



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

Anton Aluja<sup>a,c,\*</sup>, Luis F. Garcia<sup>a,c</sup>, Angel Blanch<sup>a,c</sup>, D. De Lorenzo<sup>b,c</sup>, Joan Fibla<sup>b,c,\*</sup>

<sup>a</sup> Department of Pedagogy and Psychology, University of Lleida, Avda Estudi General 4, Campus de Cappont, 25100 Lleida, Catalonia, Spain

<sup>b</sup> Department of Basic Medical Sciences, University of Lleida, Lleida, Catalonia, Spain

<sup>c</sup> 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-HTTLPR 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.

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### 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 transporter 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 serotonergic 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](mailto:aluja@pip.udl.cat) (A. Aluja), [joan.fibla@cmb.udl.cat](mailto:joan.fibla@cmb.udl.cat) (J. Fibla).

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-hydroxyindoleacetic 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 the 10 allele in the 5-HTTVNTR. 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-HTTLPR 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 Merschedorf, 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 5-HTTLPR 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 serotonergic activity. Gorenstein and Newman (1980) refer to *disinhibition* 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-HTTLPR 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 serotonergic 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 serotonergic 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,

trafficking in narcotics, fraud or domestic violence. The mean age was 33.31 (s.d.: 8.6). All subjects completed the personality questionnaires, whereas there were 143 observations in the 5-HTTLPR, and 142 in the 5-HTTVNTR polymorphisms. Genetic data for the control group were derived from a healthy subject database available at the laboratory.

Exclusion criteria for participating in the study were: (1) Non Caucasian; (2) Diagnosis of psychotic or affective disorder; and (3) Being a relative of one of the participants in the study. This information was assessed from penitentiary archive data on each subject. Subjects who agreed to participate signed a voluntary consent, and no reward was given for participating in the study. The study complied with the Code of Ethics of the Official Scientific Medical.

## 2.2. Measures

### 2.2.1. ImpSS

Impulsive sensation seeking (ZKPQ, Zuckerman et al., 1993). This scale measures lack of planning and the tendency to act impulsively without thinking. The ImpSS items are general in content and do not describe specific activities such as drinking or sex. Most can be described as experience seeking, or the willingness to take risks for the sake of excitement or novel experience. The scale has 19 items, but for this study a validated shorter 14-item scale form was used (Aluja et al., 2003a). Alpha reliability was .78 for males.

### 2.2.2. Agg-host

Aggression-hostility (ZKPQ, Zuckerman et al., 1993) is also a scale from the ZKPQ. This scale has 17 items, but we used a validated shorter form of 13 items (Aluja et al., 2003a). Half of the items describe readiness to express verbal aggression, while the other half tap rude, thoughtless or antisocial behavior, revengefulness, and spitefulness. High scores in this scale indicate a quick temper and impatience with others. Alpha reliability was 0.71 for males.

### 2.2.3. SR

Sensitivity to reward (SPSRQ; Torrubia et al., 2001), is a 24-item scale from the Sensitivity to Punishment and Sensitivity to Reward Questionnaire. The SR assesses differences in the impulsivity dimension following Grays's description of the BAS. Alpha reliability was 0.78 for males.

### 2.2.4. P

Psychoticism (EPQ-RS; Aluja et al., 2003b; Eysenck et al., 1985; Ibáñez, in press) is a 12-item scale derived from the Eysenck Personality Questionnaire. The Psychoticism scale measures lack of empathy, egocentrism and proneness to antisocial behaviour. Alpha reliability was .62 for males.

### 2.2.5. MA

Monotony avoidance (KSP; af Klinteberg, 1986; Ortet and Torrubia, 1992) is a 10 item scale from the Karolinska Personality Scales, which measures avoiding routines, thrill seeking, and need for change and action. Alpha reliability was .76 for males.

## 2.3. Genotyping

Genomic DNA was obtained from buccal swabs using the Bucca-I Amp DNA extraction kit (Epicentre, Madison, USA). Polymerase Chain Reaction (PCR) protocols were followed to detect two polymorphisms of the *SLC6A4* gene, the insertion/deletion polymorphism 5-HTTLPR, located at the promoter region (−15384–−15340 from the start site) and the variable number of tandem

repeats (VNTR) polymorphism 5-HTTVNTR, located at positions +380 to +573 at intronic sequence between exons 3 and 4 (according to *SLC6A4* genomic structure from NCBI Build 36.1 on March 2006). PCR primers and methods were performed as described by Heils et al. (1996) for 5-HTTLPR and Lesch et al. (1994) for 5-HTTVNTR. Amplified fragments were resolved in a 12% acrylamide gel using the Mini-Protean equipment (BioRad Laboratories, El Prat de Llobregat, Spain). DNA bands were detected by ethidium bromide staining. Following the literature, 5-HTTLPR alleles were coded as long allele (L), corresponding to fragments of 528 bp (insertion allele) and short allele (S) corresponding to fragments of 484 bp (deletion allele). The 5-HTTVNTR alleles were coded as long allele (12), corresponding to fragments of 300 bp (12 repeat units) and short allele (10) corresponding to fragments of 265 and 250 bp (10 and 9 repeat units, respectively).

## 2.4. Data analysis

Mean differences were analyzed for each one of the 5 personality scales and the sum of all of them for the L/L and L/S+S/S genotypes at the 5-HTTLPR locus and the 12/12 and 12/10+10/10 genotypes at the 5-HTTVNTR locus. With the purpose of studying the distribution of the frequencies of the scales the kurtosis and skewness values were obtained. The reliability of the scales was assessed by means of the internal consistency revealed by Cronbach's alpha (Cronbach, 1951). Additionally, we calculated an Impulsiveness-Disinhibition Index (ID\_Index) by adding the Z value of the 5 personality scales in order to get a standardized global continuous measure. Besides, a two value categorical variable was computed based on the ID\_Index with the percentile 75 as a cut-off value, in order to avoid the limitations derived from splitting the sample in half from the mean, or from using as groups subjects with higher or lower scores from the mean (Jobe and White, 2007). Several variants of this procedure have been used in genetic association studies with different samples (Bennet et al., 2006; Mather et al., 2007; Smoller et al., 2001). This procedure overcomes the above limitations, by allowing the analysis with the full sample. This new categorical variable allowed the classification of those subjects with "low" and "high" Z scores.

