Associations Between an Alpha 2a Adrenergic Receptor Gene Polymorphism and Adolescent Personality

Jarek Mäestu,1* Jüri Allik,1 Liis Merenäkk,2 Diva Eensoo,2 Jüri Parik,3 Toomas Veidebaum,4 and Jaanus Harro1

1Department of Psychology, Centre of Behavioural and Health Sciences, University of Tartu, Tartu, Estonia
2Department of Public Health, Centre of Behavioural and Health Sciences, University of Tartu, Tartu, Estonia
3Department of Evolutionary Biology, University of Tartu, Tartu, Estonia
4National Institute for Health Development, Centre of Behavioural and Health Sciences, University of Tartu, Tartu, Estonia

The aim of this study was to investigate the impact of the C-1291G polymorphism in the promoter region of the alpha 2A adrenoreceptor gene (ADRA2A) to the personality traits. In the present study, data of the younger cohort of the Estonian Children Personality Behaviour and Health Study was used (N = 419). Personality traits were assessed by 240-item (Estonian Personality Item Pool NEO (EPIN-NEO)). Restriction enzyme MspI was used after PCR amplification to genotype the subjects according to C-1291G polymorphism of the ADRA2A. There were no significant differences on the level of the Big Five personality domains between genotypes; however, there were three significant differences on the level of different subscales. The subjects with GG genotype had significantly higher scores on Depression and significantly lower scores on Morality and Orderliness compared to subjects with CC and CG genotypes. There was a significant interaction between sex and ADRA2A polymorphism regarding E1, Friendliness; E2, Gregariousness; and E6, Cheerfulness. With CC and CG genotypes girls had higher scores on extraversion scales than boys, but with GG genotype boys score higher than girls with GG genotype. It is concluded that the gene polymorphism in the ADRA2A has an influence on personality traits in adolescents.

KEY WORDS: α2A adrenoreceptor; gene polymorphism; personality; noradrenergic system; EPIN-NEO

INTRODUCTION

Numerous family, adoption, and twin studies have demonstrated moderate to high genetic influence on personality dispositions [Loehlin, 1992; Jang et al., 1996; Riemann et al., 1997; Plomin and Caspi, 1999]. Although the progress in identifying individual genes responsible for heritability of personality dispositions has been slower than expected, several complex polymorphisms have been demonstrated to influence personality traits [Ebstein, 2006]. However, even though several genetic polymorphisms have been reproducibly linked to personality features or abnormal behavior in psychiatric patients, success in establishing associations between personality traits in healthy population and specific genes has been remarkably limited. The original association between a facet of extraversion, novelty-seeking, and a polymorphism in the dopamine D4 receptor gene [Ebstein et al., 1996] was not well reproduced in subsequent studies [Paterick et al., 1999]. Nevertheless, this exon III variable number of tandem repeats polymorphism of the DRD4 gene has become established to be associated with the attention-deficit hyperactivity disorder [Brookes et al., 2006], even if the impact of this polymorphism alone may be small [Faraone and Biederman, 2002]. The second best characterized candidate, the serotonin transporter gene promoter polymorphism often referred to as 5-HTTLPR is linked to neuroticism and other anxiety-related traits, such as harm avoidance [Munafo et al., 2003], but when patients are excluded from meta-analyses, this association is very weak [Munafo et al., 2005]. It is thus possible that association of personality with the hereditary aspects of function of key proteins in the CNS can be established only by focusing on more specific aspects of personality.

It is conceivable that the third major monoaminergic network, the noradrenergic system, may control personality traits as well. The noradrenergic system, in particular the projections ascending from the locus coeruleus (LC), acts as a central arousal system and has been implicated in attention, vigilance and memory, its dysfunction leading to irritability, hostility, anxiety, and depression [Harro and Oreland, 2001]. A key protein in the control of balance in this system is the α2 adrenoceptor, particularly the α2A subtype. Adrenergic alpha 2A (α2A) receptors are G protein-coupled receptors that mediate important physiological responses, particularly in the cardiovascular system and CNS and therefore directly or indirectly participate in all aspects of stress and arousal, including cognitive functions, cardiovascular responses, and metabolic effects [Lafontan and Berlan, 1993]. α2A-Adrenergic receptors control the release of other neurotransmitters such as serotonin as presynaptic heteroreceptors; they are especially important in sustaining the balanced activity of noradrenergic neurotransmission by serving not only as terminal autoreceptors but also somatodendritic autoreceptors that control the noradrenergic cell firing. Thus, it is not surprising that several psychiatric conditions are associated with changes at the α2A adrenergic receptor protein level. For example, binding
studies in post mortem brains showed an increase in $\alpha_2$ receptor density in suicide victims compared to controls [De Paermentier et al., 1997], and that appears to be related to the $\alpha_2A$-subtype [Escriba et al., 2004]. Furthermore, increase in the $\alpha_2A$-adrenoceptor protein level seems to be related to a corresponding increase in mRNA transcription but not to post-translational regulatory mechanisms [Escriba et al., 2004].

