Lack of association of OXTR variants with autism spectrum disorders in a south Indian population

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Abstract

Background: Absence of an effective treatment strategy for autism spectrum disorder (ASD) has necessitated the need for extensive research on oxytocin (OT) and oxytocin receptor gene (OXTR). However, studies on the role of genetic variants in OT and OXTR gene in determining ASD risk is not equivocal owing to the disparities across different ethnicities. We investigated the association of previously reported genetic variants in the OXTR gene with ASD individuals in a south Indian population.

Methods: We recruited 222 subjects (110 ASD participants and 112 controls), from south India based on the diagnosis by the DSM-IV criteria. We genotyped single nucleotide polymorphisms (SNPs) rs2254298, rs2254295, rs60902022 and rs53576 in the OXTR gene and the allelic association between ASD participants and controls were determined.

Results: We observed higher minor allelic frequency for the OXTR SNPs, which were in linkage disequilibrium in our population. However, the controls failed to exhibit any significant allelic association at rs2254298 (p=0.784), rs2254295 (p=0.661), rs60902022 (p=0.726), rs53576
(p=0.989) or genotypic association at rs2254298 (p=0.78), rs2254295 (p=0.66), rs60902022 (p=0.72), rs53576 (p=0.99) with ASD participants. Similarly, haplotype analysis also failed to prove any association.

**Conclusion:** We suspect that the disparity in the allele frequencies for the SNPs selected in this study across populations might be the reason behind the lack of association as observed in previous studies. Thus, extensive research is necessary. Our study revealed that among south Indians, the rs2254298, rs2254295, rs60902022 and rs53576 SNPs in OXTR gene are unlikely to contribute to the susceptibility of ASD.

**Keywords:** Autism Spectrum Disorder (ASD), OXTR, SNP, case-control analysis

**Introduction**

Autism spectrum disorders (ASD) are a group of neurological conditions characterized by impaired social interaction and communication alongside restrictive or repetitive behaviour and interests. Genetic heritability is estimated at 64–91%, implying a strong genetic influence in the occurrence of ASD [1]. Roughly, 50% of the heritability seen in ASD are contributed by common variants whereas the class of rare inherited and de novo mutations account for only 3% of the genetic risks. This indicates the importance of studying these large numbers of common variants with weak effects that could contribute significantly to manifestation of ASD [2]. However, social behaviour in humans, which is a crucial aspect of human life, is diverse and could adversely impact the quality of life. A plethora of biochemical factors can modulate these social behaviours and the Oxytocin (OT) hormone is a significant contributor. OT is a nonapeptide hormone synthesized in the hypothalamus. It is one of the most studied brain signaling molecule encoding information on a person’s sociability [3, 4]. The Oxytocin Receptor (OXTR), a 389 amino acid-long G-protein coupled transmembrane receptor coded by the OXTR
gene mediates the activities of OT. This gene is mapped on chromosome 3p25 and comprises of four exons and three introns (Fig.1).

**Figure-1: Gene OXTR shows Intronic SNPs selected for present study**

![Gene OXTR showing Intronic SNPs](image)

The oxytocin-oxytocin receptor system present in the central nervous system plays a vital role in controlling a variety of behaviours that include stress, anxiety, social memory-recognition, sexual and aggressive behaviour, bonding (affiliation) and maternal behaviour [5-7]. Furthermore, OT and OXTR gene were found to drive specific actions through their early expression in development [8]. Similarly, the knockout of OXTR gene in mice model systems resulted in impaired interaction between the mother and offspring and also increased aggression [9] along with diminished skill for social memory and recognition [10].

OT has emerged as a potent therapeutic candidate for treating persons with ASD [11]. Enhanced social activity like increased memory of social information, altruistic behaviour and trust were observed when intranasal OT was administrated [12-14]. However, the efficacy and efficiency of treatment depends heavily on the genetic background of the OXTR gene and the dosage of oxytocin being administered [15].