A principal components analysis (PCA) was performed in order to assess the dimensionality of ID\_Index. The Kaiser–Meyer–Olkin measure of sample adequacy was .81 and the Bartlett test of sphericity yielded a chi-square of 298, 51 (d.f. = 10;  $p < .001$ ). Only one factor obtained an eigenvalue equal or superior to 1, accounting for 55.47% of the variance. The factorial loadings of each personality variable were: 0.85 (ImpSS), 0.78 (MA), 0.72 (SR), 0.71 (P) and 0.66 (Agg-Host). A confirmatory factor analysis (CFA) was carried out over the variance-covariance matrix through the AMOS 4.01 statistical package (Arbuckle, 1999). The estimation method was that of Maximum Likelihood. In order to achieve model identification, regression coefficients of the error terms over the endogenous variable as well as variances of the factors were fixed at 1. Chi-Square was 5.40 (df: 5;  $p < 0.369$ ). Different goodness-of-fit indices were obtained: The Goodness of Fit Index (GFI): 0.985, Adjusted Goodness of Fit Index (AGFI): 0.955, Tucker Lewis Index (TLI): 0.996, Comparative Fit Index (CFI): 0.998 and Root mean square error of approximation (RMSEA): 0.023.

Hardy-Weinberg equilibrium and pairwise linkage disequilibrium ( $D'$  and  $r^2$ ) were calculated using the Haploview 3.32 software (<http://www.broad.mit.edu/mpg/haploview>). As suggested by Munafò et al. (2003), departures from equilibrium may reflect population stratification, inbreeding or genotyping error. Overall distribution of genotypes among subjects with low and high ID\_Index scores were compared by contingency table analysis. Statistical inference of haplotypes from our genotype sample data was performed by the PHASE 2.1.1 software available at

<http://www.stat.washington.edu/stephens/software.html>. Details on the inference of haplotype pairs and estimation of haplotype counts and haplotype probabilities are in the supplementary material. Statistical analysis was performed by SPSS-14.0 software and the OpenEpi java application (<http://www.openepi.com/Menu/OpenEpiMenu.htm>). Single-marker association P-values were corrected for multiple-testing following the SNP spectral decomposition (SNPSpD) approach (<http://gump.qimr.edu.au/general/daleN/SNPSpD/>). SNPSpD allows us to estimate the effective number of independent marker *loci* and the experiment-wide significance threshold required to keep Type I error rate at 5%, which were 1.824 and 0.027, respectively.

**3. Results**

No departure from Hardy–Weinberg equilibrium was observed for both controls and inmates. Genotype and allele distribution between control subjects and inmates did not show statistically significant differences (Table 2). Two marker haplotypes were inferred from genotype data by the Phase 2.1.1 software. Haplotype distribution was not different between control subjects and inmates. The Haploview software was used to estimate linkage disequilibrium parameters; Lewontin disequilibrium coefficient (*D'*) and correlation coefficient (*r*<sup>2</sup>) were lower in controls (0.4 and 0.07, respectively) than in inmates (0.67 and 0.17, respectively).

Table 1 shows the means, standard deviations, *t*-test differences and alpha reliabilities for 5-HTTLPR and 5-HTTVNTR genotypes and extended genotypes. Subjects with S/S and S/L genotypes (S/S+S/L) of the 5-HTTLPR locus obtained higher scores than the L/L genotype, although these *t*-test differences only showed a trend to significance for MA (24.37 vs. 26.20; *p* < 0.052). In addition, subjects with the 12/12 genotype of the 5-HTTVNTR polymorphism obtained higher scores than the subjects carrying 12/10 and 10/10 genotypes (12/10+10/10), reaching statistical significance for SR (13.84 vs. 11.81; *p* < 0.012). The scores of the ID\_Index (Z scores) showed a similar trend, reaching the highest scores for those with S/S+S/L genotypes at the 5-HTTLPR locus and for those with 12/12 genotype at the 5-HTTVNTR locus (Table 1). We also analyzed extended genotypes combination and found that subjects with both S/S+S/L genotypes at 5-HTTLPR locus and 12/12 genotype at 5-HTTVNTR locus (S/S+S/L & 12/12) obtained higher scores when compared with all other genotype combinations considered together, being statistically significant for the SR (13.99 vs. 11.88; *p* < 0.018). In addition, the scores for the ID\_Index was highest for those with S/S+S/L & 12/12 extended genotype, reaching statistical borderline significance (+0.86 vs. -0.47; *p* < 0.052). Skewness and kurtosis values in the ±1 range ascertained normality assumptions. Alpha reliabilities were acceptable and similar to other studies.

