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Genes encoding for AP-2β and the Serotonin Transporter are associated with the Personality Character Spiritual Acceptance

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Abstract

In several twin studies the relative contribution of genetic factors for personality traits has amounted to figures between 40 and 60%. In the present study we investigated to which degree polymorphisms in the 5-HTT and AP-2β genes are implicated in the neural processes involved in the formation of Temperament and Character traits, as estimated by Cloninger's TCI. Considering the background of previous reports, associations with the character Self-Transcendence and its sub-scale Spiritual Acceptance in particular, were of interest. A stratified random sample of 200 individuals (total population = 5173), matched for age, gender and risk behaviors, from volunteering 16- and 19-year-old adolescents students in Sweden was investigated. Cloninger's TCI inventory was used for investigation of temperament and character traits. Blood samples were used for analyses of a promoter serotonin transporter polymorphism (5-HTTLPR) and an intron 2 polymorphism in the transcription factor AP-2β gene. Among boys individuals with presence of the short 5-HTTLPR genotype showed lower scores, whereas individuals with presence of the short AP-2β genotype showed higher scores of personality character Self-Transcendence and its sub-scale Spiritual Acceptance. Among girls no effect of either genotype was found. Both among boys and girls, significant interactive effects were found between 5-HTTLPR and AP-2β genotypes, with regard to Self-Transcendence and Spiritual acceptance. Boys and girls with the combination of presence of the short 5-HTTLPR, and homozygosity for the long AP-2β genotype scored significantly lower on Self-Transcendence and Spiritual Acceptance.

Keywords: Spirituality; Genes; Personality; Adolescent; Serotonin; Transcription factor AP-2

In several twin studies the relative contribution of genetic factors for personality traits has amounted to figures between 40 and 60% [4]. In Cloninger's biosocial theory of personality, using the Temperament and Character Inventory (TCI), especially the temperament dimensions are thought to be associated with activity in specific central neurotransmitter systems [9,10,38]. The Character dimension Self-Transcendence is, however, the most stable TCI dimension over time and is also one of the TCI dimensions showing the largest variability among individuals [7]. The TCI character Self-Transcendence consists of three subscales: Spiritual Acceptance, Transpersonal Identification and Self-Forgetfulness.

In a recent Positron Emission Tomography (PET) study, using the (^{11}C) WAY100635 ligand, an association was found between 5-HT1A receptor binding potential and Self-Transcendence scores in healthy, male subjects [3]. This association, however, rested completely on the sub-scale Spiritual Acceptance, which measures an individual's apprehension of phenomena that cannot be explained by objective demonstration. Similar findings have also been reported with regard to associations of genotypes of the 5-HT1A receptor [30], of the 5-HT2A and 5-HT6 receptors [24], and of the dopamine D4 receptor [12] with regard to Self-Transcendence.

A serotonin transporter promoter polymorphism (5-HTTLPR), consisting of a variable number of tandem repeats (VNTR), has been studied extensively in relation to personality and psychiatric disorders [11,28,32]. Functionality studies have shown that 5-HTT gene transcription is differentially

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modulated by the long and short variants of the 5-HTTLPR, where the short variant is associated with lower expression of 5-HTT and lower 5-HT re-uptake activity [11].

In the mammalian central nervous system, members of the transcription factor AP-2 family (primarily the AP-2α and AP-2β isoforms) are important regulatory proteins for gene expression and neural development [34]. Target genes for AP-2 have been identified, e.g. within in brainstem monoaminergic systems [21]. The human gene, encoding transcription factor AP-2β includes a four base-pair repeat polymorphism in the second intron, which has been linked to anxiety-related personality traits [14,16], binge-eating disorder [18] and CSF levels of homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) [13]. Moreover, brainstem levels of AP-2β are positively correlated to 5-HT and DA metabolism in the frontal cortex of rats [15]. Recently, there has also been reports on associations between an intron 1 AP-2β polymorphism and type 2 diabetes [31]. The 5′-flanking region of 5-HTT contains binding sites for AP-2, suggesting a regulatory role for AP-2 in the expression of the 5-HTT gene expression [6].

In the present study we tested the hypothesis that the 5-HTT and AP-2β genes are implicated in the neural processes involved in the formation of the TCI personality character Self-Transcendence, and, in particular, the sub-scale Spiritual Acceptance. Besides this main hypothesis, possible associations between the 5-HTT and AP-2β genotypes and other TCI temperament and character dimensions were also investigated.

