Polymorphisms of the serotonin transporter gene (*5-HTTLPR*, *A/G SNP* in *5-HTTLPR*, and *STin2 VNTR*) and their relation to personality traits in healthy individuals from Russia

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Objective **Numerous studies have reported association of the serotonin transporter gene (*5-HTT*) polymorphisms and neuroticism and traits characterizing sociability and activity. This study aimed to define a single genotype effect of three polymorphic markers in the *5-HTT* gene (*5-HTTLPR*, *A/G SNP* in *5-HTTLPR* and *STin2 VNTR*) and to check possible association of the *5-HTT* haplotypes and personality traits [assessed with Eysenck Personality Inventory (EPI) and Temperament and Character Inventory (TCI) questionnaires] in 301 healthy young individuals.**

Methods **To investigate single genotype and haplotype effects of all polymorphic markers, multivariate analysis of variance and haplotype trend regression analyses were conducted correspondingly.**

Results **Individuals with *STin2.10* allele scored significantly lower on Neuroticism (EPI) ($P=0.007$) and Harm Avoidance ($P=0.005$) in the overall sample. The same pattern of association was reported in women: carriers of *STin2.10* allele scored lower on Harm Avoidance (TCI) ($P=0.008$). Haplotype trend regression analyses revealed that carriers of *S12* haplotype had lower sociability-related traits such as Extraversion (EPI) and Novelty Seeking (TCI), whereas Harm Avoidance (TCI) (anxiety-related trait) was higher. Opposite association was observed for *S10* haplotype: Extraversion (EPI) score was higher, whereas Harm Avoidance (TCI) score was lower in carriers of this haplotype.**

Conclusion **As single polymorphism effect of *STin2* was observed in relation to anxiety-related traits, opposite *S10* and *S12* haplotype effects on Neuroticism and Harm Avoidance could be explained by the larger impact of *STin2* polymorphism. Controversially, we consider that the variance in sociability-related traits is related to specific haplotypes of *5-HTT* gene. *Psychiatr Genet* 18:167–176 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Individual differences in personality are influenced by both environmental and genetic factors. Moreover, family studies have reported that the heritable component accounted for 30–40% of the variance in personality traits (Bouchard and Loehlin, 2001). As the psychobiological model of personality was proposed (Cloninger *et al.*, 1993), molecular-genetic studies have been focusing on genes involved in neurotransmitter pathways. The model, proposed by Cloninger *et al.* (1993) (Temperament and Character Inventory, TCI), distinguishes four temperament dimensions: Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD), and Persistence (P) (Cloninger *et al.*, 1993) those are thought to be highly heritable, fully manifest in infancy, and be stable throughout life (Goldsmith *et al.*, 1987). Temperament traits refer to individual differences in automatic response to emotional stimuli, which follow the rules of associative conditioning or procedural learning of habits and skills. Character traits – self-directedness, cooperation and self-transcendence – are hypothesized to describe individual differences in self-object relationships, which begin with parental attachments in infancy and continue to mature throughout life (Cloninger *et al.*, 1997). Each of the temperament traits has been reported to be influenced by one of the neurotransmitter systems: NS is mediated by dopaminergic system functioning, HA – by serotonergic system and RD – by noradrenergic system (Cloninger *et al.*, 1993). Moreover, TCI temperament dimensions are inherited independently of one another, so all possible combinations of scores on these dimensions occur, and that predisposes individuals to qualitatively distinct

0955-8829

patterns of emotional response. The functional interactions among the temperament traits, NS, HA, and RD, produce eight traditional subtypes of temperament ('the temperament cube'): adventurous (high NS, low HA, low RD), explosive (high NS, high HA, low RD), sensitive (high NS, high HA, high RD), passionate (high NS, low HA, high RD), independent (low NS, low HA, low RD), methodical (low NS, high HA, low RD), cautious (low NS, high HA, high RD), and reliable temperament configuration (low NS, low HA, high RD). Moreover, it is postulated that the combinations of the extreme temperaments with character pathology correspond with traditional personality disorders (Cloninger *et al.*, 1997).