Table 2 shows genotype distribution compared among subjects categorized as low scorers (ID\_Index < percentile 75, *n* = 110) and high scorers (ID\_Index > percentile 75, *n* = 36). Allele S and genotypes S/S+S/L at the 5-HTTLPR locus were overrepresented in the high scoring group (56% in the high vs. 41% in the low, *p* < 0.033 and 82% in the high vs. 63% in the low; *p* < 0.035, respectively). According to this, allele S seemed to confer risk on the high scoring group with an odds ratio (OR) of 1.8, which follows a dominant model with OR = 2.7 (Table 2). Allele 12 and genotype 12/12 at the 5-HTTVNTR locus were overrepresented in the high scoring group (73% in the high vs. 61% in the low, *p* < 0.069 and 54% in the high vs. 31% in the low; *p* < 0.014, respectively). According to this, allele 12 conferred a trend for risk on the high scoring group with an OR = 1.7, which follows a recessive model with OR = 2.6 (Table 2). Extended genotype distribution was also compared between ID\_Index score groups, and those S allele carriers (S/S homozygote and S/L heterozygote) that were also 12/12 homozygote

**Table 1**  
Descriptive, *t*-test differences, distribution frequencies and Cronbach's alpha.

Items	5-HTTLPR			5-HTTVNTR			Extended genotypes 5-HTTLPR and 5-HTTVNTR						All cases						
	S/S+S/L (n = 96)			12/12 (n = 52)			12/10+10/10 (n = 89)			S/S+S/L & 12/12 (n = 43)			Other genotype combinations (n = 94)			S	K	Alpha	
	M	SD	t-test	M	SD	p <	M	SD	p <	M	SD	p <	M	SD	t-test				p <
	14	13	24	12	10	85	14	13	24	12	10	85	14	13	24	12	10	85	
ImpSS	8.60	3.07	-0.99	8.85	3.13	0.326	8.18	3.39	1.83	0.239	8.81	3.27	8.19	3.27	1.03	0.303	-0.57	-0.21	0.76
Agg-Host	6.63	3.20	-0.54	6.83	3.42	0.590	6.42	2.96	0.70	0.483	6.97	3.55	6.34	2.94	1.10	0.274	0.00	-0.91	0.75
SR	12.93	5.11	-1.27	13.84	4.38	0.206	11.81	4.88	2.55	0.012	13.99	4.72	11.88	4.69	2.39	0.018	-0.16	-0.33	0.80
P (EPQ)	4.57	2.34	-0.90	4.67	2.67	0.372	4.35	2.29	0.73	0.465	4.76	2.67	4.31	2.31	1.02	0.308	0.25	-0.61	0.61
MA (KPS)	26.20	5.03	-1.969	26.58	4.82	0.052	25.03	5.19	1.78	0.077	26.67	5.03	25.06	5.16	1.71	0.090	-0.41	0.19	0.71
ID_Index	0.29	3.68	-1.66	0.74	3.86	0.120	-0.46	3.62	1.85	0.067	0.86	4	-0.47	3.77	1.96	0.052	-	-	-

Note: ImpSS: Impulsive sensation seeking. Agg-Host: Aggressivity-hostility. SR: Sensitivity to reward. P: Psychoticism. MA: Monotony avoidance. K: Kurtosis. S: Skewness. ID\_Index: Sum of z means of all six scales.

**Table 2**  
Genotype distribution among groups analyzed.

	Distribution in inmates				Comparisons between ID_index groups <sup>b</sup> Odds ratio (95% Confidence Interval); P value
	Control subjects (n = 100) n, (%)	All inmates (n = 146) n, (%)	Inmates grouped according to ID_Index		
			Low ID_index (n = 36) n, (%)	High ID_index (n = 36) n, (%)	
<b>Genotypes<sup>a</sup> &amp; alleles</b>					
<b>5-HTTLPR</b>					
S/S	23 (23)	31 (22)	21 (19)	10 (29)	Overall distribution $\chi^2(2df) = 4.7$ ; $p < 0.096$ . S/S+L/S vs. L/L. 2.7 (1.05–7.2); $p < 0.035$ . S vs. L. 1.8 (1.04–3.1); $p < 0.033$
L/S	46 (46)	65 (46)	47 (44)	18 (53)	
L/L	31 (30)	46 (32)	40 (37)	6 (18)	
S	95 (47)	127 (45)	89 (41)	38 (56)	
L	109 (53)	157 (55)	127 (59)	30 (44)	
<b>5-HTTVNTR</b>					
12/12	40 (40)	52 (37)	33 (31)	19 (54)	Overall distribution $\chi^2(2df) = 6.3$ ; $p < 0.043$ . 12/12 vs. 12/10+10/10. 2.6 (1.2–5.7); $p < 0.014$ . 12 vs. 10. 1.7 (0.96–3.2); $p < 0.069$
12/10	49 (49)	76 (54)	63 (59)	13 (37)	
10/10	11 (11)	13 (9)	10 (10)	3 (9)	
12	131 (64)	180 (64)	129 (61)	51 (73)	
10	73 (36)	102 (36)	83 (39)	19 (27)	
<b>Extended genotypes (5-HTTLPR and 5-HTTVNTR)<sup>c</sup></b>					
S/S+S/L and 12/12	32 (32)	43 (32)	26 (25)	17 (52)	Overall distribution $\chi^2(3df) = 9.5$ ; $p < 0.024$ . S/S+S/L and 12/12 vs. other genotype combination. 3.2 (1.4–7.2); $p < 0.004$
L/L and 12/12	8 (8)	7 (5)	7 (7)	0 (0)	
S/S+S/L and 10/10+10/12	37 (37)	51 (37)	41 (39)	10 (30)	
L/L and 10/10+10/12	23 (23)	36 (26)	30 (29)	6 (18)	
<b>Haplotypes<sup>d</sup></b>					
S-12	71.2 (36)	110.7 (38)	73.1 (33)	37.5 (52)	Overall distribution $\chi^2(3df) = 8.5$ ; $p < 0.035$ . S-12 haplotype vs. other haplotypes. 2.2 (1.3–3.9); $p < 0.004$ .
L-10	50.1 (25)	85.9 (29)	69.3 (31)	16.5 (23)	
L-12	57.9 (29)	75.2 (26)	60.0 (27)	15.1 (22)	
S-10	20.8 (10)	20.2 (7)	17.4 (8)	2.8 (4)	
<b>Number of S-12 haplotype copies</b>					
Two copies	13 (13)	23.4 (16)	13 (12)	13 (29)	Overall distribution $\chi^2(2df) = 11.46$ ; $p < 0.003$ . Two copies vs. zero copies. 5.6 (1.9–16.5); $p < 0.0007$ . One copy vs. zero copies. 2.8 (1.06–7.3); $p < 0.030$ . S-12 present vs. S-12 absent. 2.8 (1.3–7.1); $p < 0.014$ .
One copy	45 (45)	63.9 (44)	47.1 (43)	16.8 (47)	
Zero copies	42 (42)	58.7 (40)	49.8 (45)	8.8 (24)	

Threshold required to keep Type I error rate at 5% was  $p < 0.027$ . P values remain significant after correction for multiple testing are indicated in bold.