All 16- and 19-year-old students in secondary school in a medium-sized county of Sweden, i.e. 2987 ninth graders and 2186 third graders, comprised the target population. The students were asked to complete a mental and psycho-social health-screening questionnaire, “Survey of Adolescent Life in Vestmanland (SALVe)” during a 1-h session under the supervision of a specially trained research assistant. A stratified random sample of 400 students, matched for age, gender and risk behaviors were drawn from the volunteers. Written informed consent was obtained from 81 boys and 119 girls who agreed to give blood samples and to take part in an interview when asked to participate a second time (in line with recommendations from the human ethical committee of the Medical Faculty, Uppsala University). For a further description of the participants, see Ref. [35].

The Temperament and Character Inventory (TCI) 238-question form, Swedish version, was used in the study. Venous blood was drawn from all interviewed students. One boy and one girl were excluded due to hepatitis infection. DNA was extracted from venous blood and PCR-based genotyping of the AP-2β intron 2 polymorphism was performed as previously described [16]. PCR-based genotyping was performed according to a modified protocol by Collier to investigate the 5-HTTLPR [11]. In order to confirm that the correct regions of the AP-2β gene and the 5-HTT gene were amplified, PCR products representing all genotypes were sequenced using BigDye®Terminator chemistry (Applied Biosystems) and analyzed by an automated ABI PRISM™, Perkin-Elmer, Foster City, CA, USA). The DNA fragments were analyzed using the Squencer™ 3.1.1 software.

Wilcoxon (Mann–Whitney) rank sum test was used to explore differences in TCI scores with regard to the 5-HTT and AP-2β genotypes. To explore gene–gene additive effects Kruskal-Wallis test was used. The gene–gene interaction was tested using a non-parametric test for interaction based on aligned ranks [36]. These tests were selected due to the skew distribution of the dependent variables in our sample. A two-sided p-value < 0.05 was considered significant in all analyses of main effects and <0.1, when testing for the presence of interactions [20].

One boy and one girl had incomplete TCI-forms and were excluded from the study. Among boys 31 individuals were homozygous for the long allele of the 5-HTTLPR gene polymorphism (5-HT-LL), 30 were heterozygous and 18 homozygous for the short allele (5-HT-LS/SS). Among girls, the corresponding figures were 31, 60 and 26, respectively. The distribution of allelic long/short variants did not differ significantly across boys and girls ($\chi^2 = 2.58$, d.f. = 1, p = n.s.). Using Wilcoxon (Mann–Whitney) rank sum test, there were significantly higher scores for Self-Transcendence ($p = 0.04$) among the boys with genotype LL. No significant association was found in girls or in boys with any other TCI temperament or character dimension (Novelty Seeking, Harm Avoidance, Reward Dependence, Persistence, Self Directedness or Cooperativeness). The difference with regard to Self-Transcendence rested completely on results with the sub-scale Spiritual Acceptance ($p = 0.02$) (Table 1).

With regard to transcription factor AP-2β intron 2 polymorphism, 33 boys were homozygous for the long $[CAAA]_5$ allele (AP-2β-LL), 34 were heterozygous (AP-2β-LS) and 12 homozygous for the short $[CAAA]_4$ allele (AP-2β-SS). The corresponding figures for the girls were 46, 52 and 19, respectively. Among the boys the only significant difference found between AP-2β-LL and AP-2β-LS/SS genotypes was that presence of the short allele (AP-2β-LS/SS) was significantly associated with high scores in the TCI character Self-Transcendence ($p = 0.03$). Similarly to the findings with the 5-HTTLPR genotype, this difference rested completely on its sub-scale Spiritual Acceptance ($p = 0.002$) (Table 1). Among the girls, no such association was found with regard to Spiritual Acceptance (Table 1) or any TCI temperament or character trait (data not shown).

In the analysis of gene–gene additive effects with Kruskal-Wallis test we found that 5-HTT and AP-2β had significant additive effects among boys in both Self-Transcendence and Spiritual Acceptance whereas no such additional effects were found among girls (Table 2, columns A and C). Boys that carried the short 5-HTTLPR allele (5-HT-LS/SS), as well as being

Table 1
Mean ranks and p-values for 5-HTTLPR and AP-2β genotype respectively

Wilcoxon rank sum test	Genotype 5-HTT			Genotype AP-2β		
	LL	LS/SS	p	LL	LS/SS	p
Boys	$n = 31$	$n = 48$		$n = 33$	$n = 46$	
Self-Transcendence	46.53	35.78	0.04	33.27	44.83	0.03
Spiritual Acceptance	47.23	35.33	0.02	30.48	46.83	0.002
Girls	$n = 31$	$n = 86$		$n = 46$	$n = 71$	
Self-Transcendence	62.05	57.21	0.49	56.73	59.62	0.65
Spiritual Acceptance	61.52	57.40	0.56	56.31	59.89	0.57