[3]R	5.14±1.17	5.11±1.28		5.14±1.22	5.11±1.2		5.32±1.19	4.69±1.15		5.12±0.25	5.14±0.22	
SD	[1]C	30.49±5.53	30.37±5.36	0.0001[a] 1>3,2	30.29±5.51	30.46±5.4	0.0001[a] 1>3,2	30.01±5.39	31.58±5.49	0.0001[a] 1>3,2	30.48±5.31	31.35±5.55	0.0001[a] 1>3,2
	[2]P	25.09±5.62	26.00±4.96		25.14±5.92	25.75±4.69		25.43±5.46	25.41±5.31		25.29±5.74	25.54±5.06	
	[3]R	26.57±5.44	27.78±5.42		26.5±5.7	27.61±5.08		27.06±5.19	26.87±6.08		26.5±5.93	27.4±5.02	
CO	[1]C	28.60±5.59	28.28±5.13	0.0001[a] 1,3>2	28.74±5.14	28.38±5.53	0.0001[a] 1,3>2	28.48±5.27	29.04±5.40	0.0001[a] 1,3>2	29.3±4.7	27.97±5.73	0.0001[a] 1,3>2
	[2]P	25.63±5.58	25.18±6.27		25.3±5.78	25.65±5.9		25.12±5.67	26.09±6.10		26.04±5.74	24.91±5.88	
	[3]R	27.67±5.56	28.89±3.08		27.57±5.58	28.76±3.68		28.30±4.94	27.65±4.66		27.82±5.07	28.33±4.68	
ST	[1]C	15.49±5.78	15.79±6.05	0.0001[a] 1<3,2	15.61±5.94	15.68±6	0.0001[a] 1<3,2	16.32±6.06	13.84±5.17	0.0001[a] **0.055[b]** 1<3,2	14.82±5.51	16.35±6.26	0.0001[a] 0.035b 1<3,2
	[2]P	18.12±4.64	17.36±4.25		18.12±4.29	17.51±4.74		18.58±4.54	16.68±4.21		17.15±4.2	18.61±3.32	
	[3]R	18.22±3.18	18.19±5.28		18.26±3.26	18.14±4.85		17.86±4.11	18.95±3.79		17.7±4.74	18.61±3.32	

*(Novelty seeking (NS), Harm avoidance (HA), Reward dependence (RD), Persistence (PS)) and three domains of character (Self-directedness (SD), Cooperativeness (CO), Self-transcendence (ST)), **Non-sig;Non-significant, ***Tukey HSD was used for post hoc comparisons.

72 °C. DAT1 VNTR polymorphism was separated in agarose gels after PCR. A total of six alleles have been detected by the number of 40-bp VNTR polymorphisms: 3-repeat (200), 7-repeat (360 bp), 8-repeat (400 bp), 9-repeat (440 bp), 10- repeat (480 bp) and 11-repeat (520 bp). Other PCR products were digested using restriction enzymes (Fermantes, Italy): Hind3 for COMT rs2075507, Nla III for rs4680 and Bcn I for SLC1A2 -181A/C polymorphisms. Then fragments were separated in 2-3.5% agarose gels and subsequently stained with ethidium bromide and visualized under ultraviolet illumination.

Statistical Analysis

Differences in genotype and allele frequencies and categorical variables between groups were tested by using χ^2-tests. One-way analysis of variance was used for continuous variables. To examine the statistical effects of selected polymorphisms and schizophrenia on differences in personality as measured by TCI scores, dependent measures were entered separately in 3x2 analyses of variances (MANCOVA) with alleles and groups (patients, relatives and healthy controls) as inter-subject factors. In order to avoid possible bias, age and gender were included in the analysis as covariates. Tukey HSD was used for post hoc comparisons. The relation between OPCRIT factors and TCI dimensions was analyzed with the Pearson correlation test. Another MANCOVA was employed to assess the main effect of genotypes and personality on OPCRIT factor scores and to analyze the interaction between the two variables. P<0.05 was accepted for significance. All statistical analyses were conducted by using the Statistical Package for the Social Sciences (SPSS for Windows, Release 16, Chicago, IL).

RESULTS

Sociodemographic characteristics and the frequencies of the COMT rs2075507, rs4680, DAT1 VNTR and SCL1A2 -181A/C polymorphisms in the groups are presented in Table 1. Rs2075507, rs4680 and SCL1A2 -181A/C polymorphisms were in HWE in all groups. We observed no significant difference in the genotype and allele frequencies of these polymorphisms between groups (p>0.05).

Personality assessment and relationship of personality and genotypes

In the investigation of personality (temperaments and characters) and relations between personality and genotypes of groups we conducted a MANCOVA, presented in Table 2. The main result of this analysis was that patients did not differ from relatives for the NS and P dimensions, and they had lower scores than the controls (p<0.0001). Patients achieved the highest scores for the HA dimensions, and they were different from the relatives and controls. The relatives had intermediate HA scores which were higher than those of the controls (p<0.0001). The RD dimension did not show statistical differences among groups. Regarding character scores, for the SD and ST dimensions, patients did not differ from relatives and they had lower scores than the controls for SD and higher scores for ST (p<0.0001). For the C dimension, patients had the lowest scores and were separate from relatives and controls (p<0.0001). Relatives did not differ from controls for the C scores (p>0.05).