<sup>a</sup> From all 146 inmate subjects analyzed, genotypes were available for 142 subjects at the 5-HTTLPR locus and 141 subjects for the 5-HTTVNTR locus.

<sup>b</sup> Comparisons were performed by contingency table analysis implemented in the SPSS 14.0 software and OpenEpi Java application.

<sup>c</sup> Genotypes at both loci were available for 137 inmates.

<sup>d</sup> Haplotypes were estimated by the PHASE 2.1.1 software.

were found to be overrepresented in the high score group (52% in the high vs. 25% in the low,  $p < 0.004$ ).

Haplotype frequencies were inferred by the Phase 2.1.1 software and compared among ID\_Index Z score groups. Haplotype S-12 (5-HTTLPR-5-HTTVNTR) was overrepresented in the high score group (52% in the high vs. 33% in the low,  $p < 0.004$ ) (Table 2). We also compared the distribution of diplotypes (each individual's haplotype combination) among index Z score groups. Carriers of two S-12 haplotype copies (S-12/S-12 homozygotes) and carriers of one single S-12 copy (S-12 heterozygotes) were overrepresented in the high score group (29% in the high vs. 12% in the low,  $p < 0.003$  and 47% in the high vs. 43% in the low). Consequently, carriers of at least one S-12 copy were more prevalent in the high score group (76% in the high vs. 55% in the low;  $p < 0.014$ ). According to this, S-12 haplotype conferred risk to be on the high score group following a dominant model with an OR = 2.8 (Table 2). The higher risk was observed for those carrying two S-12 copies when compared with non S-12 carriers, OR = 5.6 ( $p < 0.0007$ ) (Table 2).

#### 4. Discussion

This study was designed to study the relationships between two serotonin genetic polymorphisms with impulsive-disinhibited personality traits in a group of incarcerated people in accordance with the guidelines from Munafò et al. (2003). The independent results for each polymorphism pointed to an association with disinhibited personality, particularly, the S and 12 repeat alleles in the polymorphisms and the promoting gene of serotonin 5-HTTLPR and 5-HTTVNTR. Our results run against the hypothesized relation, given that it was expected that the association of the allelic combinations with impulsive-disinhibited personality would be through the S and 10 repeat alleles. However, the frequency of S alleles of one or more copies in the 5-HTTLPR tended to be associated with the ID\_Index, whereas in the 5-HTTVNTR the association was with the 12 repeat. This association was stronger when combining both polymorphisms.

While the trend to an association among the biggest frequency in S-allele with disinhibitory syndromes are in line with most of the literature, the association of 12-repeats is inconsistent with the findings of some studies. Ni et al. (2006) found that BPD patients showed higher frequencies of the 10 repeat of the 5-HTTVNTR and S-10 haplotype. Vormfelde et al. (2006) did not find significant differences between 5-HTTLPR allele groups and NEO-PI-R and TPQ scores. However, males with higher 10/10 alleles frequencies in 5-HTTVNTR obtained higher and significant scores in Extraversion, Openness, Novelty Seeking and Reward Dependence. Higher scores in novelty seeking-related dimensions were more frequent in S-10 than in S-12 carriers. Also, Pascual et al. (2008) did not find differences in the genotypes of 5-HTTLPR and 5-HTTVNTR in patients with BPD and controls. In a previous study, Pascual et al. (2007) found low and statistically significant scores in Sensations Seeking in BPD patients with 10-allelic repeat.

The phenotypic variables considered in the present study correspond to 5 scales that tap impulsive-disinhibited personality traits which share common variance, as shown by the exploratory and confirmatory factor analyses. This characteristic was empirically demonstrated since all scales loaded positively on the single extracted factor and allowed for the configuration of a general impulsivity-disinhibited index. These results at the psychometric level were supported at the genetic level, since the same genetic group scored higher in every personality scale without exception. The analysis of several scales is suitable to offer a more fine-grained discussion of the specific component that explains the relationship between serotonin polymorphisms and the impulsive-disinhibited construct. Note that the highest loadings on the extracted factor

correspond to Zuckerman's non-socialized Impulsive Sensation Seeking (0.85), Monotony Avoidance (0.78) and Gray's Susceptibility to Reward (0.72) scales. Similarly, the highest mean differences between genetic groups were found for those scales, especially for Susceptibility to Reward and Monotony Avoidance. This suggests that the specific mechanism connecting the genetic and psychological aspects of the impulsive-disinhibited personality would be the search for new stimuli to avoid an unpleasant suboptimal level of arousal. This interpretation is totally congruent with Zuckerman's psychobiological perspective of unsocialized impulsivity-sensation seeking from the optimal level of arousal theory (Zuckerman, 1994), and with evidence about the impact of serotonin on the sensibility to reward process (Rogers et al., 2003). The lowest loading on the Impulsiveness-Disinhibition Index corresponded to the Aggressiveness-Hostility scale, and no mean difference between genetic groups for this scale reached a significant level, indicating that aggressiveness would play no role in the relationship between serotonin polymorphisms and impulsiveness-disinhibited personality. It is also congruent with evidence which suggests that the relationship between sensation seeking and some biological markers is independent from aggressiveness (Aluja and Torrubia, 2004).

