RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART B
Neuropsychiatric Genetics

Significant Association Between the C(−1019)G Functional Polymorphism of the HTR_{1A} Gene and Impulsivity

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Received 17 February 2009; Accepted 16 July 2009

Serotonin-1A ($5\text{-}HT_{1A}$) receptors are known to play a role in impulsivity-related behavior. The C(−1019)G functional polymorphism (rs6295) has been suggested to regulate the $5\text{-}HT_{1A}$ receptor gene (HTR_{1A}) expression in presynaptic raphe neurons, namely, increased receptor concentration and reduced neuronal firing could be associated with the G allele. Previous studies indicate that this polymorphism is associated with aggression, suicide, and several psychiatric disorders, yet its association with impulsivity has rarely been investigated. We studied the relationship between impulsivity and the C(−1019)G polymorphism of the HTR_{1A} in a population sample of 725 volunteers using the Impulsiveness subscale (IVE-I) of the Eysenck Impulsiveness, Venturesomeness, and Empathy scale and also the Barratt Impulsiveness Scale (BIS-11). Data were analyzed using analysis of variance with age and gender as covariates and Tukey's HSD post-hoc test. Post-hoc analysis revealed that the study had 0.958 power to detect 0.15 effect size. Significant differences between the C(−1019)G genotype groups (GG vs. GC vs. CC) were found. Subjects carrying GG genotype showed significantly higher impulsiveness scores compared to GC or CC carriers for the IVE-I scale ($P = 0.014$), for the Motor ($P = 0.021$), Cognitive Impulsiveness ($P = 0.002$), and for the BIS total score ($P = 0.008$) but not for the Nonplanning Impulsiveness ($P = 0.520$) subscale of the BIS-11. Our results suggest the involvement of the HTR_{1A} in the continuum phenotype of impulsivity.

Key words: impulsiveness; serotonin-1A receptor; association; genetic; rs6295

How to Cite this Article:
Benko A, Lazary J, Molnar E, Gonda X, Tothfalusi L, Pap D, Mirnics Z, Kurimay T, Chase D, Juhasz G, Anderson IM, Deakin JFW, Bagdy G. 2010. Significant Association Between the C(−1019)G Functional Polymorphism of the HTR_{1A} Gene and Impulsivity.
Am J Med Genet Part B 153B:592–599.

INTRODUCTION

The serotonergic system plays an important role in various physiological functions [Bagdy, 1998; Hoyer et al., 2002], psychiatric disorders (e.g., anxiety disorders, depression, and schizophrenia) [Geyer and Vollenweider, 2008; Lowry et al., 2008], and regulates complex functions related to cognition and emotions [Murakami et al., 2009]. At present, there are 14 different known serotonin receptors divided into 7 classes [Hoyer et al., 2002].

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Published online 1 September 2009 in Wiley InterScience (www.interscience.wiley.com)
DOI 10.1002/ajmg.b.31025

Brain 5-HT_{1A} receptors can be found both pre- and post-synaptically. Somatodendritic 5-HT_{1A} autoreceptors are located on serotonergic neurons in the dorsal and medial raphe nuclei providing a negative feedback mechanism in the 5-HT system. These autoreceptors control the firing rate of the 5-HT neurons resulting in the regulation of 5-HT synthesis and release [Kennett et al., 1987; Bohmaker et al., 1993]. Post-synaptic 5-HT_{1A} receptors are found on multiple serotonergic targets in the brainstem and forebrain [Pazos and Palacios, 1985; Hall et al., 1997].

The role of the 5-HT_{1A} receptor subtype in the pathophysiology of anxiety, depression [Lesch et al., 1990, 2003; Griebel, 1995; To and Bagdy, 1999; Lanfumey and Hamon, 2004], and aggression [Cleare and Bond, 2000; Parsey et al., 2002] has long been studied. However, clarifying the possible role of the HTR_{1A} gene in human aggression and impulsivity has rarely been attempted.