Earlier it has been assumed that the serotonin transporter gene (*5-HTT*) is a major regulator of serotonergic neurotransmission in different regions of the brain (Lesch *et al.*, 1997). It is likely that genetically mediated variability of the *5-HTT* gene functioning can contribute to individual differences in personality traits. In addition to several regulatory domains controlling selective expression in serotonergic neurons, transcriptional activity of the *5-HTT* gene is modulated by the number of 20–23 base pairs (bp) repeats in the upstream regulatory region of the gene (*5-HTT*-linked polymorphic region, *5-HTTLPR*). As the more frequent alleles with 14 and 16 repeats were designated as S and L allele correspondingly, this polymorphism was also designated as 44 bp insertion/deletion polymorphism. Functional studies of the *5-HTT* promoter activity in cell lines, mRNA concentrations in the raphe complex of human postmortem brain, platelet serotonin uptake, and content confirmed that S allele was associated with lower levels of the *5-HTT* gene expression and function (for review, see Benjamin *et al.*, 2002). Some recent studies have reported the association of the S allele and anxiety-related traits (Munafo *et al.*, 2003; Sen *et al.*, 2004; Vormfelde *et al.*, 2006), whereas others have failed to replicate this association (Lang *et al.*, 2004; Joo *et al.*, 2007). Inconsistence of the results could be explained by the presence of *A/G* single nucleotide polymorphism (*SNP*) (*rs25531*) within the *5-HTTLPR*. G allele could be detected only in the presence of the long variant of *5-HTTLPR* (L_G) creating an aminopyridine-binding site (De Luca *et al.*, 2005). As it has been indicated that *5-HTT* mRNA expression levels of the gene containing S allele or L_G allele are equivalent (Nakamura *et al.*, 2000), it is necessary to analyze the influence of *5-HTTLPR* together with *A/G SNP*. Only a few published studies of this gene have tested the reported functional significance of this SNP: in suicidal behavior (De Luca *et al.*, 2006) and in depression (Zalsman *et al.*, 2006). To our knowledge, there have been no studies considering the functional significance of *A/G SNP* in *5-HTTLPR* in relation to personality traits.

Polymorphism of variable number of 17 bp repeats located in intron 2 of *5-HTT* [*STin2* variable number of tandem repeats (VNTR)] was found to be in linkage disequilibrium with *5-HTTLPR* in different populations (Ebstein, 2006). In addition, the *STin2* polymorphism has been implicated in gene expression in embryonic stem cells (Fiskerstrand *et al.*, 1999) and together with *5-HTTLPR* there was an observed combination effect on the rate of *5-HTT* mRNA transcription in lymphoblasts (Hranilovic *et al.*, 2004).

Another possible explanation of ambiguous results of different research groups is influence of various factors including sex, age, cultural, and environmental conditions.

Sex differences caused by hormonal and social influences on the individual during various phases of development may underlie the known sex variation in personality traits (Costa *et al.*, 2001). It has been reported that women score higher on anxiety-related traits (Feingold, 1994; Lynn and Martin, 1997, Brandstrom *et al.*, 2001) and reward dependence (Miettunen *et al.*, 2007) than men, whereas there is some inconsistency with regard to extraversion. Some of studies indicate higher extraversion scores in women (Feingold, 1994; Rouff *et al.*, 2005), whereas others reported opposite findings (Lynn and Martin, 1997). A wealth of evidence supporting sex variations in serotonin neurotransmission caused by the involvement of sexual hormones is observed. One of the ovarian hormones – estrogen is critically implicated in the sexual differentiation of the brain (McEwen, 2001) and thus likely contributes to sex differences in brain morphology and neurochemistry. By binding to intracellular receptors, estrogen mediates the transcription of genes encoded enzymes that regulate neurotransmitter pathways, nerve growth factors, and signal transduction proteins (McEwen, 2001). Human and animal studies suggested that women had higher serotonergic activity (Mann *et al.*, 2001). Moreover, anatomical sexual dimorphism has been suggested (Cordero *et al.*, 2000) in the raphe nuclei, the area with higher density of serotonin transporter (Frazer *et al.*, 1999).

Although some researchers point to the stability of personality in adulthood over the life course (McCrae *et al.*, 2000), there is some evidence of normative personality change caused by genetic influences (Caspi and Roberts, 2001) and the complex interactions between an individual and environment including systematic change of social roles, life events, and social environment (Costa *et al.*, 2000; Srivastava *et al.*, 2003). Some studies have shown a moderate decline in extraversion (McCrae *et al.*, 1999) and neuroticism (Allemand *et al.*, 2007) in adulthood. It has been reported that there were both continuity and change in personality traits during the transition from late adolescence to young adulthood (Donnellan *et al.*, 2007).

Some studies point to the cultural influence on personality traits caused by differences in traditions, social norms, and religion (Leung *et al.*, 1992). Geographically and historically related cultures show similar personality profiles. According to Zohar *et al.* (2001), there is a tendency in the western culture for men to emphasize individuality and for women to focus more on interpersonal relationships. It has been reported that Europeans and Americans generally scored higher in extraversion, NS and RD than Asians and Africans (McCrae and Terracciano, 2005; Miettunen *et al.*, 2006). Furthermore, Southern and Eastern Europeans have higher scores on neuroticism compared with those in Northern Europeans and people from South and Southeast Asia (McCrae and Terracciano, 2005). Although Russia is considered as a part of Eastern Europe, personality traits of Russians were closely related to Asians and Africans and characterized as self-conscious and vulnerable (McCrae and Terracciano, 2005).