Significant differences in temperament dimension scores according to genotypes were detected by TCI between groups. In the patient group, subjects who had COMT P2 promoter rs2075507 the A allele had lower scores in novelty seeking (15.84±3.53), than the individuals of the same group with the G allele (18.64±4.61) (p=0.007). In DAT1 VNTR alleles, we conducted division of alleles as a short (S) allele (3, 7, 8 or 9 repeats) and a long (L) allele (10 or 11 repeats) in groups, based on previous reports described earlier (39). DAT1 VNTR L alleles had lower scores in ST than the S alleles in control and patient groups (Controls L=16.32±6.06; S=13.84±5.17 and patients L=18.58±4.54; S=16.68±4.21) (P=0.055). SLC1A2 -181A/C alleles were significantly associated with ST in controls, while the A allele had lower scores (14.82±5.51) than the G allele (16.35±6.26) (p=0.035).

Table 3: Correlations (r) between personality (TCI) and five symptom dimensions of OCTRIP (Fanous et. al. 2005). *P < 0.05

	NS	HA	RD	P	SD	C	ST
Negative	-0.130	0.006	-0.275*	-0.287*	-0.219	0.106	-0.008
Delusions	-0.318*	0.101	0.009	-0.072	-0.144	0.225	-0.122
Manic	-0.194	-0.115	-0.067	-0.021	-0.141	0.125	0.011
Depressive	0.016	-0.041	-0.131	-0.224	-0.180	-0.016	0.040
Hallucinations	-0.128	0.128	-0.221	0.008	-0.246	0.181	-0.136

Relationship of symptom dimensions of schizophrenia and genotypes

Delusion and manic symptom scores of the OPCRIT were significantly associated with COMT P2 promoter rs2075507 polymorphism. The AA genotype had higher delusion (4.36±2.21) and mania (3.79±3.69) scores than AG (for delusions 3.05±1.73 and for mania 1.6±1.93) and GG genotypes (for delusions 2.43±1.39 and for mania 1.71±1.6) (for delusions p=0.035 and for mania p=0.043). The A allele had higher scores on delusions and manic symptoms (4.02±2.12 and 3.2±3.31 respectively) than the G allele (2.81±1.61 and 1.69±1.75 respectively) (p=0.004 and p=0.007 respectively). Negative, depressive and hallucination symptoms factors scores of the OPCRIT were not related to rs2075507. COMT Val/Met, DAT1 VNTR and SCL1A2 -181A/C polymorphisms were not related to the psychotic symptom dimension of the OPCRIT.

Relationship of personality and symptom dimensions of schizophrenia

Correlations were conducted between personality dimensions and five factors of OPCRIT of the patients (Table 3). NS was negatively correlated with delusions (r=-0.318; p=0.022) and RD and P were negatively correlated with negative symptoms (respectively r=-0.275; p=0.048; r=-0.287; p=0.039). Patients' PANSS scores were not associated with their personality dimension scores.

Interaction between genetics and personality in delusional symptomatology

Previous analyses have showed a significant relation between COMT P2 promoter rs2075507 polymorphism variants and OPCRIT Delusional scores, and also delusions were negatively correlated with NS. These results have allowed us to hypothesize an influence of rs2075507 variants on delusional symptomatology mediated or modulated by personality. To evaluate the influence of both genetic and individual personality traits on delusional dimensions, we performed a univariate variance analysis. Delusions were significantly affected by rs2075507 (main effect of genotype: F=8.13, df=1, P=0.005) and by personality (main effect of novelty seeking: F=14.507, df=1, P=0.050). The interaction between rs2075507 and personality on Delusion scores was not significant (F=1.785, df=2, P=0.185).

DISCUSSION

Our findings demonstrate that schizophrenic patients, even after remission, had a different personality pattern from controls, showing higher scores in HA and ST and lower scores in NS, P, SD and C, similar to some previous reports (43). Also, schizophrenic patients showed the combination of high ST, low SD and low C, which is a unique character profile, described by Cloninger and named schizotypal or disorganized character configuration (44). Only on RD scores was there no difference between patients and controls; results on RD are less consistent in the literature (45). This may be based on the remission of psychotic symptoms in patients in the present study.

First-degree relatives of patients also had different personality patterns, with higher levels on HA and ST and lower levels on NS and SD than controls. The personality profiles of first-degree relatives were distinguishable from the profiles of patients only by intermediate levels of HA and

higher levels of C. Higher cooperativeness levels may be a protective influence for relatives, as proposed by Smith et al (2). Although research assessing temperament and character in first-degree relatives has more mixed findings compared to patients (46,47), the relatives of patients exhibited very similar personality profiles to those of patients, which may support the hypothesis of personality as an endophenotype for schizophrenia, as previously suggested by Smith and colleagues (2).