The HTR_{1A} gene is located on the long arm of chromosome 5 (5q11.2–13) [Kobilka et al., 1987]. The functional C(−1019)G polymorphism (rs6295) is a common SNP in the promoter region of the gene [Wu and Comings, 1999]. The polymorphism is located within a 26 bp palindromic region, which binds the nuclear DEAF-1-related (NUDR) protein and Hes5; the G allele abolishes repression by NUDR, resulting in higher expression of HTR_{1A} enhancing the negative feedback inhibition of serotonergic raphe neurons exerted by HTR_{1A} autoreceptors and leading to lower serotonergic neurotransmission [Lemonde et al., 2003].

Previous studies indicate that the C(−1019)G polymorphism of the HTR_{1A} gene is associated with several psychiatric disorders including major depression [Lemonde et al., 2003] and anxiety disorders such as panic disorder with agoraphobia [Rothe et al., 2004]. It has also been found to be associated with suicide: Lemonde et al. [2003] found an association between the G allele and completed suicide in an isolated population of French-Canadian origin and results from Sawiniec et al. [2007] also indicated a significant role of the C(−1019)G polymorphism in the risk of suicide attempt. However, in the study of Serretti et al. [2007], haplotype analysis in relation to suicidal behavior did not reveal any significant association, although suicidal attempter females homozygous for the G allele scored significantly higher on the STAXI state anger scale. Studies investigating the possible association with suicide focused on both attempted and completed suicide; however, suicidal behavior is a more complex phenomenon. Besides its association with the serotonergic system [Audenaert et al., 2006; Wasserman et al., 2006], suicide has also been linked to aggression and impulsiveness [Horesh et al., 2003]; attempted suicides are related to impulsiveness [Baca-Garcia et al., 2005], while completed suicides to aggressiveness [McGirr et al., 2008]. Previously, both impulsiveness and aggressiveness have also been associated with the serotonergic system [for a review, see Lee and Coccaro, 2001].

Several studies have investigated a potential association between the C(−1019)G polymorphism and various personality traits; using the revised five-factor Personality Inventory (NEO-PI-R) and the Tridimensional Personality Questionnaire (TPQ), higher scores for Neuroticism and Harm Avoidance were found in carriers of the G allele compared with C allele carriers [Strobel et al., 2003], although other studies did not find any significant association between neurotisicm and this particular SNP [Koller et al., 2006; Hettema et al., 2008]. Serretti et al. [2009] failed to find any association between three SNPs in the HTR_{1A} gene or six SNPs in the HTR_{2C} gene and personality dimensions, measured by the Cloninger's Temperament and Character Inventory (TCI).

Impulsivity is a heterogeneous behavioral phenomenon that has various definitions, the main element being that impulsivity is a human behavior without adequate thought; the tendency to act without taking into consideration the consequences of action, or a general predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the possible negative consequences of these reactions [Evenden, 1999]. It plays an important role in physiological as well as in pathological forms of behavior such as personality disorders [Fossati et al., 2007], attention deficit/hyperactivity disorder [Winstanley et al., 2006], depression [Fountoulakis et al., 2004], suicide [Zouk et al., 2006], and substance abuse disorder [Clark et al., 2006].

In the present study, we aimed to test the hypothesis of the involvement of the C(−1019)G polymorphism in impulsivity-related behavior in a large sample of 725 volunteers using two specific questionnaires measuring impulsivity.

MATERIALS AND METHODS

Subjects

Eight hundred fifty-one unrelated Hungarian volunteers were recruited for the study. Subjects whose DNA sample was not successfully genotyped and subjects with missing questionnaire data were excluded from all statistical tests. Finally 725 subjects remained, 596 women and 129 men. The participants were aged 18–60 years, the mean age was 30.26 ± 10.601 years. Participants were recruited from general practices, universities, and a community-based population. The inclusion of subjects was independent of any positive psychiatric anamnesis. Each subject was given an oral and written summary of the aims and procedures of the project and gave formal written consent before entering the study. All subjects were Hungarian and of Caucasian origin. The study protocol was approved by the Central Ethics Committee in charge of genetic studies with human subjects.