As temperament traits have been reported to remain stable at the age of 11–27 years (Sigvardsson *et al.*, 1987), this study aimed to analyze the association of *5-HTT* gene and personality traits in the group of 16–27 years old people. Gene-based haplotypes could be the most precise markers for association with the trait of interest (Hoehe, 2003). Taking into account functional significance of *5-HTTLPR*, *A/G SNP* and *STin2 VNTR* polymorphisms, we aimed to designate single-genotype effect of all polymorphic markers and to check the possible association of *5-HTT* haplotypes and personality traits in young healthy individuals from the Russian population. As sexual dimorphism is known in personality traits, an association analysis was conducted in men and women separately.

Methods

Participants

This study sample was comprised of 301 healthy individuals from the general population of Bashkortostan Republic of Russia and included 59 men (mean age ± SD: 19.86 ± 2.44 years, age range: 17–26 years) and 242 women (mean age ± SD: 19.84 ± 2.41 years, age range: 16–26 years). All participants were Caucasian origin, from Russian population (Slavic group of the Indo-European language family) or Tatar population (Turkic group of the Altaic language family). All enrolled individuals were students in colleges in Ufa (Bashkortostan Republic, Russia) and had no individual or family (a first-degree relative) history of any psychiatric disorder based on self-reports.

The study was approved by the Biological Ethics Committee of Bashkortostan Republic and written informed consent was obtained from all the participants after they were acquainted with all the procedures. All participants were informed about the voluntary and confidential nature of their participation.

Psychometric evaluation

Personality traits were assessed using the Russian version of psychological inventories, Eysenck Personality Inventory (EPI) and Temperament and Character Inventory (TCI) (Raygorodskiy, 2003). All volunteers completed these self-reported questionnaires. The EPI (57 items) measures two global personality domains: Extraversion (the tendency to perform high social activity and dominance) and Neuroticism (the tendency to show emotional lability and anxiety). As these psychological factors have been considered to be genetically influenced, this study was determined to evaluate genetic influence of the serotonin transporter on any of the EPI factors.

The Russian variant of TCI includes 125 items with yes/no answers designed to evaluate four temperament traits: NS, HA, RD, P, and three character traits: self-directedness, cooperation, and self-transcendence. According to the Cloninger's model, temperament traits are assumed to be highly heritable and manifest early in development, whereas character traits are thought to be influenced by different socio-cultural factors and change during the lifespan. In this study we evaluated the influence of serotonin transporter gene polymorphisms on four temperament traits.

Genotyping

Genomic DNA was isolated from the whole blood using a standard phenol-chloroform technique. PCR primers for three polymorphisms of the *5-HTT* gene were designed as described earlier (Fiskerstrand *et al.*, 1999; Wendland *et al.*, 2006). PCR for *STin2 VNTR* was performed in total volume of 15 µl with 20–50 ng of genomic DNA, Taq polymerase (Silex, Moscow, Russia) under the following conditions: initial denaturation 95°C 3 min, 34 cycles consisting of 94°C 30 s, 58°C 30 s, 72°C 1 min, final extension step on 72°C 10 min. The sizes of amplified products were: *STin2.9* = 249 bp; *STin2.10* = 266 bp; *STin2.12* = 299 bp. Thermal PCR conditions for *5-HTTLPR/rs25531* were the following: initial denaturation 94°C 4 min, 35 cycles consisting of 94°C 30 s, 69°C 1 min 30 s, 72°C 1 min, final extension step on 72°C 10 min. The PCR products were then analyzed in 7% polyacrylamide gels stained with ethidium bromide. Subsequently, for detection of *rs25531* PCR products were digested with 3U of MspI (Fermentas, Canada) according to manufacturer's recommendations and resolved in 7% polyacrylamide gels. Product sizes for cleaved products were: L_A = 512 bp; L_G = 402 + 110 bp; S = 469 bp.

Statistical analyses

Genotype and allele frequencies of all polymorphisms, as well as Hardy–Weinberg equilibrium, were calculated

using Microsoft Excel macro PHARE version 2.1 (*http://bioinformatics.org/macroshack/programs/PHARE/description.html*).