In the present study, we hypothesized that manifestation of the disease was potentially modulated by personality. In accordance with this, negative symptoms were less strong in patients with high scores on RD, P and C, in line with the literature (48-50), and delusional symptoms were more frequent in patients with lower scores on NS, in contrast to the findings of Guillem et al (3). However, the study population of Guillem et al. (3) did not reach remission as described by Andreasen et al. (34).

We did not detect any relationship of COMT Val/Met polymorphisms to personality in patients or in healthy subjects. The novelty seeking/extroversion trait has been repeatedly found to be related to COMT, but with contrasting results; the rs4680 (Val/Met) Met allele has been found to be related to higher NS scores (14,51) and to greater stimulus/sensation seeking (52,53), but on the other hand the same allele has been also related to lower extroversion (54-56), although not in all studies, (16,17) similarly with ours. The rs2075507 is another functional polymorphism in the COMT gene, located in the P2 promoter and defines the activity of the gene. The rs2075507 was related with NS scores in schizophrenic patients in remission in the current study. The patients with the rs2075507 G allele had significantly higher NS scores than in those with the A allele. To the best of our knowledge, rs2075507 polymorphism has not been investigated before for association with personality in schizophrenic patients or healthy subjects.

In our study both dopaminergic and glutamatergic gene polymorphisms were related to self-transcendence. Self-transcendence is considered to represent greater magical ideation, lack of intrapsychic boundaries, and difficulties in self/non-self identification, which are highly correlated with positive symptoms in schizophrenic patients and their siblings (35). DAT1 VNTR L (10 or 11 repeats) alleles were demonstrated to show a non-significant trend with higher ST scores than in those with the S (3, 7, 8 or 9 repeats) alleles in control samples and patients. Previously published findings have demonstrated a relation between DAT1 VNTR and novelty seeking (24,57) and persistence (58), but others have not demonstrated such a relation (25,59).

SLC1A2 promoter -181A/C polymorphism was also related to self-transcendence in healthy subjects. In healthy controls, the C allele has significantly higher ST scores than in those with the A allele. Negative correlations have been shown between glutamate levels and the sensation-seeking personality trait (5). In SLC1A2 promoter -181A/C polymorphism, the C allele induces lower promoter activity of the SLC1A2 gene and higher plasma glutamate concentrations (29); therefore, the presence of a negative correlation between glutamate activity and ST may also be suggested. To the best of our knowledge there has been only one report of a relationship between reward dependence and SLC1A2 gene-181A/C polymorphism in healthy subjects (32).

There is a large body of convergent evidence implicating COMT Val158Met in the symptomatology of schizophrenia and bipolar disorders, suggesting that the Val allele and Val/Val homozygosis are related to delusions, mania scales, a greater severity of psychotic symptoms and a worse outcome, and a greater risk of developing psychotic features in schizophrenia than the Met allele (60-62,65). However, a number of studies have not found any relationship (63-64). We did not find any relationship between the psychotic symptom dimensions of patients and COMT Val/Met polymorphism consistent with these negative studies (63-64). In the present study however, COMT P2 promoter rs2075507 polymorphism showed a relationship with the delusion and mania factor scores. Effects of COMT P2 promoter polymorphism on COMT activity in lymphocytes have been reported previously, with higher activity

linked to the frequent promoter of the A allele (8). Rs2075507, the A allele (the high activity allele), was related to higher delusion and mania factor scores than the G (low activity) allele. To the best of our knowledge this is the first report to investigate the relationship between rs2075507 and the symptom dimensions of schizophrenia.

In conclusion, schizophrenia patients showed different personality patterns from those of controls (higher HA and ST and lower NS, P, SD and C) and some personality dimensions may be associated with the appearance of psychotic symptoms (negative symptoms may be negatively correlated with RD, P and C, and delusional symptoms may be negatively correlated with NS). The profiles of the personalities of first-degree relatives (higher HA and ST, lower NS and SD) were distinguishable from the profiles of patients in our study only by intermediate levels of HA and higher levels of C. Our findings suggest that personality might be an endophenotype in schizophrenia. The same genes may be responsible for the development of the disease, with personality patterns seen in at least one group of patients. Our findings suggest a role of COMT gene promoter rs2075507 polymorphisms both in some personality features (NS) and in the symptom dimensions (delusion and mania) of schizophrenia. Self-transcendence may be related with SLC1A2 promoter -181A/C and DAT1VNTR polymorphism in healthy subjects or patients. The small number of patients with schizophrenia in remission is a major limitation of our study. Further studies on bigger samples may be needed to clarify the effects of genotypes on personality. More than one region of the gene that determines activity may be responsible for conflicting results in the literature, and haplotype analysis of a larger case study is needed to clarify the situation.

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