Measures

Background information was obtained from all participants. The background questionnaire was adapted from the version developed by the Epidemiology Unit at the University of Manchester. The self-rating questionnaire consisted of 22 items and collected detailed information about socioeconomic background, and medical history including personal and family psychiatric history.

Impulsivity was measured by two questionnaires: the Impulsiveness subscale of the Eysenck Impulsiveness, Venturesomeness, and Empathy scale (IVE-I) [Eysenck and Eysenck, 1978] and the Barratt Impulsiveness Scale (BIS-11) [Patton et al., 1995].

The Eysenck IVE scale [Eysenck and Eysenck, 1978] consists of 54 true/false items and contains 3 unidimensional subscales: Impulsiveness, Venturesomeness, and an Empathy scale. In our study we only used the Impulsiveness subscale (IVE-I), which contains 19 items (e.g., "Do you often do things on the spur of the moment?"). The total score is the sum of the points; a high score indicates a high level of impulsivity.

The most recent version of BIS-11 [Patton et al., 1995] consists of 30 items asking about impulsivity-related behaviors and cognitions. According to Barratt's most recent proposal [Barratt, 1994] that there are three subtraits (measured by three subscales) which are Motor Impulsiveness (e.g., "I do things without thinking," 11 items), Cognitive Impulsiveness (e.g., "I don't pay attention," 8 items), and Nonplanning Impulsiveness (e.g., "I plan tasks carefully," inverted item, 11 items). The BIS total score is the sum of the three scales. Each item is measured on a 4-point scale, 4 indicates the most impulsive response. The total score is the sum of the points.

Genotyping

Buccal mucosa samples were collected from each subject, and genomic DNA was extracted according to a protocol previously described [Freeman et al., 2003]. DNA quality and quantity were determined with NanoDrop B-100 spectrophotometer, and all samples were diluted to a DNA concentration of 20 ng/ml.

The SNP rs6295 was genotyped at the Centre for Integrated Genomic Medical Research at the University of Manchester using Sequenom MassARRAY technology (Sequenom, San Diego, CA). The iPLEX assay, based on post-PCR single base primer extension, was performed according to manufacturer's instructions. Forward (5-GTCAGTCTCCCAATTATTGC-3), reverse (5-CGAGAACGG-AGGTAGCTTTT-3), and extension (5-AGACCGAGTGTGTCTTC-3) primers were designed using the Assay Design 3.0 software of Sequenom. The iPLEX reaction products were dispensed onto a 384-well SpectroChip (Sequenom), processed and analyzed in a Compact Mass Spectrometer by MassARRAY Workstation 3.3 software (Sequenom).

Statistical Analysis

Haploview 4.0 software was used for computing Hardy–Weinberg equilibrium and minimal allele frequency [Barrett et al., 2005; Wigginton et al., 2005].

Association tests were performed by means of analysis of variance (ANOVA) with the rs6295 SNP (GG vs. GC vs. CC) as an independent variable and IVE-I and BIS-11 scales entered as dependent variables. Tukey HSD post-hoc test was used for multiple comparisons.

Age and gender were included in the ANOVA model as covariates. Statistical analyses were carried out using SPSS 15.0 (SPSS Inc., Chicago, IL). $P < 0.05$ was accepted as level of significance. Results are presented as mean ± standard error (SEM). For power calculations we used G*Power 3 [Faul et al., 2007].

RESULTS

Descriptive Statistics

The demographic characteristics of the study population are shown in Table I. There was no significant deviation from the Hardy–Weinberg equilibrium ($P = 0.655$), and minimal allele frequency of rs6295 polymorphism was more than 5%. Frequencies of the GG, GC, and the CC genotypes were 27% (n = 193), 51% (n = 368), and 22% (n = 163), respectively. Frequencies of the G and C alleles were 52% (n = 754) and 48% (n = 694), respectively.