Genome-wide linkage studies provided the first crucial evidence of the involvement of OXTR in ASD [16, 17]. Several lines of evidence have emerged subsequently showing the association of
OXTR polymorphisms with various social behaviours like empathy, social communication [18], increased generosity [19], parental sensitivity [20] and reduced physiological reactivity to stress [21]. However, rs53576 and rs2254298 two of the most frequently studied Single Nucleotide Polymorphisms (SNPs) in the OXTR gene were shown to be associated with severe social deficits in persons with ASD [22]. Similarly, the rs53676 G>A was significantly related to behaviour and brain activity in the context of social cues [23, 24] while the variant rs2254298 G>A was linked to ASD [25]. Previous research across populations have led to the identification of a positive correlation between behaviour [26-28] and genotype functioning [29-31] with the OXTR allele frequency. Two other SNPs found in the vicinity of SNP rs2254298 were rs60902022 and rs2254295. Among them, rs60902022 was thought to affect gene expression by modulating the binding of transcription factors [32].

The current study is of significant interest because this is the first study to genotype SNPs on OXTR in the Indian subcontinent. Recently, rs2254298 was identified to show positive association with serum OT levels with ASD in the Han Chinese population [33]. This was previously supported by family-based studies for rs2254298, which showed over transmission of G allele to probands in Caucasian children and adolescent with autism but not with rs53576 [25]. Moreover, five-locus haplotype block (rs237897-rs13316193-rs237889-rs2254298-rs2268494) was significantly associated with ASD in Israeli population [34] and Japanese ethnicity-based studies suggests the risk allele of rs2254298 was 'A', which was consistent with the previous study in Chinese population, but was not observed in Caucasian population [35] (Table.1).
### Table-1: Studies performed on rs53576, rs2254298 across populations: Association with ASD

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Ethnicity</th>
<th>Study type</th>
<th>Sample size</th>
<th>Male (M)-Female (F)</th>
<th>Age Range or Mean</th>
<th>Diagnosis</th>
<th>rsID</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wermter et al. (2010) [36]</td>
<td>Caucasian</td>
<td>Case-Control</td>
<td>100</td>
<td>95M-5F</td>
<td>6–24 years</td>
<td>ICD-10, ADOS-G, ADI-R</td>
<td>rs53576, rs2254298</td>
<td>No Association</td>
</tr>
<tr>
<td>Campbell et al. (2011)[37]</td>
<td>Caucasian</td>
<td>Family based</td>
<td>5432</td>
<td>Not reported</td>
<td>Not reported</td>
<td>ADI-R, ADOS, and SRS</td>
<td>rs53576, rs2254298</td>
<td>No Association</td>
</tr>
<tr>
<td>Bakermans-Kranenburg and van Ijzendoorn (2014)[38]</td>
<td>Mixed</td>
<td>Meta-analysis</td>
<td>17559</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>rs53576, rs2254298</td>
<td>No Association</td>
</tr>
<tr>
<td>Wu et al. (2005)[39]</td>
<td>Chinese</td>
<td>Trios</td>
<td>195</td>
<td>174M-21F</td>
<td>6.7-2.9 years</td>
<td>DSMIV</td>
<td>rs53576, rs2254298</td>
<td>Association</td>
</tr>
<tr>
<td>Jacob et al. (2007)[25]</td>
<td>Caucasian</td>
<td>Trios</td>
<td>57</td>
<td>45M-12F</td>
<td>up to 6.4 years</td>
<td>ADI-R, and ADOS</td>
<td>rs2254298</td>
<td>Association</td>
</tr>
<tr>
<td>Lerer et al. (2008)[34]</td>
<td>Israelie</td>
<td>Family based</td>
<td>152</td>
<td>128M-24F</td>
<td>2-33.8 years</td>
<td>DSM IV, ADI-R, ADOS-G</td>
<td>rs2254298</td>
<td>Association</td>
</tr>
<tr>
<td>Liu et al. (2010)[35]</td>
<td>Japanese</td>
<td>Family based &amp; Case-control</td>
<td>728</td>
<td>518M-210F</td>
<td>18.35-25.20 years</td>
<td>DSMIV</td>
<td>rs2254298</td>
<td>Association</td>
</tr>
<tr>
<td>Parker et al. (2014)[40]</td>
<td>Not Reported</td>
<td>Case/Control/Siblings</td>
<td>193</td>
<td>131M-62F</td>
<td>3-12 age</td>
<td>ADI-R, ADOS-G</td>
<td>rs53576, rs2254298</td>
<td>Association</td>
</tr>
<tr>
<td>LoParo and Waldman (2015)[41]</td>
<td>Mixed</td>
<td>Meta-analysis</td>
<td>3941</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>rs2254298</td>
<td>Association</td>
</tr>
<tr>
<td>Yang et al.(2017)[33]</td>
<td>Chinese Han</td>
<td>Case-Control</td>
<td>332</td>
<td>266M-66F</td>
<td>2-18 years</td>
<td>DSMIV, CARS</td>
<td>rs2254298</td>
<td>Association</td>
</tr>
</tbody>
</table>
Since the SNPs selected for this study were already known to be associated with ASD for different ethnicities, further studies in independent cohorts of the same or different ethnicities are quite essential to ascertain a robust genotype-phenotype association. Therefore, to address the discrepancies in association status and to obtain information on genotype variance and inter-ethnic differences, our current efforts are aimed at unravelling the role of four genetic variants in OXTR-rs2254298, rs2254295, rs60902022 and rs53576 in south-Indian persons with ASD in a case control-based study.