In the Eysenck model, impulsiveness is included in the Psychoticism dimension, which has been related to psychopathologic characteristics, aggressiveness and lack of social conformism. In Grays' model, impulsiveness is associated with susceptibility to reward (SR), which in turn has been moderately related to Psychoticism, and positively related to the Eysenck's Impulsiveness scale and Zuckerman's Sensation Seeking scale (Torrubia et al., 2001). Zuckerman (1994) took a psychobiological perspective of impulsiveness from the optimal level of arousal theory, where sensation seeking is an essential component of disinhibitory behavior. In this model, impulsiveness was related to the SSS disinhibition scale, although impulsiveness was later grasped by the non-socialized Impulsive Sensation Seeking scale from the ZKPQ (Zuckerman et al., 1993). In the Karolinska Scales of Personality constructed in the 1970s by Schalling, the dimensions of impulsivity and novelty seeking were included in the impulsiveness and Monotony Avoidance scales (Schalling et al., 1987). Overall, the five applied scales from these personality models are capable of representing the impulsive-disinhibited personality construct from a comprehensive approach, showing a strong relationship with the hypothesized biologic markers in their respective theories (Aluja and Torrubia, 2004; Aluja and García, 2005; Barros-Loscertales et al., 2006; King et al., 1995; Schalling et al., 1988).

Disinhibitory syndromes are mainly characterized by deficient control of impulses (Gorenstein and Newman, 1980). In recent decades, the investigators have found a strong association which appears to exist between actions based on impulsivity and aggression and low serotonin activity, specially alcohol and violence problems (af Klinteberg et al., 1993; af Klinteberg et al., 2004), different kinds of violence (Virkkunen et al., 1994), and criminal behaviour and psychopathic characteristics (Blackburn, 1969). Low 5-hydroxyindoleacetic acid (5-HIAA) levels in the cerebrospinal fluid (CSF) have been found in individuals committing suicide and alcoholics (Virkkunen et al., 1994). Also, several authors have reported some evidence for an association between low platelet MAO activity and vulnerability to alcohol abuse. For af Klinteberg et al. (2005) this association is consistent with the fact that the genes involved in the serotonergic pathway are involved in the development of type II alcoholism. Aggressiveness in children is associated with low platelet MAO activity (af Klinteberg and Oreland, 1995). Sander et al. (1998) showed that the allele S was related to low activity, and at a phenotypic level, increased the susceptibility to alcohol consumption and aggression-related conduct disruptions. Moreover, it was found that the allele S was

associated with an early onset of alcoholism, a greater risk of Antisocial Personality Disorder (APD), and a more common pattern of violent behaviours (Bennett et al., 2002). A higher frequency of the 5-HTTLPR S-allele has also been observed in young adults with a higher level of alcohol tolerance (Turker et al., 1998). In addition, college students homozygous for the S-allele reported more episodes of binge drinking and drinking to “get drunk”, and in impulsive and common violent behavior among clinically referred alcoholics in comparison with non-antisocial subjects (Hallikainen et al., 1999). Further, a relationship between heroin addiction and SS genotype was evidenced in subjects with antisocial traits (Gerra et al., 2005). Novelty Seeking and APD correlate negatively with prefrontal 5HT transporter density in alcoholics (Hill et al., 2002; Laine et al., 2003). Note that disorders commented above are strongly related to the personality traits analysed in the present study (Matthews and Deary, 1998; Zuckerman, 1999). Therefore, it is not surprising that, putting aside the unexpected effect for the 5-HTTVNTR, results obtained from studies focusing on disorders and on personality traits were quite congruent. In this sense, the present study may be useful to understand the genetic substratum of the disorders related to a deficient control of impulses. As mentioned above, the role of the 5-HTTVNTR in personality is still not well understood. In the present study, the combination of one or two copies of S and 12 consistently associates with higher scores in the impulsiveness-disinhibition index.

A limitation in our study is the relatively low sample size. This is an intrinsic difficulty to carry out this kind of study with incarcerated people, and with consent regarding DNA sampling. Therefore, our results might not generalize to penitentiary or delinquent populations, even though the extreme group analysed in the impulsiveness-disinhibited personality index highlights the genotypic differences in the direction hypothesized. Future studies should increase the number of polymorphisms in regard to impulsiveness-disinhibited personality, also considering the two SLC6A4 polymorphisms, the X-linked mono-aminase oxidase A (MAO A), the AP-2 ( $\beta$  form), the dopamine receptor gene (DRD2 and DRD4; Schinka et al., 2002), and the Androgen receptor genes (AR). Caspi et al. (2002) found evidence for genetic-environment interaction, whereby childhood abuse predicted later life antisocial behavior in men homozygous for the MAO-Low allele. MAO A has the clearest link with aggressiveness (Meyer-Lindenberg et al., 2006). Significant associations were found between genotype of AP-2 $\beta$  and impulsive personality variables. Males homozygous for the long allele displayed significantly lower platelet MAO activity as compared to those with one or two short alleles (Damberg et al., 2000), and as the shorter alleles of the CAG and GGC polymorphisms of the AR gene are associated with increased gene expression, we sought to determine whether they were also associated with externalizing behaviors (Comings et al., 1999; Prichard et al., 2007).

The present study gives support to the recommendations made by Munafò et al. (2003) since: (1) Genetic relationships were stronger for the composite index of Disinhibition than for almost every independent personality scale, (2) the size of the association and the risk level (odds ratio) were higher when an extreme groups design was conducted, compared to a whole sample analysis, and (3) when both polymorphisms were analysed conjointly, statistical power generally increased. In conclusion, the combination of allelic variants S-12 from the 5-HTTLPR and 5-HTTVNTR polymorphisms is associated with an increased risk of impulsive-disinhibited personality in offenders, as reflected by a comprehensive measure through different psychometric scales tapping a single unified construct. Despite the fact that the frequency of short alleles in the 5-HTTLPR in aggressive and impulsive subjects has been widely reported in the literature, the 5-HTTVNTR functioning is still unknown. Therefore, these results should be considered with

caution and replicated in more extensive samples of both incarcerated people and the general population.