TABLE I. Demographic Characteristics

Sociodemographic data (self-reported)	N (%)
Total	725 (100%)
Female	596 (82.2%)
Male	129 (17.8%)
Mean age ± SD	30.26 ± 10.601
Education	
No qualification	4 (0.6%)
Technical school	55 (7.6%)
High school	552 (76.1%)
Degree	187 (25.8%)
Marital status	
Single	367 (50.6%)
Married	228 (31.4%)
Couple	70 (9.7%)
Divorced	37 (5.1%)
Separated	13 (1.8%)
Widowed	5 (0.7%)
Personal history (anamnesis)	
Anxiety/panic/phobia	147 (20.3%)
Suicide attempt	33 (4.6%)
Manic episode/manic depression/bipolar disorder	10 (1.4%)
Depression	147 (20.3%)
Obsessive-compulsive disorder	15 (2.1%)
Psychotic episode/schizophrenia	4 (0.6%)
Eating disorders	46 (6.3%)
Drug or alcohol problem	16 (2.2%)

IVE-I, BIS-11 Scales, and rs6295

Using the IVE-I scale, there were significant differences ($P = 0.014$) in the test scores between the three genotype groups (Table II). Test results (Fig. 1), indicate that subjects with the GG genotype show significantly higher impulsivity, and with no over-lap at 95% confidence, compared to CC subjects; the scores for the GC heterozygotes lying approximately midway.

A very similar pattern with significant difference ($P = 0.008$) was observed using the BIS total scores (Fig. 2a); subjects with the GG genotype show significantly higher impulsivity, and with no over-lap at 95% confidence, compared to CC subjects; the scores for the GC heterozygotes lying approximately midway. On the Motor Impulsiveness subscale of BIS-11 (Fig. 2b), the GC subjects behaved like CC individuals, with a significant difference ($P = 0.021$) between the GC and the GG genotypes; whereas on the Cognitive Impulsiveness subscale (Fig. 2c), GC subjects behaved more like GG individuals, with significant differences ($P = 0.002$) between each of these two groups and the CC homozygotes; however, there was no significant difference ($P = 0.520$) between the different genotype groups in the Nonplanning Impulsiveness subscale (Fig. 2d).

Post-hoc analysis revealed that the study had 0.958 power to detect 0.15 effect size (Table II).

TABLE II. Analysis of Variance Table for the Barratt Impulsiveness Scale (BIS-11) and the Impulsiveness Subscale (IVE-I) of the Eysenck Impulsiveness, Venturesomeness and Empathy Scale Associated With Genotypes GG, GC and CC

	GG			GC			CC						
BIS-11 and IVE-I scales	**n**	**Mean**	**SE**	**n**	**Mean**	**SE**	**n**	**Mean**	**SE**	**df**	**F**	***P*-value***	**Observed power**
BIS total	193	59.178	0.698	368	57.093	0.505	163	56.112	0.759	2.719	4.862	**0.008**	0.98
BIS motor	193	20.15	0.236	364	19.40	0.171	161	19.34	0.258	2.713	3.886	**0.021**	0.88
BIS cognitive	193	16.31	0.204	364	15.97	0.148	161	15.25	0.223	2.713	6.337	**0.002**	0.99
BIS nonplanning	193	22.70	0.313	364	22.34	0.228	161	22.21	0.343	2.713	0.654	0.520	0.29
IVE-I	192	6.47	0.291	368	5.75	0.210	161	5.228	0.318	2.716	4.302	**0.014**	0.97

*$P < 0.05$ is shown in bold.

Although age and gender were included in the ANOVA model as covariates, separate analyses of males and females were also performed. These analyses revealed that on the IVE-I scale, genotype had significant effect in both groups (males: $P = 0.017$, females: $P = 0.005$). On the Motor and the Cognitive Impulsiveness subscales of the BIS-11, the effect of genotype remained significant only among females ($P = 0.016$ and $P = 0.006$) but not among males ($P = 0.09$ and $P = 0.23$). Because the ratio of females to males was higher than 4 in our study group, we attribute the lack of significance in males due to the smaller sample size in the latter case. Indeed, the general patterns were the same for both groups and subjects carrying GG genotypes had the highest impulsiveness scores in all comparisons.

