A study of 5-HTT (SLC6A4) gene polymorphisms and antisocial behaviour in a population sample of young Portuguese adults

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Introduction

The 5HTT (SLC6A4) gene, encoding the serotonin transporter protein, is a key molecule in the regulation of serotonin (5HT) levels in the synaptic cleft [1].

Within the promoter region the VNTR polymorphism 5HTTLPR consists of different lengths of a repetitive sequence containing 20- to 23-bp long repeat elements. The most common alleles are a L (long, 16-repeats) and a S (short, 14-repeats) allele [2]. The 5HTTLPR polymorphism is associated with variations in transcriptional activity: the long (L) variant has approximately three times the expression of the short (S) variant.

In addition, SNP rs25531 A>G, located immediately outside the 5HTTLPR polymorphism [3], results in two forms of the L-allele denoted L-A and L-G, and two corresponding S-A and S-G alleles. The G-allele was shown to reduce the long-repeat expression levels to those of the short-repeat, resulting in a higher-expressing LA class (L') and lower-expressing LG and S classes (clustered as S') [3].

Several studies have described an association between the S allele of 5HTTLPR and a variety of neuropsychiatric conditions including impulsivity and aggression, while other studies reported non-replications of these data [2; 4].

This study aimed to investigate the association between the two promoter 5-HTT polymorphisms (5HTTLPR and rs25531) and antisocial behaviour in a Portuguese sample of young adults.

Methods

Sample: A sample of 202 individuals (102 males; 100 females), aged 18-37 years, mainly from the central region of Portugal, were enrolled in the study. A questionnaire assessing a variety of problematic behaviours was constructed based on a previously reported delinquency scale [5]. A mean score value to measure aggressive behaviour was determined for each individual.

Genotyping: DNA was extracted from buccal cells collected with written informed consent. Genotyping was performed by PCR followed by agarose gel electrophoresis for 5-HTTLPR and PCR-RFLP using MspI for rs25531, as described elsewhere [3].

Statistical analysis: Allele frequencies were estimated by mere counting. Hardy-Weinberg equilibrium probability values was achieved using an exact test. Mann-Whitney test was used to compare the mean score values between sexes and score distributions for rs25531 genotypes. The Kruskal-Wallis test was used to analyse score distribution between HTTLPR genotypes and haplotypes. These statistical tests and graphical analysis were done using SPSS v.20 software.

References

[1] Heils A *et al.* 1996. Allelic variation of human serotonin transporter gene expression. *Journal of Neurochemistry*. **66** (6): 2621 – 2624.

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Results and Discussion

Genotype distributions and allele frequencies for the two 5HTT polymorphisms among the studied sample are shown in Table 1.

Table 1: Genotypes and allele frequency distributions of 5HTTLPR, rs25531 polymorphisms and clustered phased haplotypes among the studied sample of young Portuguese adults.

Polymorphism	n	Genotypes n (%)			Allele frequencies		p
		11	12	22	1	2	
5HTTLPR	194	61 (31.4)	95 (49.0)	38 (19.6)	217 (55.93)	171 (44.07)	0.936
rs25531	193	172 (89.1)	21 (10.9)	-	365 (94.56)	21 (5.44)	0.424
Clustered Phased haplotypes	193	51 (26.4)	95 (49.2)	47 (24.4)	197 (51.0)	189 (49.0)	-

Alleles: 5HTTLPR 1:L; 2:S; rs25531 1:A; 2:G; Phased haplotypes 1: L' (LA) 2: S' (LG, SA, SG)
n, number of individuals
p, Exact p-value for the Hardy-Weinberg equilibrium (p significant < 0.05).

Figure 1 shows the obtained mean score of aggression among the different genotypes for the two studied 5HTT polymorphisms as well as for the clustered phased haplotypes.

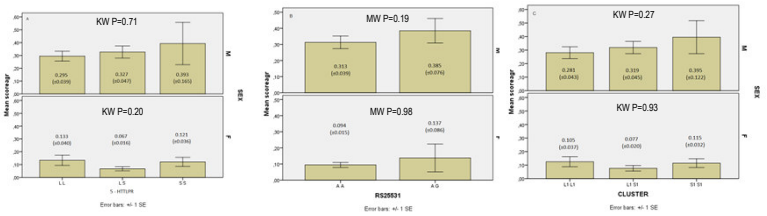

Fig. 1: Mean score of aggression among genotypes of 5HTTLPR, rs25531 polymorphisms and clustered phased haplotypes in the studied sample.
KW: Kruskal-Wallis test; MW: Mann-Whitney U test.

Significant differences for the score distribution of self-reported aggressive behaviour were found between sexes: 0.326 in males *vs.* 0.100 in females (P<0.001).

The score distributions between genotypes showed no significant differences for 5-HTTLPR, rs25531 and haplotype combinations according to the SLC6A4 allele expression levels, nor in the total sample neither within sexes (P>0.05).

Nevertheless, it was observed, mainly in males, a tendency towards greater scores of aggression in the 5HTTLPR S-allele carriers (mean scores LL 0.29; LS 0.32; SS 0.39), rs25531 G-allele carriers (mean scores AA 0.31; AG 0.38) and haplotype LG and S classes (mean scores L'L' 0.28; L'S' 0.31; S'S' 0.39), favouring the previous studies that describe an association between the S allele of 5HTTLPR and aggressive behaviour.

Conclusions

Even with the lack of a significant association between 5HTT polymorphisms and aggressive behaviour, it is evident mainly in males a tendency in the short allele carriers for a higher self-reported antisocial problems compared to carriers of the long allele.

A Gene x Environment relationship with childhood maltreatments could highlight stronger interactions between 5HTT and anti- social behaviours. A replication study with a larger sample is also needed to conclude for significant associations.

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