## Conflict of interest

None declared.

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*Contributors:* Anton Aluja, Luis F. Garcia and Angel Blanch, designed the study, performed the literature searches and collected the genetic and phenotypic data. David de Lorenzo and Joan Fibla performed the genetic and data analyses, contributing as well in the final editing of the manuscript.

## References

- af Klinteberg B, Orelund L. Hyperactive and aggressive behaviors in childhood as related to low platelet monoamine oxidase (MAO) activity at adult age: a longitudinal study of male subjects. *Pers Indiv Differ* 1995;19:373–83.
- af Klinteberg B, Schalling D, Magnusson D. Self-report assessment of personality traits. Data from the KSP inventory on a representative sample of normal male and female subjects within a development project. Reports from the Project Individual Development and Adjustment 1986;No. 64, Department.
- af Klinteberg B, von Knorrig L, Orelund L. On the psychobiology of impulsivity. In: Stelmack RM, editor. *On the psychobiology of personality*. Amsterdam: Elsevier; 2004.
- Aluja A, García LF. Sensation seeking, sexual curiosity and testosterone in inmates. *Neuropsychobiology* 2005;51:28–33.
- Aluja A, Torrubia R. Hostility-aggressiveness, sensation seeking, and sex hormones in men: reexploring their relationship. *Neuropsychobiology* 2004;50:102–7.
- Aluja A, García Ó, García LF. Psychometric properties of the Zuckerman–Kuhlman personality questionnaire (ZKPQ-III-R): a study of a shortened form. *Pers Indiv Differ* 2003a;34(7):1083–97.
- Aluja A, García Ó, García LF A. Psychometric analysis of the revised Eysenck Personality Questionnaire short scale. *Pers Indiv Differ* 2003b;35(2):449–60.
- Arbuckle JL. *AMOS 4.0 [Computer software]*. Chicago, IL: SmallWaters; 1999.
- Barros-Loscertales A, Meseguer V, Sanjuán A, Belloch V, Parcet MA, Torrubia R, et al. Striatum gray matter reduction in males with an overactive behavioral activation system. *Eur J Neurosci* 2006;24:2071–4.
- Bennet AM, van Maarle MC, Hallqvist J, Morgenstern R, Frostegard J, Wiman B, et al. Association of TNF- $\alpha$  serum levels and TNFA promoter polymorphisms with risk of myocardial infarction. *Atherosclerosis* 2006;187:408–14.
- Bennett AJ, Lesch KP, Heils A, Long JC, Lorenz JG, Shoaf SE, et al. Early experience and serotonin transporter gene variation interact to influence primate CNS function. *Mol Psychiatr* 2002;7:118–22.
- Blackburn R. Sensation seeking, impulsivity and psychopathic personality. *J Consult Clin Psychol* 1969;33:571–4.
- Cadoret RJ, Langbehn D, Caspers K, Troughton EP, Yucuis R, Sandhu HK, et al. Associations of the serotonin transporter promoter polymorphism with aggressivity, attention deficit, and conduct disorder in an adoptee population. *Compr Psychiatr* 2003;44:88–101.
- Cronbach LJ. Coefficient alpha and the internal structure of tests. *Psychometrika* 1951;16:297–335.
- Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, et al. Role of genotype in the cycle of violence in maltreated children. *Science* 2002;297:851–4.
- Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. *Arch Gen Psychiatr* 1993;50:975–90.
- Comings DE, Chen C, Wu S, Muhleman D. Association of the androgen receptor gene (AR) with ADHD and conduct disorder. *Neuroreport* 1999;10(7):1589–92.
- Corr PJ, J.A. Gray’s reinforcement sensitivity theory: tests of the joint subsystems hypothesis of anxiety and impulsivity. *Pers Indiv Differ* 2002;33:511–32.