To investigate single-genotype effects of all polymorphic loci on personality traits, we performed two-way multivariate analysis of variance (MANOVA) under SPSS 13.0 with sex as the second factor, followed by one-way analysis of variance (ANOVA). In these analyses, the genotypes were the independent factors, and the mean scores on the EPI and TCI scales were dependent variables. The distribution pattern of the psychological data was not different from a normal distribution. With respect to *5-HTTLPR* we conducted analyses under three models: dominant S model ($S/S + S/L_A + S/L_G + L_G/L_G + L_A/L_G$ vs. L_A/L_A), dominant L model ($L_A/L_A + L_A/L_G + S/L_A$ vs. $S/S + S/L_G + L_G/L_G$), genotype model ($S/S + L_G/L_G + S/L_G$ vs. $S/L_A + L_A/L_G$ vs. L_A/L_A), as there is evidence of equivalent expression of S and L_G alleles (Nakamura *et al.*, 2000). Although analyzing *STin2* polymorphism we distinguished the following two models: dominant 10R-model (*STin2.9* and *STin2.10* allele carriers vs. *STin2.12*/12) and dominant 12R-model (*STin2.12* carriers vs. other genotypes). The Bonferroni correction for multiple comparisons was applied for each questionnaire when performing ANOVA and MANOVA. The critical *P* value was established at 0.0083 (0.05/6) as considering six measured personality traits.

A measure of linkage disequilibrium between markers (D′, r^2) was obtained with EMLD software package (*http://epi.mdanderson.org/~qhuang/Software/pub.htm*). To test haplotype effects of the *5-HTT* gene on personality traits measured by EPI and TCI, we performed haplotype trend regression (HTR) analyses (Zaykin *et al.*, 2002) (*http://statgen.ncsu.edu/zaykin/htr.zip*). The critical *P* values less than 0.05 were considered statistically significant.

Results

Three hundred and one unrelated individuals were involved in genotyping and psychological assessment. The distributions of genotypic frequencies of all investigated markers were consistent with Hardy–Weinberg equilibrium (data available from the first author on request).

To test the hypothesis whether sex influences personality scores measured by EPI and TCI, we performed MANOVA with genotypes and sex as factors and personality scores as dependent variables. The obtained results indicate that women scored significantly higher on Neuroticism (EPI) ($P = 0.000$, $F = 17.393$), HA (TCI) ($P = 0.016$, $F = 5.838$), NS (TCI) ($P = 0.037$, $F = 4.389$), and RD (TCI) ($P = 0.000$, $F = 19.110$). Subsequently ANOVA was carried out separately in the male and female groups and in the overall sample. Although analyzing single-genotype effect of *5-HTTLPR* polymorphism, we did not find any significant effect on personality traits in the groups of males and females and in the overall sample. We have, however, revealed an effect of *STin2.10* allele on lower scores of HA (TCI) ($P = 0.008$, $F = 7.126$), whereas *STin2.12* allele scored higher on *P* (TCI) ($P = 0.016$, $F = 5.864$) in female carriers (Table 1). In the overall sample ANOVA revealed an effect of *STin2.10* allele on lower scores of Neuroticism (EPI) ($P = 0.007$, $F = 7.380$) and HA (TCI) ($P = 0.005$, $F = 7.971$) (Table 2).

Maximum likelihood analysis of haplotype distributions demonstrated the presence of linkage disequilibrium between all polymorphic loci in the overall sample (Table 3). Means for each personality trait in the overall sample using HTR analyses sorted by *5-HTT* haplotypes are shown in Table 4. HTR analyses showed that the most frequent haplotypes were L_A10, L_A12, and *S12* (Tables 4 and 5). Analyses of the distribution of the estimated haplotype frequencies revealed association of *S12* haplotype and low sociability-related traits such as Extraversion (EPI) ($P = 0.000$) and NS (TCI) ($P = 0.017$) and high anxiety-related personality traits such as HA (TCI) ($P = 0.043$). With respect to *S10*

Table 1 EPI and TCI mean scores and one-way ANOVA for *STin2* polymorphism in the overall sample

	STin2	Mean ± SD	F	*P* value	*n*
EPI					
Extraversion	10R-group	14.25 ± 3.66	2.276	0.132	166
	12R-group	13.89 ± 3.90	0.679	0.410	264
Neuroticism	10R-group	13.30 ± 4.48	7.380	**0.007**	166
	12R-group	14.02 ± 4.28	1.480	0.225	264
TCI					
Novelty seeking	10R-group	10.11 ± 3.35	0.115	0.735	166
	12R-group	9.97 ± 3.02	1.938	0.165	264
Harm avoidance	10R-group	8.28 ± 4.39	7.971	**0.005**	166
	12R-group	9.09 ± 4.65	2.240	0.136	264
Reward dependence	10R-group	8.57 ± 2.64	0.134	0.715	166
	12R-group	8.55 ± 2.62	1.930	0.166	264
Persistence	10R-group	2.57 ± 1.06	0.000	0.995	166
	12R-group	2.61 ± 1.10	3.398	0.066	264

10R-group: STin2.9 and STin2.10 allele carriers; 12R-group: STin2.12 allele carriers.
ANOVA, analysis of variance; EPI, Eysenck personality inventory; TCI, temperament and character inventory.
$P < 0.05$ are shown in bold.

