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Running title: *ABCA1* and harm avoidance

ABCA1 polymorphism, a genetic risk factor of harm avoidance

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Abstract

Even though cholesterol homeostasis and self-harm behaviors have shown to be associated, gene polymorphisms of the cholesterol system have not been studied yet in the context of self-harm related personality traits. Here we present an association study between six *ABCA1* polymorphisms and temperament scales measured by Cloninger's Temperament and Character Inventory on 253 young adults. An association between ABCA1 rs4149264 and harm avoidance has been observed. This association remained significant after Bonferroni correction. Haplotype analysis confirmed an independent association between rs4149264 and harm avoidance. ABCA1, a cholesterol homeostasis gene is a candidate gene for harm related personality traits.

Keywords:

Genetic association, personality, suicide behavior, harm avoidance, *ABCA1* gene polymorphisms

1. Introduction:

1.1. Suicidal behavior and the cholesterol system

Evidence from twin studies of suicide strongly suggests genetic contributions to suicidal behavior (Voracek & Loibl, 2007). Even though association studies have provided little information about the specific genetic contributors (Brezo et al., 2008), genetic variants of the associated neural mechanisms might be good targets for the genetic association analysis of suicidal behavior.

Intriguingly, recent research suggests that the cholesterol homeostasis might be one of such neuronal mechanisms. Associations between serum and brain cholesterol levels and suicide attempts have been studied extensively (Atmaca et al., 2003; Guillem et al., 2002; Kim & Myint, 2004; Lalovic et al., 2007; Lee & Kim, 2003; Vuksan-Cusa et al., 2009) and reviewed recently (De Berardis et al., 2012). For example it was shown that lower levels of cholesterol in the prefrontal cortex is associated suicidal behavior (Freemantle et al., 2013). Others have observed an association between low serum cholesterol level and suicide attempts in a sample of child and adolescent psychiatric patients (Plana et al., 2010). Another study found a difference in cholesterol level between those who attempted violent and non-violent suicide (e.g. Vevera et al., 2003)) suggesting that low level of cholesterol is associated with increased tendency for impulsive behavior, aggression and contribute to a more violent pattern of suicidal behavior as well. Others also confirmed that low level of cholesterol is associated with impulsive and violent behavior (Buydens-Branchey et al., 2000; Garland et al., 2000). Furthermore, associations have been found between cholesterol levels and different aspects of aggression, such as severity of aggression (Hillbrand & Foster, 1993), frequency of aggression (Spitz et al., 1994) and non-physical aggression (Hillbrand et al., 2005).

1.2. Suicidal behavior and personality

A meta-analyses of personality traits and suicidal behavior suggests a strong relationship between certain personality traits (e.g. neuroticism, extraversion) and suicidal behavior (Brezo et al., 2006). This review suggests that most studies have focused on serotonergic gene variants and only eight genes involved in lipid and cholesterol metabolism have been investigated as candidates for suicidal behavior. Successful replications are rare amongst these studies. They also cited a gene association study of cholesterol-metabolizing genes which could not relate cholesterol genes such as HMGCR, DHCR7, LPL, LDLR, and APOE to the increased risk for suicide or to impulsivity and aggression (Lalovic et al., 2004). The authors propose that given the multifactorial character of suicidal behavior, future research should also focus on testing second-order moderation to uncover possible interactional effects. They also emphasize the importance of personality traits as useful markers of maladaptive behaviors, such as suicidal behavior.

Others also proposed that certain central neuro system functions and personality traits such as harm avoidance are interrelated phenomena, which may increase the probability of the occurrence of attempted suicide (van Heeringen et al., 2003). Furthermore, it seems that increased harm avoidance personality trait is associated with increased age of suicide (McGirr et al., 2008). The relationship between suicidal behavior and personality traits was also investigated on clinical samples. For example, a study carried out on bipolar patients (Engstrom et al., 2004) showed that bipolar patients with suicide attempts were significantly higher in harm avoidance compared with patients without suicide attempts. On the other hand, in borderline personality disorder it was found that harm avoidance might be a protective factor against suicidal behavior (McGirr et al., 2007)

1.3. Cholesterol system and personality

It has been proposed early on that psychological characteristics like the Type A-pattern and depression are positively correlated with serum-cholesterol levels (e.g. (van Doornen & Orlebeke, 1982). More recently, LeBlanc and Ducharme (2005) have also investigated the influence of personality on plasma levels of cholesterol and found that extraversion was positively correlated with the level of cholesterol while the correlation was negative for neuroticism. These correlations are similar to findings previously reported regardingtype A individuals. Another study also showed on a large and well-characterized sample that certain personality traits (such as conscientiousness and impulsivity) are in association with cholesterol (Sutin et al., 2010).

