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Impulsive-disinhibited personality and serotonin transporter gene polymorphisms: Association study in an inmate's sample

Anton Aluja [a,c,*], Luis F. Garcia [a,c], Angel Blanch [a,c], D. De Lorenzo [b,c], Joan Fibla [b,c,*]

[a] Department of Pedagogy and Psychology, University of Lleida, Avada Estudi General 4, Campus de Cappont, 25100 Lleida, Catalonia, Spain
[b] Departament of Basic Medical Sciences, University of Lleida, Lleida, Catalonia, Spain
[c] Institut of Biomedical Research of Lleida (IRB-Lleida), Lleida, Catalonia, Spain

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ABSTRACT

The association between different impulsive-disinhibited personality traits with 5-HTTLPR and 5-HTTVNTR genetic polymorphisms was examined in an imprisoned male sample. Higher scores of the impulsive-disinhibited personality traits tended to be associated with carrying one or two copies of the 5-HTTPLR S allele (S/S homozygous and S/L heterozygous), and carrying two copies of the 5-HTTVNTR 12 allele (12/12 homozygous). Genotype, allele, haplotype and extended genotype distribution between low and high impulsive-disinhibited groups confirmed this association. Allele S and genotypes S/S+S/L at the 5-HTTLPR locus and allele 12 and genotype 12/12 at the 5-HTTVNTR locus were overrepresented in the high scoring group. Accordingly, allele S and allele 12 conferred a trend for risk to be in the high scoring group with an odds ratio (OR) of 1.8 ($p < 0.035$) and 1.7 ($p < 0.014$), respectively. In addition, extended genotype distribution shows that those S allele carriers (S/S homozygote and S/L heterozygote) that were also 12/12 homozygote, were overrepresented in the high scoring group (OR = 3.2; $p < 0.004$). The main risk of being in the high scoring group was assigned to those carrying two copies of the S-12 haplotype (OR = 5.7; $p < 0.0007$). We discuss the possible relationship between the two genetic serotonin polymorphisms and the personality impulsive-disinhibited traits investigated.

1. Introduction

More than ten years have been devoted to the study of the association between personality and several genetic polymorphisms (Munafò et al., 2003; Munafò et al., in press; Schinka et al., 2004), with most of these studies focussing on the serotonin transported gene (5-HTT: 5-Hydroxytryptamine transporter), the SLC6A4, also known as the 5-HTTLPR, -linked polymorphic region-; Heils et al., 1995). The SLC6A4 has been located in the 17q11.1-q12 chromosome, with several identified polymorphisms such as the promoter region, 5-HTTLPR (Lesch et al., 1996), or the Variable Number Tandem Repeats in intron 2 (5-HTTVNTR; Kunugi et al., 1997; Ogilvie et al., 1996).

Basal and induced-human SLC6A4 gene transcription is differentially modulated by the two allelic variants of the promoter, insertion or deletion of 44-base pair sequence localized 1.2 kb upstream the gene. The 5-HTTLPR is a short (S) allele comprising 14 copies of a 20–23 base pair repeat unit and a long (L) allele comprising 16 copies. This gene controls the availability of this neurotransmitter by regulating its absorption (Lesch et al., 1994). The 5-HTTVNTR displays three common alleles in regard to the number of repetitions: 12, 10 or 9. The first is usually identified as the long allele (12), whereas the presence of 10 or 9 repetitions would correspond to the short allele (10).

The findings reported in the psychopathological literature show that the 5-HTTLPR has been associated with personality traits such as anxiety- depression and aggressiveness (Munafò et al., 2003; Sen et al., 2004). On the other hand, significant but weaker associations have been found between the 5-HTTVNTR with attention deficit and hyperactivity disorder, suicide, borderline personality disorder, drug abuse, and epilepsy (Hranilovic et al., 2004; Kim et al., 2005; Manna et al., 2007; Ni et al., 2006; Pascual et al., 2008; Patkar et al., 2002; Zoroglu et al., 2002), and in addition, to novelty-sensation seeking personality traits (Pascual et al., 2007; Patkar et al., 2002; Vormfelde et al., 2006).

