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Interaction of monoamine transporter genes and personality dimensions

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There is evidence for an association between allelic variants of the monoamine transporter genes and the temperamental personality traits. Recent findings show that also an interaction of the different genes may contribute to the personality factors. Character dimensions of personality, which theoretically depend mainly on the ontogenetic development, were suggested to be under the genetic influence as well. We studied the association between personality dimensions measured with Temperament and Character Inventory (TCI) and polymorphism of the dopamine (DAT), norepinephrine (NET) and serotonin (5-HTT) transporter genes. The sample studied consisted of 128 healthy volunteers: 76 females and 52 males, mean age 23.8±1.7 years, derived from two cities in the western part of Poland. We found statistically significant association between character dimension of Self-Directedness (SD) and NET polymorphism. There was a statistically significant effect of the interaction of NET and DAT polymorphisms on the dimension of Self-Transcedence (ST). The temperamental dimension of Reward Dependence (RD) was associated with interaction of 5-HTT and DAT polymorphisms. Character dimensions of personality, Self-Directedness and Self-Transcendence were associated with genetic differences. Interaction effect of the transporter polymorphisms was demonstrated in the Self-Transcendence and Reward Dependence dimensions. These findings warrant further study on the interplay of the different genes contributing to the complex traits.

Key words: monoamine transporter genes, personality, dimensions

Introduction

In 1993, the seven-dimensional model of personality including three scales assessing the temperament and four scales for the assessment of character was proposed [1]. Temperament and Character Inventory (TCI) based on that model, consisted of 240 questions for the self-assessment of personality. According to Cloninger, tem-

peramental dimensions of personality depend mainly on the genetic influence and character dimensions are the result of ontogenetic development. It was proposed that, the temperament consists of four dimensions: novelty seeking (NS), harm avoidance (HA), reward dependence (RD) and persistence (P). Novelty seeking is defined as the tendency to respond actively to novel stimuli. Harm avoidance reflects a tendency for inhibitory response to signals of aversive stimuli. Reward dependence measures the tendency for a positive response to the signals of reward, and persistence is understood as the ability towards sustaining the activity despite the obstacles. The measures of character include self-directedness (SD), cooperativeness (C) and self-transcendence (ST). Self-directedness refers to the ability to control and adapt the behaviour to the situation in accord with one's goals. Cooperativeness is related to identification with and understanding of the other people. The third dimension of the character- self-transcendence may be perceived as associated with spirituality and reflects the one's ability to identify with the world as the whole.

Monoamine transporters are the membrane proteins localised in the presynaptic neurones, whose main function is the uptake of neurotransmitters from the synaptic cleft, and thus termination of transmission [2]. Dopamine (DA), norepinephrine (NE) and serotonin (5-HT) are monoamines, which are essential in mediating behaviour. Transporter proteins were shown to regulate the turnover and metabolism of DA, NE and 5-HT. Monoamine transporter genes were recently mapped and reported to show polymorphisms- existence of the different alleles in the same loci. Dopamine transporter (DAT) gene was located on chromosome 5p15.3 [3]. Serotonin transporter (5-HT) gene and norepinephrine transporter (NET) gene were assigned respectively to chromosomes 17q12 [4, 5] and 16q12 [6, 7].

The evidences from the twin studies show, that variation in the personality factors may be in part genetically determined [8]. Due to the essential role of the neurotransmitters in behaviour and the existence of allelic variants of the monoamine transporter genes, these were proposed to be associated with differences in personality dimensions. Polymorphism in the promoter region of serotonin transporter 5-HTTLPR was suggested as a factor in anxiety related traits, such as neuroticism and harm avoidance [9]. However, the attempts to replicate this finding did not show any conclusive results [10, 11].

The psychological constructs, such as personality dimensions might be perceived as highly complex phenotypic effects. This allows the suggestion that, the cooperation of many genes is important in influencing such traits (thus personality dimensions are called the quantitative traits). Genes with a relatively small effect on the specific phenotype are described as situated at quantitative trait loci (QTL).

In the light of the role of monoamine transporters in the many functional systems in the brain, a suggestion that a single transporter gene variant may affect different personality factors seems also highly probable.

Interaction of monoamine neurotransmitter systems was proven in the pharmacological studies. Despite their relative specificity, monoamine transporters may be responsible for the uptake of the non-specific transmitters from the synaptic cleft [12]. The effect of the single allelic variant of the gene may create the different environment for another gene, which made us to look for the combined influence of the different transporter genes on the personality dimensions.

Methods

Probands

One hundred twenty eight healthy volunteers, medical students, 76 females and 52 males, mean age 23.8±1.7 years, derived from two cities in western part of Poland: Szczecin (52 probands) and Poznań (76 probands) were recruited for the study. The study protocol was approved by the Ethics Committees of the University of Medical Sciences in Poznań and Pomeranian Medical University in Szczecin. Written informed consent was obtained from all participants. All subjects were unrelated individuals of Polish descent.

TCI assessment was performed without knowledge of the genotypic status. In this study we used the Polish translation of TCI, which was validated earlier [13].