- Däderman AM, Lidberg L. Relapse in violent crime in relation to cerebrospinal fluid monoamine metabolites (5-HIAA, HVA, HMPG) in male forensic psychiatric patients convicted of murder: a 16-year follow-up. *Acta Psychiatrica Scandinavica* 2002;106(Suppl. 412):71–4.
- Damberg M, Garpenstrand H, Berggard C, Asberg M, Hallman J, Oreland L. The genotype of human transcription factor AP-2beta is associated with platelet monoamine oxidase B activity. *Neurosci Lett* 2000;313:204–6.
- Davidge KM, Beitchman JH, Atkinson L, Douglas L, Lee V, Shapiro S, et al. Association of the serotonin transporter and 5-HT1Dbeta receptor genes with extreme, persistent and pervasive aggressive behaviour in children. *Psychiatr Genet* 2004;14:143–6.
- Ebstein RP. The molecular genetic architecture of human personality: beyond self-report questionnaires. *Mol Psychiatr* 2006;11:427–45.
- Eysenck SGB, Eysenck HJ, Barrett P. A revised version of the psychoticism scale. *Pers Individ Differ* 1985;6:21–9.
- Gerra G, Garofano L, Castaldini L, Rovetto F, Zaimovic A, Moi G, et al. Serotonin transporter polymorphism genotype is associated with temperament personality traits and illegal drugs use among adolescents. *J Neural Transm* 2005;112:1397–410.
- Goodman M, New AS. Impulsive aggression in borderline personality disorder. *Curr Psychiatr Rep* 2000;2:56–61.
- Gorenstein E, Newman P. Desinhibitory psychopathology: a new perspective and a model for research. *Psychol Rev* 1980;87:301–15.
- Hallikainen T, Saito T, Lachman HM, Volavka J, Pohjalainen T, Ryyanen OP, et al. Association between low activity serotonin transporter promoter genotype and early onset alcoholism with habitual impulsive violent behavior. *Mol Psychiatr* 1999;4(4):385–8.
- Heils A, Teufel A, Petri S, Seemann M, Bengel D, Balling U, et al. Functional promoter and polyadenylation site mapping of the human serotonin (5-HT) transporter gene. *J Neural Transm Gen Sect* 1995;102:247–54.
- Heils A, Teufel A, Petri S, Stober G, Riederer P, Bengel D, et al. Allelic variation of human serotonin transporter gene expression. *J Neurochem* 1996;66:2621–4.
- Hennig J. Personality, serotonin and noradrenaline. In: Stelmack RM, editor. *On the psychobiology of personality*. Amsterdam: Elsevier; 2004.
- Hill EM, Stoltenberg SF, Bullard KH, Li S, Zucker RA, Burmeister M. Antisocial alcoholism and serotonin-related polymorphisms: association tests. *Psychiatr Genet* 2002;12:143–53.
- Hranilovic D, Stefulj J, Schwab S, Borrmann-Hassenbach M, Albus M, Jernej B, et al. Serotonin transporter promoter and intron 2 polymorphisms: relationship between allelic variants and gene expression. *Biol Psychiatr* 2004;55:1090–4.
- Ibáñez MI. Adaptación al castellano del cuestionario revisado de personalidad de Eysenck: versión extensa (EPQ-R) y abreviada (EPQ-RS). Tesis de Licenciatura. Castelló de la Plana: Universitat Jaume I; in press.
- Jobe LE, White SW. Loneliness, social relationships, and a broader autism phenotype in college students. *Pers Individ Differ* 2007;42:1479–89.
- Jonsson EG, Nothen MM, Gustavsson JP, Neidt H, Bunzel R, Propping P, et al. Polymorphisms in the dopamine, serotonin, and norepinephrine transporter genes and their relationships to monoamine metabolite concentrations in CSF of healthy volunteers. *Psychiatr Res* 1998;79:1–9.
- Kaiser R, Muller-Oerlinghausen B, Filler D, Tremblay PB, Berghofer A, Roots I, et al. Correlation between serotonin uptake in human blood platelets with the 44-bp polymorphisms and the 17-bp variable number of tandem repeat of the serotonin transporter. *Am J Med Genet* 2002;114:323–8.
- Kim S, Badner J, Cheon K, Kim B, Yoo H, Kim S, et al. Family-based association study of the serotonin transporter gene polymorphisms in Korean ADHD trios. *Am J Med Genet* 2005;139B:14–8.
- King A, Errico A, Parsons O. Eysenck's personality dimensions and sex steroids in male abstinent alcoholics and non-alcoholics: an exploratory study. *Biol Psychol* 1995;39:103–13.
- Kunugi H, Hattori M, Kato T, Tatsumi M, Sakai T, Sakai T, et al. Serotonin transporter gene polymorphisms: ethnic difference and possible association with bipolar affective disorder. *Mol Psychiatr* 1997;2:457–62.
- Laine TPJ, Ahonen A, Räsänen P, Tiihonen J. Novelty seeking correlates negatively to prefrontal monoaminergic activity among alcoholics. *The Icelandic Med J* 2003;48:30.
- Larsson H, Tuvblad C, Rijdsdijk FV, Andershed H, Grann M, Lichtenstein P. A common genetic factor explains the association between psychopathic personality and antisocial behavior. *Psychol Med* 2007;37:15–26.
- Lesch KP, Merschdorf U. Impulsivity, aggression, and serotonin: a molecular psychobiological perspective. *Behavior Sci Law* 2000;18:581–604.
- Lesch KP, Balling U, Gross J, Strass K, Wolozin BL, Murphy DL, et al. Organization of the human serotonin transporter gene. *J Neural Transm* 1994;95:57–162.
- Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 1996;274:1527–31.
- Liao DL, Hong CJ, Shih HL, Tsai SJ. Possible association between serotonin transporter promoter region polymorphism and extremely violent crime in Chinese males. *Neuropsychobiology* 2004;50:284–7.
- Lidberg L, Bellfrage H, Bertilsson L, Evenden M, Asberg M. Suicide attempts and impulsive control disorder are related to low cerebrospinal fluid 5-HIAA in mentally disordered violent offenders. *Acta Psychiatrica Scandinavica* 2000;101:395–402.
- Lyons-Ruth K, Holmes BM, Sasvari-Szekely M, Ronai Z, Nemoda Z, Pauls D. Serotonin transporter polymorphism and borderline/antisocial traits among low-income young adults. *Psychiatr Genet* 2007;17(6).
- Manna I, Labate A, Gambardella A, Forabosco P, La Russa A, Le Piane E, et al. Serotonin transporter gene (5-Htt): association analysis with temporal lobe epilepsy. *Neurosci Lett* 2007;421:52–6.
- Mather KA, Caicedo AL, Polato NR, Olsen KM, McCouch S, Purugganan MD. The extent of linkage disequilibrium in rice (*Oryza sativa* L). *Genetics* 2007;177:2223–32.