Many different SNPs have been found in the ADRA2A gene including some really rare mutations. Studies [Park et al., 2005; Deupree et al., 2006] have also investigated the haplotype effects of the three different polymorphisms in the ADRA2A gene identified by the MspI-HhaI-DraI restriction enzymes. These studies demonstrated a significant MspI-DraI haplotype effect in the aetiology of ADHD in children. However, those studies had conflicting results whether the dominant or recessive alleles have the increased risk to ADHD. Since polygenic disorders are due to the effect of multiple genes, Comings et al. [2000] examined the relative role of 59 candidate genes in the seven traits of the Cloninger’s Temperament and Character Inventory. They found that over 25% of the total explained variance of Reward Dependence was due to the noradrenaline genes, however, when analyzing the single gene, ADRA2A was found to play a modest role having a significant association with Harm Avoidance. Tsai et al. [2001] showed however, that ADRA1A and ADRA2A polymorphisms were not associated with TPQ personality factor scores in Han Chinese subjects.

It has been shown that the C-1291G polymorphism in the promoter region of the $\alpha_2A$ adrenoreceptor [ADRA2A] gene is associated with attention-deficit hyperactivity disorder (ADHD) in children with reading and other cognitive disabilities compared to ADHD children without learning disabilities [Comings et al., 1999]. Recently, Schmitz et al. [2006] showed that the homozygosity for the G allele of ADRA2A gene is associated with ADHD-inattentive type in the sample of Brazilian ADHD patients. In the Schmitz et al. study only ADHD-inattentive subjects were used which gives more precise results on this type of ADHD and reduces the possibility of spurious associations. Recently it was demonstrated that the C-1291G genotype is not only associated with the ADHD, but also with the response of its inattentive symptoms to treatment with methylphenidate [Polanczyk et al., 2007].

While direct evidence that this promoter polymorphism is responsible for differences in transcription is still lacking, several other studies have provided evidence for its physiological significance. Carrying the G allele has an effect on body composition [Garenc et al., 2002], glucose levels and dexamethasone non-suppression of cortisol [Rosmond et al., 2002], and body weight gain during treatment of clozapine [Wang et al., 2005]. We have recently found that in children and adolescents the GG genotype subjects consume more sweet food products than subjects with genotypes CC and CG [Mäestu et al., 2007]. Furthermore, preliminary evidence indicates that subjects with the GG genotype have significantly slower reaction time in the visual discrimination task [Harro et al., 2007], which suggests that this genotype may influence the noradrenaline-mediated attentional mechanisms.

Given the contribution of noradrenergic system to hostility, irritability, and depression that are facets of Neuroticism scales of NEO-PI-R we hypothesized that the ADRA2A polymorphism may have a specific impact on aspects of Neuroticism score. The aim of this study was to investigate the C-1291G polymorphism of the ADRA2A gene to the personality traits according to the five-factor model with the assessment of different facets of general traits.

**MATERIALS AND METHODS**

**Participants**

The sample was originally formed for the European Youth Heart Study in 1998/99 and subsequently incorporated into the longitudinal Estonian Children Personality Behaviour and Health Study. The selection of the original sample and procedure of data collection has been described in detail previously [Harro et al., 2001]. In brief, this is a representative sample of the Tartu city and county with a school as the sampling unit, and in the present analysis, data of the younger cohort was used. Data for present study were collected during the follow-up in 2004 where we managed to recruit 83% (n = 483) from the original sample, including 222 boys and 261 girls. Children and their parents gave their informed consent. Permission for the study was obtained from the Committee of Ethics of the University of Tartu, Estonia. The mean age of the subjects studied in 2004 was 15.3, SD = 0.5. The study procedure was approved by the Ethics Committee of the University of Tartu.