Biochemical studies show that low levels of serotoninergic activity have been consistently related to aggressiveness and impulsivity, considering serotonin, its metabolites and inhibitory enzymes such as MAO (Hennig, 2004; Zuckerman, 1994). The studies performed with the 5-HTT show that L/L homozygotes have a higher rate of 5-HTT mRNA transcription, 5-HTT ligand binding,

* Corresponding authors. Present address: Àrea de Personalitat, Avaluació i Tractament Psicològic, Universitat de Lleida, Avda, Estudi General 4, 25100 Lleida, Spain. Tel.: +974 70 65 37; fax: +973 70 65 02 (A. Aluja), Present address: Genetic of Complex Diseases Research Group, Departament de Ciències Mèdiques Bàsiques, Universitat de Lleida, Montserrat Roig 2, 25199 Lleida, Spain. Tel.: +973 70 24 73 (J. Fibla).
E-mail addresses: aluja@pip.udl.cat (A. Aluja), joan.fibla@cmb.udl.cat (J. Fibla).

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and 5-HT uptake than those containing at least one copy of the S allele (Lesch et al., 1996). Moreover, it has been found that the 5-HTTVNTR intron 2 region could act as a transcriptional regulator of the 5-HTT gene, with 12-repeat allele having stronger enhancer-like properties than 10-repeat allele. In addition, the S allele is dominantly connected to the lower expression in the 5-HTTLPR, whereas the 10 allele of the 5-HTTVNTR is also related to a lower expression (Hranilovic et al., 2004). The low expression of the gene should provide lower 5-HTT or uptake levels, although the research works so far have produced inconclusive results. The operational consequences of the 5-HTTVNTR polymorphism in native-expressing cells have yielded no significant effects of the genotype on platelet 5-HT uptake (Kaiser et al., 2002) or on 5-hydroxindoleacetic acid level (Jonsson et al., 1998). Considering the relationship between low serotonin levels and impulsivity, aggressiveness, and disinhibited behaviour (Hennig, 2004), a relationship should be expected between a low expression of the 5-HTT gene with low levels of serotonin, a higher frequency of a single or two S copies in the 5-HTTLPR, and one or two copies of the10 allele in the 5-HTVNTR. In general terms, the present results in regard to the serotonin polymorphisms and impulsive-disinhibited personality are not consistent with this hypothesis.

In relation to the 5-HTPLPR polymorphism and impulsive-disinhibited syndromes, several studies have found a relationship between different kinds of aggressiveness, violence, alcoholism, antisocial personality and impulsivity (Däderman and Lidberg, 2002; Goodman and New, 2000; Larsson et al., 2007; Lesch and Merschdorf, 2000), and mental disorders (Lidberg et al., 2000), including antisocial (APD) or borderline personality disorders (BPD) (Reif and Lesch, 2003). The frequency of short S allele 5-HTT promoter polymorphism seems to be higher in male individuals with conduct disorder, aggressiveness and ADHD (Cadoret et al., 2003). The S allele seems to confer susceptibility to a temperamental profile of high novelty seeking and low harm avoidance that has been postulated to underlie dissocial alcoholism (Gerra et al., 2005; Hallikainen et al., 1999; Sander et al., 1998;) and impulsive-Sensation Seeking in BPD (Pascual et al., 2007). Furthermore, Liao et al. (2004) reported that the S allele was associated with extremely violent criminal behaviour, even though there was no relation with antisocial personality disorder in a sample of Chinese felons. Additionally, Lyons-Ruth et al. (2007) inform that the 5HTTLPR S-alleles were significantly associated with the presence of APD and BPD traits. Nevertheless, there are some discrepancies in regard to this type of results (Ebstein, 2006). For instance, there has been no supporting evidence of the association of the 5-HTTLPR and impulsive-aggressive personality traits with cocaine addicts (Patkar et al., 2002).