Table 2 EPI and TCI mean scores and one-way ANOVA for *STin2* polymorphism in the group of healthy females

	STin2	Mean ± SD	F	*P* value	*n*
EPI					
Extraversion	10R-group	14.19 ± 3.83	1.255	0.264	129
	12R-group	13.84 ± 4.00	0.668	0.415	212
Neuroticism	10R-group	13.97 ± 4.24	3.861	0.051	129
	12R-group	14.56 ± 3.91	1.234	0.268	212
TCI					
Novelty seeking	10R-group	10.42 ± 3.44	1.033	0.310	129
	12R-group	10.12 ± 3.12	1.789	0.182	212
Harm avoidance	10R-group	8.55 ± 4.56	7.126	**0.008**	129
	12R-group	9.42 ± 4.61	1.801	0.181	212
Reward dependence	10R-group	8.96 ± 2.56	0.010	0.922	129
	12R-group	8.83 ± 2.62	3.586	0.059	212
Persistence	10R-group	2.54 ± 1.07	0.514	0.474	129
	12R-group	2.65 ± 1.09	5.864	**0.016**	212

10R-group: STin2.9 and STin2.10 allele carriers; 12R-group: STin2.12 allele carriers.
ANOVA, analysis of variance; EPI, Eysenck personality inventory; TCI, temperament and character inventory.
$P < 0.05$ are shown in bold.

Table 3 Linkage disequilibrium between each of two markers of the *5-HTT* gene

Marker 1	Marker 2	D′	r^2
5-HTTLPR	*STin2*	0.368	0.121
5-HTTLPR	*rs25531*	0.999	0.068
STin2	*rs25531*	0.753	0.054

haplotype, an association was observed with Extraversion (EPI) and HA (TCI).

As sex effect has been demonstrated earlier to affect some personality traits, we performed HTR analyses separately for men and women. We did not show any significant haplotype associations with personality traits in males that could be because of the small sample size. Haplotype frequencies for females did not significantly differ from those reported for the overall sample (Table 5). We observed that females with L_A10 haplotype, however, scored significantly lower on Neuroticism (EPI) ($P = 0.034$). Additionally, we observed that extraversion (EPI) ($P = 0.001$) and HA (TCI) ($P = 0.023$) scores in females were associated with *S12* and *S10* haplotypes, correspondingly, and that finding is in accordance with our results received for the overall sample.

Discussion

The main finding of this study is that *5-HTT* gene influences both anxiety-related and sociability-related traits in healthy young individuals from Russia. The association of the same haplotype and both anxiety-related and sociability-related traits was found to be in an opposite direction in some cases. Moreover, although performing statistical analyses, we grouped individuals in accordance with functional significance of *A/G* substitution polymorphism in *5-HTTLPR*. Although direct effect of *5-HTTLPR* polymorphism on any personality trait was not established, nevertheless the presence of haplotype effect on anxiety-related and sociability-related traits indicated the involvement of this polymorphism in the genetic architecture of personality. Furthermore, direct effect of *STin2* polymorphism was observed in HA (TCI) both in the overall sample and in the female group, and on Neuroticism (EPI) only in the overall sample. HTR analyses demonstrated that *S12* haplotype of the *5-HTT* gene was associated with Extraversion (EPI), NS (TCI), and HA (TCI), whereas *S10* haplotype was associated only with Extraversion and HA in the overall sample. Although controlling for sex, we observed the same trend for association in the female group. In addition, haplotype effect of L_A10 haplotype was found to influence Neuroticism in the female group only.

The frequencies of *5-HTTLPR* genotypes in our overall sample were in accordance with those of Nakamura *et al.* (2000) for the Caucasian population. The frequency of *STin2.10/10* genotype was higher and of *STin2.12/12* genotype was lower in our sample in comparison with those of earlier studies (Collier *et al.*, 1996; Melke *et al.*, 2001). Estimated allele frequencies of *rs25531* were congruent with those described earlier by Wendland *et al.* (2006). HTR analyses suggested that the most frequent haplotypes were L_A10, L_A12, and *S12*, what is consistent with earlier published data (De Luca *et al.*, 2006).