Furthermore, the association between cholesterol and personality has been established not only in healthy samples, but in clinical samples as well. For example, it was demonstrated that patients with borderline personality disorder have lower cholesterol than healthy controls in all dimensions of the disorder-impulsivity, aggression and suicidal behavior (Atmaca et al., 2002). A review on cholesterol and mental disorder also provided strong support that serum cholesterol levels may be associated with variations in mental state or personality (Boston et al., 1996).

These studies indicate that cholesterol levels may be an intermediate biomarker between personality and certain health problems. When analyzing the connection between personality and health, the cholesterol system should as well be considered.

Taking together the above findings, a relationship between cholesterol level and violent, suicidal, aggressive behaviors has been extensively studied. Moreover, there is evidence that self-harm and suicidal behavior has a strong personality aspect. Therefore studies have focused on the direct association between personality traits and level of cholesterol. However, direct associations between gene variants of cholesterol homeostasis and personality traits have not been tested yet.

Thus, we aimed to investigate possible associations between genetic variants of a cholesterol transporter (ABCA1) and personality temperament scales measured by Cloninger's Temperament and Character Inventory (Cloninger et al., 1993). ABCA1 is a member of the ATP-binding cassette family of transporters which plays an important role in cholesterol homeostasis and high-density lipoprotein (HDL) metabolism via mediating efflux of cellular cholesterol onto HDL apolipoproteins (Schmitz & Langmann, 2001).

2. Materials and methods:

2.1. Participants

Non related Caucasian (Hungarian) subjects participated on a voluntary basis. The study protocol was designed in accordance with guidelines of the Declaration of Helsinki, and was approved by the Scientific and Research Ethics Committee of the Medical Research Council. The participants signed a written informed consent, provided buccal samples and filled out the Cloninger's Temperament and Character Inventory. Selection criteria included no past or present psychiatric history (based on self-report), age between 18-37 years, valid self-report data for the TCI subscales and valid ABCA1 SNP (single nucleotide polymorphism) data for all of the six analyzed SNPs (in order to a analyze the same database in the single association analysis and in the haplotype analysis). As a result, data from 253 participants were included to the analyses (43.6% males, 56.4% females; mean age: 21.5 ± 2.5 years).

2.2. Phenotype measures

Personality was assessed with the Hungarian version of the TCI-56 based on Cloninger's Temperament and Character Inventory (Cloninger et al., 1993). The questionnaire consists of two dimensions (Temperament and Character), and 7 subscales. Novelty Seeking, Harm Avoidance, Reward Dependence and Persistence belong to the temperament dimension which are heritable

and involve preconceptual biases in perceptual memory and habit formation. Self-Directedness, Cooperativeness and Self-Transcendence belong to the Character dimension. The present genetic association analysis was carried out on the Temperament dimension scales. Cronbach-Alpha values were as follows: Novelty Seeking: 0.697, Harm Avoidance: 0.621, Reward Dependence: 0.680, Persistence: 0.742.

2.3. Genotyping

SNPs of the ABCA1 gene were selected based on minor allele frequency (SNPs with a minor allele frequency greater than 0.05 were selected), position (the aim was to obtain proper coverage of the gene) and previous genetic association studies.

DNA sample preparation was described in details elsewhere (Kotyuk et al., 2013). Intercalation assay was measured to test the concentration of the isolated DNA. DNA samples were only included if their concentration reached at least 15 ng/µl. Genotyping of the six *ABCA1* polymorphisms (rs1800977, rs4149264, rs2230805, rs2472384, rs2472386, rs2230808) were made by sequence-specific, fluorescent TaqMan probes of Applied Biosystems. 7% of the DNA samples were measured in duplicates, showing a higher than 99% reproducibility.

To examine genotype validity of the present sample Hardy-Weinberg equilibrium (Hardy, 1908) was tested (Supplementary Table 1). None of the tests showed a significant difference in the expected and observed genotype frequencies.

