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 usingMspI 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 (KW) and Mann-Whitney test was used to compare the mean score values between genotypes.

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.

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>n</th>
<th>Genotypes n (%)</th>
<th>Allele frequencies</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11</td>
<td>12</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>5HTTLPR</td>
<td>194</td>
<td>61 (31.4)</td>
<td>95 (49.0)</td>
<td>38 (19.6)</td>
</tr>
<tr>
<td>rs25531</td>
<td>193</td>
<td>172 (89.1)</td>
<td>21 (10.9)</td>
<td>-</td>
</tr>
</tbody>
</table>

Clustered Phased haplotypes

<table>
<thead>
<tr>
<th>Alleles:</th>
<th>5HTTLPR 1; 2: S</th>
<th>rs25531 1; A</th>
<th>2: G</th>
<th>Phased haplotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>193</td>
<td>172 (89.1)</td>
<td>21 (10.9)</td>
<td>365 (94.50)</td>
</tr>
</tbody>
</table>

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 LL 0.28; LS 0.31; 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 SHTT 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 SHTT and anti-social behaviours. A replication study with a larger sample is also needed to conclude for significant associations.

References