DNA Analyses

Genomic DNA was extracted from anticoagulated venous blood samples or lymphoblastoid cell lines using a salting out method [14]. The DAT VNTR is located in the 3' untranslated region of the gene. It was genotypised as described by Sano et al. [15]. Oligonucleotide primers DATF1 (5'-TGT GGT GTA GGG AAC GGC CTG AGA-3') and DATR1 (5'-TGT TGG TCT GCA GGC TGC CTG CAT-3') were used to amplify across the VNTR region. A functional polymorphism in the promoter region of serotonin transporter gene, where 44 bp are either inserted (long allele- l) or deleted (short allele- s) was analysed. Oligonucleotide primers 5HTTF1: (5'-CAA TGT CTG GCG CTT CCC CTA CAT AT-3') and 5HTTR1: (5'-GAC ATA ATC TGT CTT CTG GCC TCT CAA G-3') [16] were used to amplify using PTC 100 thermocycler. An exonic silent RFLP (1287A) in the NET gene was analysed as previously described by Jonssons et al. [17]. Oligonucleotide primers 8F (5'-TCC AGG GAG ACC CTA ATT CC-3') and 8R (5'-TTG ACT TTA TTG AAA TGC GGC-3') were used to amplify a PCR fragment of 241 bp lenght.

Psychometric evaluation

Assessments of personality trait markers with Temperamental and Character Inventory – (Polish version – 240 questions items) [13] was performed in a Polish group of 128 medical students.

The TCI is a self-report instrument of yes/no answers assessing the personality dimensions, Novelty Seeking (40 items), Harm Avoidance (35 items), Reward Dependence (24 items), Persistence (8 items), Self – Directedness (44 items), Cooperativeness (42 items), Self-Transcendence (33 items).

Statistical analysis

All statistical analyses were performed using SPSS for Windows. The effect of genotype on personality factors was examined by ANOVA. 5-HTT polymorphsim was grouped accordingly to its functional significance (l/l and l/s, s/s) [9]. NET polymorphism was grouped according to the results of Jönson et al. [17] analysis (g/g and g/a,

a/a). DAT polymorphism was divided on the (10/10) and (10/9 and 9/9) genotypes, according to the suggested role of the 9 allele on the dopaminergic function [18, 19]. Thus we assumed, that (s), (a) and (9) alleles of respectively serotonin, norepinephrine and dopamine transporters have the dominant effect.

Results

Analysis of main effects

There were no significant relationships between the temperamental dimensions of TCI (NS, RD, P, HA) and examined neurotransmitter gene transporters compared by ANOVA. There was a statistically significant increase in the Self-Directedness (SD) score in individuals with genotype g/g of NET in comparison with heterozygotes and a/a homozygotes (F=6.26, df=1;97, p=0.014), results shown in Table 1. No association was found between NET, DAT and 5-HTT polymorphism and the two others character dimensions (C, ST).

Analysis of two-way interactions

Table 1

Means and standard deviations in the self-directedness (SD) scores in individuals with different NET genotypes

NET genotype	N	Mean SD score	Sd
G/G	46	32.54	5.85
G/A+A/A	59	29.39	6.54

[Main effect: F=6.26; df=1; 97; p=0.014]

There was a statistically significant effect of the interaction of NET and DAT polymorphisms on the dimension of Self-Transcedence (ST). The homozygotes 10/10 (DAT) and with concurrent genotype g/g (NET) scored significantly lower on the ST, than homozygotes 10/10 (DAT) with genotypes a/a and a/g (NET) (F=5.51, df=1;99, p=0.021). Individuals 9/10 and 9/9 (DAT) show no difference in respect to the ST dimension, whether they present NET homozygosity g/g or other NET genotype (a/a or a/g), results shown in Table 2.

The dimension of reward dependence was associated with interaction of 5-HTT and DAT polymorphisms. Individuals with DAT homozygosity 10/10 and the concurrent

Table 2

Means and standard deviations in the self-transcendence (ST) scores in individuals with different DAT and NET genotypes.

	NET genotype						Simple effect
	G/G			A/G+A/A			
DAT genotype	N	Mean	Sd	N	Mean	Sd	
10/10	25	11.88	5.30	35	16.54	5.78	P=0.01
9/9 +9/10	23	14.04	6.41	24	14.21	6.70	NS
Simple effect	NS			NS			

[Interaction effect: F=5.51; df=1; 99; p=0.021]

homozygosity l/l (5-HTT) scored lower on the RD scale than homozygotes 10/10 with deletion in 5-HTT (s/l and s/s) ($F=117.54$, $df=1; 100$, $p<0.01$). For individuals with genotype 9/10 and 9/9 (DAT) no differences were found between individuals with and without deletion in 5-HTT.

Individuals with deletion in 5-HTT (s/l and s/s) scored higher in RD if they were homozygous 10/10 (DAT) than individuals with accompanying genotypes 9/9 and 9/10 (DAT) ($F=108.52$, $df=1; 100$, $p<0.01$). Individuals without deletion in 5-HTT (l/l) showed no differences in RD whether they present DAT genotype 10/10 or 9/10+9/9. Results are shown in Table 3.