In this study, although performing MANOVA with sex as a second factor, significant differences on personality traits were observed between men and women. To our knowledge, many studies observed sex differences in personality traits indicating increased anxiety-related traits (neuroticism, HA) and decreased sociability-related traits (extraversion, NS) in women (Costa *et al.*, 2001; Else-Quest *et al.*, 2006). Although results for anxiety-related traits reported in this study are in accordance with those indicated above, high NS score in women could be compared with another study indicating higher

Table 4 Mean scores for *5-HTT* haplotypes for personality traits measured by EPI and TCI in the overall sample

Haplotype	L_A10	L_A12	L_G9	L_G12	*S10*	*S12*	Overall sample
Frequency[a]	0.271	0.187	0.016	0.051	0.055	0.385	–
Mean for EPI scales							
Extraversion	14.146 (0.650)[b]	14.200 (0.607)	14.505 (0.685)	15.029 (0.136)	**15.600[c] (0.006)**	**13.322 (0.0004)**	**13.953 (0.004)**
Neuroticism	13.576 (0.315)	13.672 (0.598)	14.403 (0.697)	14.134 (0.740)	14.501 (0.356)	13.967 (0.686)	13.894 (0.976)
Mean for TCI scales							
Novelty seeking	10.074 (0.787)	10.240 (0.407)	10.178 (0.872)	10.340 (0.548)	10.398 (0.412)	**9.686 (0.043)**	10.023 (0.254)
Harm avoidance	8.542 (0.232)	9.341 (0.279)	9.009 (0.953)	7.372 (0.061)	**7.440 (0.035)**	**9.506 (0.017)**	8.923 (0.130)
Reward dependence	8.471 (0.397)	8.743 (0.586)	8.702 (0.927)	8.766 (0.762)	8.887 (0.506)	8.536 (0.553)	8.618 (0.892)
Persistence	2.525 (0.663)	2.495 (0.497)	2.302 (0.435)	2.432 (0.503)	2.651 (0.578)	2.640 (0.153)	2.568 (0.686)

[a]The rare haplotype frequencies represent 0.035.
[b]*P* values are shown in brackets.
[c]Mean scores with $P<0.05$ are shown in bold.
EPI, Eysenck personality inventory; TCI, temperament and character inventory.

Table 5 Mean scores for *5-HTT* haplotypes for personality traits measured by EPI and TCI in the female group

Haplotype	L_A10	L_A12	L_G9	L_G12	*S10*	*S12*	Overall sample
Frequency[a]	0.264	0.189	0.017	0.053	0.067	0.406	–
Mean for EPI scales							
Extraversion	14.137 (0.483)[b]	14.407 (0.076)	14.043 (0.970)	14.435 (0.352)	14.559 (0.142)	**13.560 (0.001)[c]**	**13.973 (0.016)**
Neuroticism	13.188 (0.034)	13.476 (0.524)	14.418 (0.442)	13.535 (0.839)	14.164 (0.244)	13.938 (0.073)	13.900 (0.459)
Mean for TCI scales							
Novelty seeking	10.196 (0.361)	10.154 (0.604)	9.994 (0.974)	10.123 (0.847)	10.314 (0.449)	9.754 (0.051)	10.020 (0.179)
Harm avoidance	8.444 (0.134)	9.389 (0.169)	9.571 (0.577)	7.864 (0.202)	**7.568 (0.023)**	9.216 (0.098)	8.897 (0.182)
Reward dependence	8.633 (0.630)	8.703 (0.962)	8.648 (0.946)	8.791 (0.856)	8.988 (0.406)	8.710 (0.981)	8.630 (0.964)
Persistence	2.458 (0.318)	2.479 (0.600)	2.284 (0.406)	2.389 (0.452)	2.602 (0.574)	2.598 (0.125)	2.567 (0.600)

[a]The rare haplotype frequencies represent 0.004.
[b]*P* values are shown in brackets.
[c]Mean scores with $P<0.05$ are shown in bold.
EPI, Eysenck personality inventory; TCI, temperament and character inventory.

extraversion-like behavior in female captive lion-tailed macaques (*Macaca silenus*) (Rouff *et al.*, 2005). Both animal and human studies showed that females had higher serotonergic activity (Mann *et al.*, 2001). Different levels of personality traits in men and women could be explained under biological theories considering sex-linked hormonal differences. Particularly, Lu *et al.* (2003) reported that ovarian hormones influence on *5-HTT* protein expression in female macaques.