**Personality Assessment**

Personality traits were assessed by in 2004 when the subjects were 15.3 ± 0.5 years old by 240-item EPQN-NEO questionnaire [Mottus et al., 2006], which like NEO Personality Inventory (NEO-PI-R) [Costa and McRae, 1992] measures each of the Big Five personality dimensions—Neuroticism (N), Extraversion (E), Openness (O), Agreeableness (A), and Conscientiousness (C)—with six subscales. The participants were asked to answer on a 5-point scale how they agree with different descriptions. For example, the item “Often feel blue” measures Depression (N) as a facet of Neuroticism and the item “Take advantage of others” is measuring Morality (A) as an aspect of Agreeableness. The convergent validity between EPQN-NEO and the Estonian version of NEO-PI-R [Kallasmaa et al., 2000] was excellent: correlation between corresponding domain scales of the EPQN-NEO and the NEO-PI-R were in the range from 0.83 to 0.90 [Mottus et al., 2006]. Self-reports were completed in the laboratory where other procedures of the study were carried out. EPQN-NEO data were available for 419 subjects.

**Genotyping**

The MspI polymorphism in the promoter region of the ADRA2A gene was amplified by the polymerase chain reaction (PCR) using the primers and protocols previously reported [Lario et al., 1997; Comings et al., 2003]. The forward primer was 5’-TCA CAC CGG AGG TTA-3’ and the reverse primer was 5’-TCC GAC GAC AGC GCG-3’. These primers generated the product of 552 bp. After PCR amplification, the PCR product was digested overnight at 37 °C after adding 6 U of the restriction enzyme MspI to the PCR mixture. The allele without the MspI restriction site is designated here as C-1291G allele and G-1291G allele is with the restriction of the MspI site.

**Statistical Analysis**

The T-scores were calculated separately for boys and girls to eliminate the gender effect on the personality scores and the general linear modeling was used to detect significant ADRA2A effects on personality. The effect was considered significant if $P < 0.05$.

**RESULTS**

In both, boys and girls, the distribution of the C-1291G polymorphism did not significantly deviate from the Hardy-Weinberg equilibrium. Table I presents the mean values of the EPQN-NEO domains according to three ADRA2A C-1292G
genotypes, CC, CG, and GG. On the level of the Big Five personality domains there were no significant differences between genotypes. Closest to the 5% significance level was Conscientiousness ($P = 0.069$): individuals with CG genotype had a slight tendency to be more purposeful, strong-willed, and determined than individuals with other genotypes.

In order to study association between ADRA2A polymorphisms and personality in more detail, personality profiles for three genotypes were formed (Fig. 1). Analysis of covariance with sex as a covariate revealed three significant differences: N3: Depression ($F = 5.34; P = 0.001$), A2: Morality ($F = 9.89; P < 0.0001$), and C2: Orderliness ($F = 3.09; P = 0.027$) with the subjects with GG genotype scoring highest in Depression and lowest in Morality and Orderliness compared to CC and CG genotypes. We used Newman-Keuls test for pairwise comparison because it is based on the studentized range statistic. In all three subscales the mean value of GG genotype remained different from at least one of other two genotypes.

Not only the mean scores can carry relevant information about personality. The profile or segments of it can contain additional information about behavioral dispositions. For example, it may be indicative how similar is the subject to the mean scores of all subjects. In order to estimate similarity to a prototypical person it is possible to compute the correlation, called construct similarity index, between a subject’s means on all scales and the means of the entire sample on these scales [Chaplin, 1991]. A large positive correlation implies that the responses of the subject were similar to the mean of all subjects. The lack of correlation or its negative value indicates that the individual profile is thoroughly different from the profile of an average person of this sample. The mean construct similarity indices were not significantly different for three ADRA2A genotypes.

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<th>TABLE I. The Mean and Standard Deviation of the EPIP-NEO Domains According to the Genotype of ADRA2A</th>
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Fig. 1. Personality profiles of three ADRA2A genotypes (asterisks show significant differences). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
Next, we analyzed the personality profiles by each of the five domains separately. For example, the mean scores of six Neuroticism subscales across all subjects were ranked in the following order: the largest value was on N1: Anxiety, followed by N3: Depression, N6: Vulnerability, N4: Self-Consciousness, N2: Anger, and finally the lowest score on N5: Immoderation. This means that average adolescents, at least in Estonia, score higher on scales revealing internalizing (anxiety and depression) rather than those revealing externalizing (anger and immoderation) their neurotic tendencies. For each subject we computed the rank order correlation between his or her ranking of subscale scores and the mean ranking of all subjects. Except Neuroticism there was no association between similarities to a prototypical order of personality scales. Those subjects whose scores on Neuroticism subscales ranked more like the average ranking of all subjects belonged more likely to CG group of polymorphisms \(F(2,416) = 5.11, P = .006\) (Fig. 2). In other words, heterozygotic individuals with CG genotype are more inclined to internalize their neurotic dispositions compared with two other genotypes.