Analysis of three-way interactions

Table 3

Means and standard deviations in the reward dependence (RD) score in individuals with different 5-HTT and DAT genotypes

	5-HTT genotype						Simple effect
	S/S +S/L			L/L			
DAT genotype	N	Mean	Sd	N	Mean	Sd	
10/10	10	16.70	2.67	6	11.83	3.43	P<0.01
9/9 +9/10	18	13.61	3.46	5	16.00	1.67	NS
Simple effect	P<0.01			NS			

[2-way interaction effect: $F=8.72$; $df=1; 100$; $p=0.004$]

Examination of combined effects of all the three polymorphisms did not show any significant association with any of the personality dimensions measured with TCI.

Discussion

The personality dimensions are constructs of high complexity and probably are affected with the genetic and the environmental influences. Recently, theoretical division of the personality on the temperament (genetically determined) and character (environmentally determined) was questioned. The association between the functional polymorphism in the 5-HTT with the character traits of cooperativeness and self- directedness was reported [20]. In our study we cannot replicate this finding, however we report an association between polymorphism in the NET gene and self-directedness. Genotype g/g was associated with higher scores in the self-directedness, than genotypes a/g and a/a. The NET polymorphism does not necessarily results in functional changes in the norepinephrine system however, we cannot exclude the existence of functional polymorphism located in the NET gene which is in a linkage disequilibrium with the studied polymorphism. Association between G1287A polymorphism and cerebrospinal fluid levels of 3-methoxy-4-hydroxyphenylglycol- main NE metabolite may support this assumption [17].

Increasing number of studies [21, 22, 23, 24] reveal that complex traits, such as personality dimensions are influenced with interactions of the genes. We found, that co-occurrence of the homozygosity in DAT loci (10/10) and in the NET loci (g/g) leads to the lower scores in the ST scale, than occurrence of the DAT genotype 10/10 with a/g and a/a genotypes of NET. The other combinations of these genotypes did not show association with any personality dimension. We report no other association between character dimensions and combined two- and three-way effects of the genetic polymorphisms studied.

These findings should be interpreted cautiously. However, we may suggest that g/g genotype- linked hypothetically to increased norepinephrine metabolism [17] is associated with higher SD (the ability to realise one's goals). And the concurrent homozygosity (10/10)- causing higher expression of the DAT [25] leads to lower ST score (spirituality).

We found only one of the temperamental dimensions- Reward Dependence is associated with the combined effects of the polymorphisms in the 5-HTT and DAT genes. 5-HTT polymorphism was proposed to be related to neuroticism and HA, and allelic variant of DAT (9) was found to be associated with low scores on the NS scale [26]. In our study we did not replicate these findings. However we found that combined effects of these polymorphism may affect Reward Dependence. Individuals with deletion in 5-HTT alleles (s/l and s/s) associated with a reduced level of serotonin transporter, if they are homozygous for 10 allele of DAT score higher in RD scale than 9 DAT allele carriers. Individuals without deletion in 5-HTT gene do not show differences in RD scale, whether they carry 9 DAT allele or not. At the same time, homozygotes (10/10) (DAT) score lower on RD scale, if they are homozygous for the long variants of 5-HTT, than carriers of the short allele of the 5-HTT. For 9 allele DAT carriers there were no differences between homozygotes l/l 5-HTT and 5-HTT short allele carriers.

These results may implicate that combined DAT and 5-HTT polymorphisms are associated with RD. DAT polymorphism is situated in the non-translated part of the gene, however it is possible that the functional polymorphism exists in the linkage disequilibrium with the studied polymorphism, which affects dopamine transmission. DAT (9) allele is associated with the more severed effects of ethanol withdrawal [19] and the lower risk of cigarette smoking [18] and in the neuroimaging studies was related to lower expression of dopamine transporter. Regarding the two genes studied, the highest score in RD scale would be associated with a combination of low serotonergic function and concurrent high DAT expression - genotype (10/10).

Our study has some limitations. The sample studied was relatively small. Due to the low number of the specific allele carriers we decided to group genotypes according to dominant/ recessive gene model, nevertheless this procedure was consistent with the conclusions of previous studies. The population studied was homogenous and consisted only of medical students of young age, thus the results warrant confirmation on the larger population. We used a Polish version of the TCI, however its reliability was confirmed earlier on the same sample of individuals. Individuals studied did not undergo thorough psychiatric nor psychological examination.

In conclusion, our results confirm the assumption that differences in personality dimensions are influenced by genetic factors. We replicated somewhat counterintui-

tive findings of Hamer et al. [20] that character traits may also depend on the genetic influence. Despite earlier propositions that a single neurotransmitter system is linked to the single dimension of temperament, we postulate that multiple interactions of allelic variants, belonging to different monoamine transmitter systems, may affect personality traits. The influence of NET polymorphism on both self-directedness and self-transcedence suggests also that single polymorphism may affect several personality dimensions.

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