DISCUSSION

In the present study, we found a significant association between the C(−1019)G functional polymorphism of the HTR_{1A} gene and impulsivity. Subjects with the GG genotype scored significantly higher on the IVE-I, and on the Motor Impulsiveness and Cognitive Impulsiveness subscales but not on the Nonplanning Impulsiveness subscale of BIS-11 compared to subjects with the GC or CC genotypes.

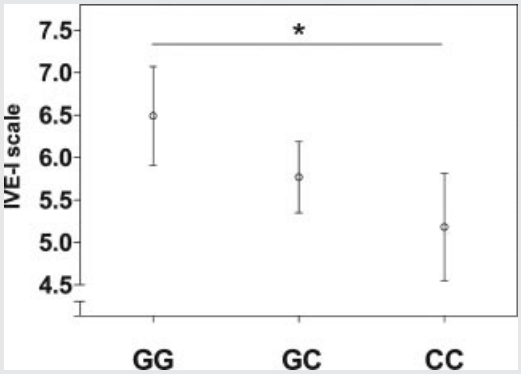

FIG. 1. Comparison of GG, GC, and CC genotypes for the IVE-I scale. Error bars show 95% confidence interval. *$P < 0.05$ post-hoc Tukey's HSD test.

Impulsivity is a multifaceted trait, and there are several scales developed to measure impulsivity based on slightly different theoretical concepts. We used two of these scales in our study to be able to analyze impulsivity in a more complex and global way. The BIS-11 contains three subscales describing three different components of impulsivity: motor impulsiveness is a tendency to act without thinking, cognitive impulsiveness is involved in making quick cognitive decisions, and nonplanning impulsivity refers to a lack of sense of the future. Barratt defined impulsivity as a personality trait, and linked it to Eysenck's extraversion and sensation seeking personality traits. The questionnaire originally measured impulsivity as a unidimensional personality trait, the three dimensions were characterized only later [Patton et al., 1995].

Previous animal and human research showed that serotonin is implicated in impulsivity [Buhot, 1997; Robbins, 2000], for example, low brain serotonin level has been associated with increased impulsive choice in animals [Bizot et al., 1999] and in humans [Schweighofer et al., 2008], but contradictory findings have also been described [Dalley et al., 2002; Homberg et al., 2007]. The role of 5-HT receptors, mainly 5-HT_1 and 5-HT_2 receptors, have been well studied in the regulation of impulsivity. Agonists that act on 5-HT_{1A} receptors decrease impulsive behavior [de Boer and Koolhaas, 2005]. In brain areas where post-synaptic 5-HT_{1A} receptors are located, such as the amygdala and frontal cortex, the density of 5-HT_{1A} receptors was found to be decreased in aggressive rats [Popova et al., 2007].

The genetic background of impulsivity has long been investigated. Paaver et al. [2007] reported that subjects with low platelet MAO activity carrying the s allele of 5-HTTLPR showed a higher mean score of self-reported impulsiveness as measured by BIS-11. Knockout mice lacking MAOA differed from wild types by increased aggression [Popova et al., 2007]. Of the 14 different known subtypes of serotonin receptors, the 5-HT_{1A} and 5-HT_{1B} receptor genes have been investigated more thoroughly. Enhanced aggression was revealed in 5-HT_{1B} receptor knockout mice [Saudou et al., 1994]. At the same time 5-HT_{1A} receptor knockout mice showed anxiety-related behavior [Lucki et al., 1994] rather than enhanced aggression [Zhuang et al., 1999]. In contrast, low aggression and high social anxiety parallel with rapid desensitization of 5-HT_{1A} receptors during chronic SSRI treatment were found in Fawn-Hooded rats compared to other rat strains [Kantor et al., 2000, 2001].