As for the 5-HTTVNTR, the association of allelic variations with disinhibitory syndromes, including impulsive-disinhibited personality, are generally inconsistent. For instance, no differences were found for S-10 haplotypes between controls and suicide victims (Hranilovic et al., 2004). In a sample of children with attentional deficit and hyperactivity disorder (ADHD), it was found that the 12/12 variant was more frequent in controls than in children with ADHD (Zoroglu et al., 2002). Also, a significant excess of the S-allele and the b S/S genotype have been reported in violent individuals with a childhood history of ADHD related symptomatology (Retz et al., 2008). Further, 12 repeats were positively associated with attention (Kim et al., 2005). Patients with temporal lobe epilepsy showed lower frequencies of the 10 repeat alleles than the controls (Manna et al., 2007). However, no differences were found in any allelic variation between borderline personality disorder (BPD) patients and control subjects (Pascual et al., 2008), whereas BPD patients showed significantly higher frequencies of the 10 repeat markers and the S-10 haplotype than controls (Ni et al., 2006). Considering impulsive-disinhibited personality traits, it has been found that men with 10/10 allele variation obtained significantly higher scores in novelty-seeking and reward dependence than other genotype combinations (Vormfelde et al., 2006). Davidge et al. (2004) revealed a significantly reduced frequency of the 10 repeat alleles in children with a high-aggression phenotype compared with normal controls. Furthermore, individuals with 10 allelic repeat obtained higher scores in impulsive sensation seeking than those not carrying 10 alleles repeat (Pascual et al., 2007). Nevertheless, no differences were found between allelic variations in aggressivity, impulsivity and sensation seeking scores (Patkar et al., 2002).

It has been found that individuals with a lack of inhibitory control showing high levels of impulsivity and aggressiveness also show a lower serotoninergic activity. Gorenstein and Newman (1980) refer to *disinhibiton* as a disruption of active inhibitory processes regulating tendencies to respond. It refers to human behaviour that has been interpreted as arising from lessened controls on response inclinations. Disinhibited individuals appear unable to control their immediate response inclinations as a means of achieving long-range goals. Among the behavioural syndromes characterized primarily by disinheriting are the personality construct of impulsiveness, aggressiveness, antisocial behaviour, hyperactivity in children or primary alcoholism. The common feature of disinhibitory syndromes, however, is impulsivity (af Klinteberg et al., 2004), a personality trait related with Psychoticism (Eysenck et al., 1985), Sensitivity to Reward (Corr, 2002), and with the diverse definitions of the Sensation Seeking trait (Cloninger et al., 1993; Schalling et al., 1987a; Schalling et al., 1987b; Zuckerman, 1994).

In their review on personality and genetic polymorphisms, Munafò et al. (2003) suggested several modifications in regard to future studies: (1) The use of several conceptually related phenotypic measures (see also Caspi et al. (2002)); (2) The application of comparative designs of extreme groups; (3) Investigation of the interactions between different genotypic markers. In the present work, we investigate the relationship between the construct of impulsive-disinhibited personality and the combination of the 5-HTTPLR and 5-HTTVNTR. No single study has considered the role that the 5-HTTVNTR might have in disinhibition and antisocial behaviour individual differences, or in regard to the combined effect with the 5-HTTLPR. It has been found that incarcerated individuals obtain higher scores than the general population in this kind of personality traits, especially in males. Therefore, it would be the optimal population to perform this kind of study.

In the light of the findings reported about the association between serotoninergic system and personality, it seems plausible to expect an association between the serotonin genetic polymorphisms and impulsive-disinhibited personality traits. Given the inconsistent results reported in the literature, we want to review all genotypic combinations and haplotypes for both polymorphisms in relation to personality traits. Therefore, if the 5-HTTLPR S-allele is related to a low serotoninergic activity, and the 5-HTTVNTR 10-allele, then it will increase susceptibility to present impulsive-disinhibited personality trait, like Psychoticism, Sensitivity to Reward, Impulsive-Sensation Seeking and Aggressiveness. We hypothesised that this association would be stronger in extreme groups of impulsive-disinhibited personality traits.

2. Method

2.1. Participants

The participants in the current study were 147 male inmates. Ninety-eight per cent of the individuals had been sentenced for one or more of the following crimes: robbery (more than 50% of the sample), murder, assault or threatening behaviour, rape,