Finally, there was a considerable interaction between sex and \(ADRA2A\) polymorphisms in the expression of extraversion tendencies. ANOVA revealed that E1: Friendliness, E2: Gregariousness, and E6: Cheerfulness demonstrated significant interaction between sex and \(ADRA2A\) genotype \((F(5,413) = 2.30, 5.52, \text{ and } 7.69 \text{ for E1, E2, and E6, respectively}; P < .05)\). The meaning of this interaction becomes clear in Figure 3. Boys with CC and CG genotype score lower on these three Extraversion subscales: E1, E2, and E6. They are less friendly, gregarious, and cheerful than girls of the same age. However, the situation reverses for boys or girls who have GG genotype: on all six Extraversion scales boys scored rather higher.

**DISCUSSION**

This study provides evidence that basic personality traits are influenced at the \(\alpha_{2A}\) adrenergic receptor level. There was no significant difference in the broad personality dispositions—Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness—between individuals carrying different \(ADRA2A\) C-1292G genotypes. However, on a more specific level of personality traits there was a remarkable association between personality and genotypes. We established three specific associations between \(ADRA2A\) genotype and personality.

In the present study, individuals with GG genotype were found more likely than their peers to experience depression and at the same time not too much concerned about moral issues and keeping environment in which they live in a good order. Clinical depression has traditionally been associated with low efficiency of the noradrenergic neurotransmission, and given the present results this in some individuals might be caused by genetically determined lower levels of postsynaptic receptors. However, because depression is probably rather related to an upregulation of \(\alpha_{2A}\)-adrenoceptors, it should rather be hypothesized that homozygocity to the less efficient allele can lead to weaker autoreceptor-mediated control of neurotransmitter release, either at the level of the somatodendritic control of the LC firing or in the inhibitory control of the release of monoamines in the projection areas. Which interpretation is correct can be revealed with measurement of the efficacy of transcription of the gene alleles and functional imaging studies in genotyped individuals using pharmacological challenge tests.

Second, heterozygous individuals with CG genotype are more inclined to internalize their neurotic dispositions compared with homozygotes. In turn, homozygotes are more likely than heterozygotes in externalizing their neurotic...
tendencies and being ready to demonstrate openly their anger and immoderation. The genetic basis for this phenomenon remains obscure. One possible explanation is allele-specific overdominance when heterozygous combination of alleles is more vigorous than either corresponding homozygotes resulting in a more expressed outcome of some traits.

Finally, there was a considerable interaction between sex and ADRA2A polymorphisms in the expression of extraversion tendencies. In general, girls are more extraverted (friendly, gregarious, and cheerful) than boys unless they have a recessive genotype GG that makes them more introverted than boys. Sex effect has also been described in 5-HTT polymorphism—Allele carrier girls are more sensitive to social environment but boys are not [Sjoberg et al., 2006].

This study has some possible limitations. It is known that the percentage of the variance accounted for a single gene is quite small for behavioral variables, that is, usually less than 1.5%. To overcome this effect, larger sample size for association studies using multiple genotyping is required to examine the effect of different genes on personality traits due to their additive or nonadditive effects [Comings et al., 2000]. In this study, substantially large sample size of 419 subjects was used which, however might have been too small, especially for the GG group, to detect the gene impact on the broad personality dispositions. Belfer et al. [2005] reported that a haplotype block of nine SNPs spanned ADRA2A gene, which could suggest that one or more polymorphisms are also involved that act within other coding or control regions of the gene that is in linkage disequilibrium with the C-1291G polymorphism. It has been known that if an individual inherits enough genes to develop any given behavioral disorder, their risk of developing a second behavioral disorder is two to four times higher than for the general population [Comings et al., 2005]. This is probably because different behavioral disorders share the same genetic variants and the more a person exceeds the required threshold number of gene variants, the greater would be the likelihood of the development of behavioral problem. Therefore, the novel results presented in this study cannot be solely relied on the C-1291G polymorphism in the ADRA2A gene. Despite of these limitations we conclude that the gene polymorphism in the ADRA2A of the noradrenergic system has the influence on basic personality traits in adolescents.

REFERENCES