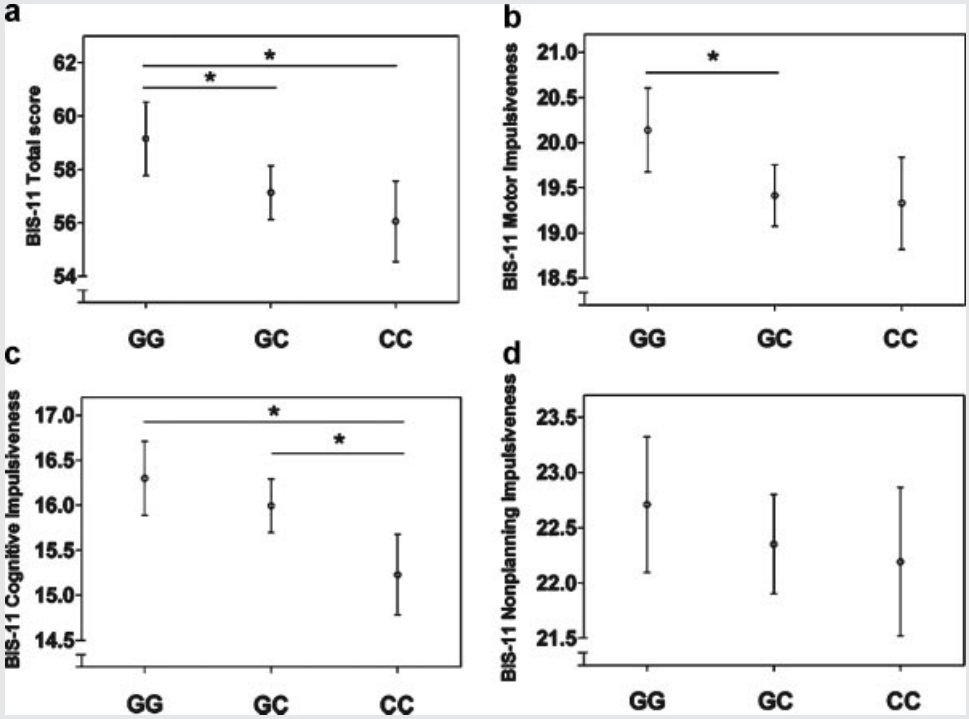

FIG. 2. Comparison of GG, GC, and CC genotypes for the Barratt Impulsiveness scale (BIS-11). Error bars show 95% confidence interval. (a) BIS-11 total score, (b) BIS-11 Motor Impulsiveness, (c) BIS-11 Cognitive Impulsiveness, and (d) BIS-11 Nonplanning Impulsiveness. *$P < 0.05$ post-hoc Tukey's HSD test.

It has been suggested that the C(−1019)G polymorphism regulates the HTR_{1A} gene expression through altered control of the promoter in presynaptic raphe neurons. The polymorphism is located in a 26 bp palindrome region recognized by the transcription factors DEAF-1 and Hes5 that bind efficiently to the C allele, but not to the G allele. Thus the 5-HT_{1A} receptor function is altered by this polymorphism—the G allele leading to reduced serotonergic neurotransmission due to impaired binding of the NUDR repressor protein [Lemonde et al., 2003]. Impulsive behavior has been suggested to occur due to a dysfunction of the serotonergic neurotransmission. Walderhaug et al. [2002] reported that impulsive behavior increased after acute tryptophan depletion causing a decrease in 5-HT neurotransmission in healthy individuals. Another study investigating the effects of ecstasy (3,4-methylenedioxymethamphetamine, MDMA) found a long-term reduction in 5-HT level and increased impulsivity measured by IVE in ecstasy users compared to nonusers [Morgan, 1998]. These findings support earlier evidence that elevated levels of impulsivity are associated with reduced serotonergic function. Our findings support the involvement of a genetic polymorphism of the 5-HT_{1A} receptor in the regulation of impulsive behavior.