Linkage disequilibrium values of the studied SNPs are presented in Figure 1. These values are similar to those found in the 1000 Genome Project. Please note, that rs4149264, which were shown to significantly associate with Harm avoidance in this study, was not in linkage disequilibrium with the other studied SNPs. This is also in good agreement with the results of the 1000 Genome Project.

2.4. Statistical Analysis

One way analysis of covariance (ANCOVA) has been used to test genetic associations, in an allelewise method. Only participants with valid genetic data for all six analyzed *ABCA1* gene polymorphisms were included in the genetic association analyses (2N=506). Possible false positive associations were ruled out by correcting for multiple testing. Bonferroni correction (Bonferroni, 1936; Miller, 1981) has been applied with a corrected level of significance of 0.002083 as the nominal p value (0.05) was divided by the number of analyses (24). Lewontin's D' as well as R^2 values of linkage disequilibrium were determined using HaploView 4.2 (Barrett et al., 2005). Haplotypes were determined by the Phase program (Stephens & Donnelly, 2003; Stephens et al., 2003; Stephens et al., 2001).

3. Results:

3.1. Influence of Age and Gender

Age had no significant association with the TCI scales but there was a significant difference by gender on the Reward Dependence ($p=0.005$) and Harm Avoidance ($p<0.001$) scales. Females showed a higher mean score on Reward Dependence (22.6±3.5) and Harm Avoidance (17.1±4.1) compared to males (20.2±3.5, 15.7±4.0, respectively).

Rs2230805 and rs2472384 polymorphisms showed significant associations with age ($p = 0.038$ and $p = 0.013$, respectively). The mean ages for the rs2230805 genotype groups were as follows: CC: 21.79, CT: 21.14, TT: 20.79 years. For the rs2472384 CC genotype group it was 20.84, for the CT group 21.03 and for the TT group 21.84 years. There was no significant difference in genotype frequencies by gender. In summary, age and gender was used as covariant in all association analyses.

3.2. Single marker association analyses of *ABCA1* SNPs and TCI scales

To test if there is any association between *ABCA1* polymorphisms and TCI scales ANCOVA tests were used. Table 1 summarizes the results of the single marker association analyses. Minor allele frequencies and scale mean scores by the alleles of each tested SNPs are presented in the table with the corresponding *p* values. Based on the analyses three nominally significant associations were found. An association between the rs4149264 SNP of the *ABCA1* gene and Harm Avoidance has been observed [F(1,502) = 10.616, p = 0.001, η2 = 0.021, power = 0.902]. The minor (C) allele of this polymorphism was in association with a lower Harm Avoidance mean score (15.25 ± 3.7), as compared with the other G allele (16.71 ± 4.2). As it can be seen from the statistical estimates, the association with this polymorphism explains 2.1% of the variance of Harm Avoidance personality trait with an adequate statistical power.

Furthermore, Novelty Seeking showed a significant association with rs2472384 [*F*(1,502) = 4.809, *p* = 0.029, η2 = 0.009, power = 0.591]. According to the results the minor allele of the rs2472384 is associated with lower Novelty Seeking mean scores (23.76 ± 4.9) than the T allele (24.86 ± 5.3). Another polymorphism, rs2472386 also showed a significant association with Novelty Seeking [*F*(1,502) = 6.843, *p* = 0.009, η2 = 0.013, power = 0.742] where the minor (A) allele was also associated with lower Novelty Seeking mean score (23.71 ± 5.2), than the other allele (24.98 ± 5.1). We did not observe any significant associations between the other polymorphisms and personality traits. After Bonferroni correction for multiple testing, from the three nominally significant results the association between rs4149264 and Harm Avoidance remained significant with a p value of 0.001195.

3.3. Post hoc analyses – Gender differences

Because of the significant relationship between gender and the TCI scales of Harm Avoidance, and Reward Dependence, as a next step, we tested if the effect of rs4149264 differs across genders. The Two-way analysis of variance has showed a significant gender main effect

[F(1,501)=7.968, p=0.005, η2=0.016, power=0.804]. Also a significant genotype main effect has been observed [F(1,501)=10.512, p=0.001, η2=0.021, power=0.899]. No significant interaction has been found.