Several earlier studies suggested an association of *STin2* VNTR polymorphism and personality traits and different psychiatric disorders. According to Collier *et al.* (1996) the frequency of *STin2.12* allele in patients with bipolar affective disorder is elevated in comparison with controls. With respect to personality traits, it has been shown that carriers of *STin2.12* allele scored higher on one of the anxiety scales of Karolinska Scales of Personality (Melke *et al.*, 2001). Tsai *et al.* (2002) however, reported the association of *STin2.10/12* genotype and higher score on one of the subdimensions of HA (Tridimensional Personality Questionnaire) in healthy Han Chinese. In this study we found that individuals with *STin2.10* allele scored lower on neuroticism (EPI) and HA (TCI), traits related to anxiety, neuroticism and depression, whereas individuals with *STin2.12/12* genotype had higher scores on these personality traits. Our findings are in accordance with earlier published data indicating the presence of association of *STin2.12/12* genotype and HA (TCI) (Park *et al.*, 2006), *STin2.12* allele and anxiety-related traits (Karolinska Scales of Personality) (Melke *et al.*, 2001). Although performing ANOVA in the female group, we revealed association of *STin2.12* allele and higher P scores (TCI), however, it was lost after correction for multiple comparisons. Earlier published studies did not reveal influence of *STin2* polymorphism on P scores, however, there are some data indicating the association of S allele of *5-HTTLPR* polymorphism and high P scores (Benjamin *et al.*, 2000; Kim *et al.*, 2005). As *STin2.12* allele has been reported earlier to be in a partial linkage with S allele of the *5-HTTLPR* polymorphism (Ebstein, 2006), association of *STin2.12* allele and high P scores could be also observed.

Numerous studies have reported an association of *5-HTTLPR* polymorphism and anxiety-related traits and neuroticism (Lesch *et al.*, 1996; Gerra *et al.*, 2005; Dragan and Oniszczenko, 2006). It is, however, shown that the type of inventory used in a study plays a crucial role for detection of association (Munafo *et al.*, 2003). In this study, personality traits were assessed using two different questionnaires (EPI and TCI). Psychobiological model of personality (Cloninger *et al.*, 1993) assumes that mechanisms of neurotransmitter systems functioning underlie the personality traits measured by TCI. The Eysenck theory (Eysenck and Eysenck, 1994) also proposes that Extraversion and Neuroticism are biologically based traits, moreover, they underlie other traits assessed by

different questionnaires (for review, see Paris, 2005). Although some studies revealed positive associations of the *5-HTT* gene polymorphisms and neuroticism assessed by Eysenck Personality Questionnaire (Lerman *et al.*, 2000), most of the published studies involved tridimensional personality questionnaire/TCI measured traits (Hamer *et al.*, 1999; Benjamin *et al.*, 2000; Tsai *et al.*, 2002).

In this study, we found that individuals with S allele of *5-HTTLPR* polymorphism in a combination with *STin2.12* allele scored higher on HA (TCI), whereas opposite association was observed between *S10* haplotype and this personality trait in the overall sample. As single effect of *STin2* polymorphism on anxiety-related traits was reported, this finding points to the stronger effect of *STin2* polymorphism on HA score, indicating that the presence of *STin2.12* allele predispose to the higher HA score. At the same time many studies did report that S allele was associated with neuroticism and anxiety-related traits (Lesch *et al.*, 1996; Gerra *et al.*, 2005; Dragan and Oniszczenko, 2006). As we considered the hypothesis that L_G allele of *5-HTTLPR* is functionally equal to S allele and correspondingly grouped individuals, our data could not be directly compared with the published one, examining only the direct influence of S or L allele of *5-HTTLPR* on anxiety-related traits in healthy individuals.

It has been known that anxiety-related traits could predispose to suicide behavior; curiously, the direction of the association seems to be opposite to that shown in our earlier study (Gaysina *et al.*, 2006) in which Russian female carriers of *S12* haplotype had a lower risk of suicidal behavior. This discrepancy could be explained by the difference in the mean age of the participants recruited for these studies. Moreover, some decline in anxiety-related traits with age was revealed (Allemand *et al.*, 2007). Age of the individuals plays a critical role in the assessing of personality traits that are covered by influence of socio-cultural factors during the life. The mean age of our sample is 19.85 years, whereas in the previously mentioned study women were nearly twice as old: 39.24 years (controls) and 33.42 years (suicide attempters).

We also revealed a significant association of *S12* and *S10* haplotypes and Extraversion (EPI) and NS (TCI). Furthermore, individuals with *S12* haplotype had lower scores on these traits, whereas carriers of *S10* haplotype scored higher on Extraversion (EPI) in the overall sample. In the female group association remained significant only in direction to carriers of *S12* haplotype and lower Extraversion score. As there was no observed single-genotype effect either of *5-HTTLPR* or *STin2* polymorphisms, the presence of specific haplotype could explain variation in direction to sociability-related traits. There is some evidence of influence of S allele of *5-HTTLPR* on lower scores of sociability-related traits, such as Agreeableness (Greenberg *et al.*, 2000); Exploratory excitability (one of the subdimensions of NS) (Samochowiec *et al.*, 2004); Activity and Endurance (Dragan and Oniszczenko, 2006). Here, we described the tendency to score in opposite direction for *S10* and *S12* haplotypes with respect to anxiety-related and sociability-related traits. According to Vormfelde *et al.* (2006) this finding may have contributed to inconsistencies in earlier studies with populations not stratified for the *STin2* polymorphism. Together with observed opposite trends of association with *S12* and *S10* haplotypes, this scientific group revealed that male carriers of *S10* haplotype scored lower on anxiety-related traits and higher on NS, whereas *S12* haplotype was associated with higher anxiety-related traits in men (Vormfelde *et al.*, 2006). Controversially, we revealed the same association for women and for the overall sample, but not for men. As anxiety-related and sociability-related traits are mediated by the same haplotype but in the opposite direction, obtained results could be interpreted in line with the hypothesis suggested by Comings *et al.* (2000). According to this hypothesis, genes of each neurotransmitter system are implicated in the development of most personality traits; moreover, genes of one system may be positively correlated with one trait, but negatively with another trait. Our results support the idea that a single neurotransmitter can influence multiple personality traits.