Lemonde et al. [2003] reported an association of the G allele of the C(−1019)G polymorphism with completed suicide but not with suicidality among depressed patients. In the study of Serretti et al. [2007] the G allele and STAXI state anger scale showed an association with suicide attempt in females, supporting previous reports that 5-HT_{1A} receptor plays an important role in aggression. Data of Sawiniec et al. [2007] also support the hypothesis that the G allele of the C(−1019)G polymorphism is a biological risk factor of suicide attempt, while Wasserman et al. [2006] found that this polymorphism is not associated with suicide attempts generally and pointed out that this discrepancy in the literature is due to suicidal behavior being a complex phenomenon.

Strobel et al. [2003] examined anxiety- and depression-related personality traits using the NEO-PI-R and the TPQ questionnaires in a German cohort of 284 students. They found association between the G allele and Neuroticism (NEO-PI-R) and Harm Avoidance scales (TPQ). However, other studies failed to detect significant association of this polymorphism with neuroticism [Koller et al., 2006; Hettema et al., 2008], although subsequent analyses showed no significant association with the C(−1019)G polymorphism and Impulsiveness as one of the subscales of the Neuroticism scale [Strobel et al., 2003]. Recently, Serretti et al. [2009] investigated the association between HTR_{1A} and HTR_{2C} SNPs and personality traits, measured by the TCI, in a sample of suicide patients and healthy volunteers. According to their results, SNPs—including rs6295—and haplotypes were not associated with any personality dimensions including Novelty Seeking (NS), that contains an Impulsivity subscale, too.

The TPQ, TCI, and NEO-PI-R provide a broad characterization of personality traits. By contrast, the BIS-11 and other impulsivity-related questionnaires focus on one personality trait in detail [Kreek et al., 2005]. The different construct of impulsivity measured by the personality inventories and specific impulsivity questionnaires may

provide an explanation for the different results. The TCI was designed to measure four temperament and three character dimensions. One of the temperament dimensions is the abovementioned NS. The NS scale was designed to measure exploratory, impulsive, and extravagant behavior, and has been related to the dopamine system by Cloninger et al. [1993], while the BIS-11 provides an integrated measure of impulsivity. Impulsivity can be viewed as having multiple dimensions, rather than being measured as a unidimensional, single, or narrow component [White et al., 1994].

Studies investigating the possible association of C(−1019)G and aggression focused on suicide attempters and completers. Impulsivity is a risk factor of suicide and we found a significant association between the impulsivity scales and C(−1019)G, suggesting that 5-HT_{1A} receptor function may be one of the biological predispositions to suicidality. Impulsivity is not the main risk factor of suicidal behavior; however, this trait has been consistently found to characterize suicide attempters [Mann et al., 1999].

In our study we found a significant association between C (−1019)G, and the Impulsiveness subscale of the Eysenck IVE scale, and also the Motor and Cognitive Impulsiveness subscales but not the Nonplanning Impulsiveness subscale of the BIS-11. Our results thus indicate a profound relationship between this polymorphism and impulsiveness, as indicated by the significant relationship we found in case of two different scales. Furthermore, our result of no significant association between nonplanning impulsiveness and the C(−1019)G polymorphism indicates that this relationship is valid only for the basic and elementary manifestations of impulsiveness-related behavior but not for nonplanning impulsiveness which incorporates more complex and higher mental processes. Other genes regulating these processes are likely to play an important role in the background of nonplanning impulsiveness.

Our study cohort was a reasonable size (n = 725), although the number of males was relatively small (n = 129). Candidate gene studies can produce false positive results [Sullivan, 2007], and thus, precise (same genetic marker, phenotype, genotype, statistical analyses, and questionnaire) replication studies are required focusing on impulsivity and this particular SNP. Subjects with psychiatric disorders were also included and these may have some unknown bias on the results. However, our results suggest the involvement of the HTR_{1A} gene in the continuum phenotype of impulsivity.

ACKNOWLEDGMENTS

This study was supported by the Sixth Framework Program of the EU, LSHM-CT-2004-503474, ETT 460/2006, and the Ph.D. Fellowship Program of Semmelweis University, Ministry of Culture and Education, Hungary. Thanks to Hazel Platt and Krisztina Mekli for the genotyping procedures.

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