3.4. Haplotype analysis

Even though the presented significant single marker genetic associations were observed with two different phenotypes (Novelty Seeking and Harm Avoidance), these phenotypes are in correlation (r = -0.258, p < 0.001) allowing us to carry out a haplotype analysis. . .As for the genetic side: as can be seen from Figure 1, the main significant SNP (rs4149264) was not in linkage disequilibrium with the other two SNPs which showed significant associations (rs2472384 and rs2472386), however there is a strong pairwise linkage disequilibrium between these two loci (D' = 75, r2 = 44). Thus, haplotype analysis has been carried out only between rs4149264 and rs2472384; rs4149264 and rs2472386; and haplotype effect of rs2472386 - rs2472384; or rs4149264 - rs2472386 - rs2472384 has not been tested. Results of the haplotype analyses are presented in Table 2. Although, the haplotype effect of rs4149264 and rs2472386 was significant on both NS and HA, the results seem contradicting. For example, with Harm Avoidance results do not suggest an additive effect of the risk alleles, but rather an effect of rs4149264 G allele. The haplotype analysis of rs4149264 and rs2472384 also revealed an rs4149264-driven significant effect on Harm avoidance. As can be seen from Table 2, the mean Harm Avoidance scores seem to be higher in both analyses by the risk allele of rs4149264.

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4. Discussion:

The present genetic association analyses aimed to test the possible relationship between polymorphisms of a cholesterol transport gene and personality temperament dimensions on a

sample of 253 healthy young adults. During sample description analysis we found a significant gender difference in the TCI subscales as expected (Miettunen et al., 2007) and a significant age effect in genetic markers (rs2230805 and rs2472384). Further studies are needed to identify if this is a random effect or it has an effect on lifespan as found in cases (Brooks-Wilson, 2013).

Variance analyses of the data showed three nominally significant results. *ABCA1* rs2472384 and rs2472386 showed associations with novelty seeking, and rs4149264 with the harm avoidance TCI temperament personality dimension. After correcting for multiple testing, the association between rs4149264 and harm avoidance remained significant. In case of the minor (C) allele of this polymorphism lower mean harm avoidance score was observed as compared with the G allele. This association was present both in females and males. The haplotype analysis of rs4149264_rs2472386 and rs4149264_rs2472384 suggests that rs4149264 has an individual effect and no real haplotype associations seem to be present.

It is well established in the literature that genetic factors play an important role in suicidal behavior (Baldessarini & Hennen, 2004). However, most of the studies have focused on variants of the serotonergic or dopamine system (Bondy et al., 2006; Mann et al., 2001; Zai et al., 2012). Unfortunately, recent genome wide studies did not yield significant findings thus far, probably because of the genome wide significance threshold of 5^10 (Zai et al., 2012). These also indicate that the genetic architecture underlying suicidal behavior is complex with moderate effects of multiple genes. The authors indicated that certain intermediate phenotypes, such as personality traits should be taken into consideration when searching for the genetic factors of suicidal behavior. Others also proposed that certain traits might be good endophenotypes for genetic studies of suicidal behavior (Mann et al., 2009).

An earlier study hypothesized that the novelty seeking temperament dimension might be an intermediary variable, correlating with both serum cholesterol level and suicidal behavior

(Guillem et al., 2002). The study was carried out on a sample of 155 psychiatric inpatients, of whom 34 patients had attempted suicide. They found an association between low cholesterol and suicidal behavior, but this association was independent from the novelty seeking personality dimension and other scales of the Temperament and Character Inventory as well. However, due to the low number of participants in the suicide attempt group, and the possible confounding effects of somatic diseases not assessed in the study, further analysis is needed. Even though cholesterol levels and self-harm behaviors (e.g. suicide) have been shown to be related, cholesterol transport related polymorphisms have not yet been studied in the context of self-harm related personality traits.

Earlier studies have mostly investigated the ABCA1 gene in relation to Coronary Diseases (for a recent meta-analysis see Fan et al., 2014) and Alzheimer's Disease (Di Paolo & Kim, 2011; Notkola et al., 1998; Puglielli et al., 2003; Reid et al., 2007), but according to our best knowledge, this is the first genetic association study regarding personality traits and *ABCA1* gene variants.

In conclusion, results of the present study showed a significant association between rs4149264 and harm avoidance measured by Cloninger's Temperament and Character Inventory. However, certain limitations should be considered when interpreting the results. One of the limitations is the relatively low sample size. It would also be interesting to test this association e.g. on those, who attempted suicide already or on an older sample as well. Also, further polymorphisms of the very long *ABCA1* gene should be considered for future analyses. Thus, replication of the present study is needed to confirm and further specify this association.

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Declaration of interests

The authors have no competing interests to declare.

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