Our data indicate that healthy female individuals with L_A10 haplotype have lower scores on Neuroticism scale (EPI). As it is mentioned above, *STin2.10* allele is associated with anxiety-related traits in this study. Moreover, many studies showed that carriers of *5-HTTLPR*L/*L* genotype scored lower on anxiety-related traits (Osher *et al.*, 2000; Sen *et al.*, 2004; Dragan and Oniszczenko, 2006). We should, however, emphasize that the association of L_A10 haplotype was true for women only. A biological explanation of this finding may involve the presence of strong linkage disequilibrium between L allele of *5-HTTLPR* and *STin2.10* allele and hormonal influence on *5-HTT* gene.

Recently, Zalsman *et al.* (2006) showed that lower expressing L_G allele predicted greater severity of major depression compared with the higher expressing L_A allele. No data representing influence of *A/G* substitution located in *5-HTTLPR* (*rs25531*) or haplotype-mediated associations on personality traits in healthy individuals is, however, observed. Taking into account an expression profile of S and L_G allele, we hypothesized that carriers of L_G allele probably would have influence on the same traits as carriers of S allele. Unfortunately, HTR analyses did not reveal associations of L_G12 haplotype either with anxiety-related traits or with sociability-related traits as in the case of *S12* haplotype association. As the frequency of L_G12 haplotype was rather small in this study (0.051)

the influence of this haplotype on personality traits could become statistically significant taking more individuals into analyses.

Although these findings are in agreement with earlier studies, the results should be interpreted with caution. First, some haplotypes (L_G9, L_G12) were observed with low frequencies suggesting that larger sample size probably could allow detection of associations of these haplotypes and personality traits. Second, we considered the effect of one gene (*5-HTT*) on the personality traits. Growing evidence, however, shows that polymorphisms of neurotransmitter systems genes can interact at the molecular level. Third, despite the age and education homogeneity of our sample we were not able to consider the influence of different environment factors, such as parenting treatment, the order of birth, and religiousness. As the study was conducted in the group of individuals from Russia, the country geographically located between European and Asian regions, there could be cultural influence of either traditional or progressive society on personality traits.

It should also be noted that association studies of unrelated individuals, such as reported here, warrant cautious interpretation as unknown sources of population stratification may affect the results (Greenberg *et al.*, 2000). Differences in allele frequencies of *5-HTTLPR* and *STin2* polymorphisms have been observed in various populations. It has been reported that frequency of *5-HTTLPR*L* allele was higher than 70% in African and African–Americans (Esau *et al.*, 2008), 60% in Europeans (Hranilovic *et al.*, 2003; Reneman *et al.*, 2006) and a 30% or lower in the Japanese (Murakami *et al.*, 1999) and Indian populations (Guhathakurta *et al.*, 2006). Population differences in frequencies of *STin2*.9, *STin2.10*, and *STin2.12* repeat alleles are known as follows: 3, 30, and 67%, correspondingly, in Europeans (Gelernter *et al.*, 1998; Lauzurica *et al.*, 2003), 1, 24, and 75% in Africans (Gelernter *et al.*, 1998) and 0, 10, and 90% in Chinese (Shen *et al.*, 2004).

Considering known allele frequency differences among different ethnic groups, further cross-cultural studies with a larger sample should be carried out. Further studies are needed to consider gene–gene and gene–environment interactions to produce reliable data on genetic mechanisms of personality traits.

In conclusion, this study demonstrates the influence of *STin2* polymorphism rather than haplotype effect of *5-HTT* gene polymorphisms on anxiety-related traits in women and in the overall sample. Controversially, significant haplotype effect was observed on sociability-related traits. The presence of association of the same haplotype and both anxiety-related and sociability-related traits does not confirm Cloninger's hypothesis. In contrast, the hypothesis suggested by Comings *et al.* (2000) is supported by our results, indicating that a single neurotransmitter can influence multiple personality traits. This study implies the necessity of further investigation of *5-HTTLPR* together with *A/G* substitution (*rs25531*) in relation to personality traits in healthy individuals.

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