- Matthews G, Deary IJ. *Personality traits*. Cambridge, UK: Cambridge University Press; 1998.
- Meyer-Lindenberg A, Buckholtz JW, Kolachana B, Hariri AR, Pezawas L, Blasi G, et al. Neural mechanisms of genetic risk impulsivity and violence in humans. *Proceedings of Natural Academy Science USA* 2006;103:6269–74.
- Munafò MR, Clark TG, Moore LR, Payne E, Walton R, Flint J. Genetic polymorphisms and personality in healthy adults: a systematic review and meta-analysis. *Mol Psychiatr* 2003;8:471–84.
- Munafò MR, Brown SM, Hariri AR. Serotonin transporter (5-HTTLPR) genotype and amygdala: a meta-analysis. *Biological Psychiatry*; in press.
- Ni X, Chan K, Bulgin N, Sicard T, Bismil R, McMain S, et al. Association between serotonin transporter gene and borderline personality disorder. *J Psychiatr Res* 2006;40:448–53.
- Ogilvie AD, Battersby S, Bubb VJ, Fink G, Harmar AJ, Goodwin GM, et al. Polymorphism in serotonin transporter gene associated with susceptibility to major depression. *Lancet* 1996;347:731–3.
- Ortet G, Torrubia R. Spanish language version of the Karolinska Scales of Personality (KSP): first data. In: VI European conference on personality. Groningen; 1992.
- Pascual JC, Soler J, Baiget M, Cortés A, Menoyo A, Barrachina J, et al. Association between the serotonin transporter gene and personality traits in borderline personality disorder patients evaluated with Zuckerman–Kuhlman Personality Questionnaire (ZKPQ). *Actas Españolas de Psiquiatría* 2007;35(6):382–6.
- Pascual JC, Soler J, Barrachina J, Campins MJ, Álvarez E, Pérez V. Failure to detect an association between the serotonin transporter gene and borderline personality disorder. *J Psychiatr Res* 2008;42:87–8.
- Patkar AA, Berrettini WH, Hoehe M, Thornton CC, Gotthel E, Hill K, et al. Serotonin transporter polymorphisms and measures of impulsivity, aggression, and sensation seeking among African-American cocaine-dependent individuals. *Psychiatr Res* 2002;110:103–15.
- Prichard ZM, Jorm AF, Mackinnon A, Easteal S. Association analysis of 15 polymorphisms within 10 candidate genes for antisocial behavioural traits. *Psychiatr Genet* 2007;17:299–303.
- Reif A, Lesch KP. Toward a molecular architecture of personality. *Behav Brain Res* 2003;139:1–20.
- Retz W, Freitag CM, Retz-Junginger P, Wenzler D, Schneider M, Kissling C, et al. A functional serotonin transporter promoter gene polymorphism increases ADHD symptoms in delinquents: interaction with adverse childhood environment. *Psychiatr Res* 2008;158(2):123–31.
- Rogers RD, Tunbridge EM, Bhagwagar Z, Drevets WC, Sahakian BJ, Carter CS. Tryptophan depletion alters the decision-making of healthy volunteers through altered processing of reward cues. *Neuropsychopharmacol* 2003;28:153–62.
- Sander T, Harms H, Dufeu P, Kuhn S, Hoehe M, Lesch KP, et al. Schmidt LG serotonin transporter gene variants in alcohol-dependent subjects with dissociative personality disorder. *Biol Psychiatr* 1998;43:908–12.
- Schalling D, Edman G, Asberg M, Oreland L. Platelet MAO activity associated with impulsivity and aggressiveness. *Pers Individ Differ* 1987a;9:597–605.
- Schalling D, Asberg M, Edmand G, Oreland L. Markers for vulnerability to psychopathology: temperaments traits associated with platelet MAO activity. *Acta Psychiatrica Scandinavica* 1987b;96:172–82.
- Schalling D, Asberg M, Edmand G, Oreland L. Markers for vulnerability to psychopathology: temperaments traits associated with platelet MAO activity. *Acta Psychiatr Scand* 1987;96:172–82.
- Schalling D, Edman G, Asberg M, Oreland L. Platelet MAO activity associated with impulsivity and aggressiveness. *Pers Individ Differ* 1988;9:597–605.
- Schinka JA, Letsch EA, Crawford FC, DRD4 and novelty seeking: results of meta-analyses. *Am J Med Genet* 2002;114:643–8.
- Schinka JA, Busch RM, Robichaux-Keene N. A meta-analysis of the association between the serotonin transporter gene polymorphism (5-HTTLPR) and trait anxiety. *Mol Psychiatr* 2004;9:197–202.
- Sen S, Burmeister M, Ghosh D. Meta-analysis of the association between serotonin transporter polymorphism (5-HTTLPR) and anxiety-related personality traits. *Am J Med Genet Part B: Neuropsychiatr Genet* 2004;127:85–9.
- Smoller JW, Rosenbaum JF, Biederman J, Susswein LS, Kennedy J, Kagan J, et al. Genetic association analysis of behavioral inhibition using candidate loci from mouse models. *Am J Med Genet* 2001;105:226–35.
- Torrubia R, Avila C, Moltó J, Caseras X. The Sensitivity to Punishment and Sensitivity Reward Questionnaire (SPSRQ) as a measure of Gray's Anxiety and Impulsivity Dimensions. *Pers Individ Differ* 2001;31:837–62.
- Turker T, Sodmann R, Goebel U, Jatzke S, Knapp M, Lesch KP, et al. High ethanol tolerance in young adults is associated with the low-activity variant of the promoter of the human serotonin transporter gene. *Neurosci Lett* 1998;248:147–50.
- Virkkunen M, Rawlings R, Tokala R, Poland RE, Guidotti A, Nemeroff C, et al. CSF biochemistry, glucose metabolism, and diurnal activity rhythms in alcoholic, violent offenders, fire setters, and healthy volunteers. *Arch Gen Psychiatr* 1994;51:20–7.
- Vormfelde SV, Hoell I, Tzvetkov M, Jamrozinski K, Sehr D, Brockmüller J, et al. Anxiety and novelty seeking-related personality traits and serotonin transporter gene polymorphisms. *J Psychiatr Res* 2006;40:568–76.



Zoroglu SS, Erdal ME, Alasehirli B, Erdal N, Sivasli E, Tutkun H, et al. Significance of serotonin transporter gene 5-HTTLPR and variable number of tandem repeat polymorphism in attention deficit hyperactivity disorder. *Neuropsychobiology* 2002;45:176–81.

Zuckerman M. Behavioral expressions and biosocial bases of sensation seeking. Cambridge, UK: Cambridge University Press; 1994.

Zuckerman M. Vulnerability to psychopathology: a biosocial model. Washington, DC: American Psychological Association; 1999.

Zuckerman M, Kuhlman DM, Teta P, Joireman J, Kraft M. A comparison of three structural models of personality: the big three, the big five, and the alternative five. *J Pers Social Psychol* 1993;65:757–68.