Methods

Selection of subjects

We recruited 222 subjects, comprising 110 ASD participants (83 males and 27 females) and 112 controls (67 males and 45 females), between the ages of 2 to 25 years (mean 7.12 ± 10.13) of a south Indian population. Ethnicity was self-reported; we recruited ASD participants of parents who were south Indian language speakers, residing in any of the south Indian states. Diagnosis of ASD was made by a neurologist on the basis of clinical symptoms and evaluation by a multidisciplinary team consisting of speech language pathologist and psychologist. DSM-IV was used for diagnosis [42] and severity was assessed clinically by the neurologist. Reports of clinical evaluation and medical history of ASD participant were thoroughly checked. Children born by consanguineous marriages, with history of epilepsy and/or Fragile X syndrome diagnosis were excluded from this study. Cytogenetic tests were carried out for some cases to exclude syndromic forms of ASD showing chromosomal abnormalities. All participants/guardians received a full explanation of the study protocols and objectives before obtaining their informed and written consent. Ethical clearance for this study was obtained from the Mahatma Gandhi National Institute of Research and Social Action -affiliated research center, University of Mysore.
and also from the Institute of Communicative and Cognitive Neuroscience (ICCONS) Ethical Committee.

**Selection of SNPs and genotyping**

We selected four SNPs rs2254298, rs53576, rs2254295 and rs60902022 located in the chromosome position 3p25 in the third intronic region of *OXTR* gene. Role of these SNPs in ASD risk has not been tested in Indian population. The primers for rs2254298 and rs53576 were chosen based on a previous study [26]. The same primers for rs2254298 also covered other SNPs rs2254295 and rs60902022 that are in linkage Disequilibrium (LD) with SNP-rs2254298 and were therefore included into the analysis (Table 1). DNA extraction was performed from 5mL of a peripheral blood sample collected in BD K2vacutainer® (BD, NJ, USA) containing EDTA as an anticoagulant. DNA extraction was conducted by the phenol-chloroform (Zumbo.P - Weill Cornell Medical College) and salting out method [43]. PCR conditions were as follows: denaturation 95°C–3min, annealing 95°C–30s, 60°C–30s, 72°C–45s (35 cycles) and extension 72°C–7min. Amplicons were electrophoresed on a 2% agarose gel containing ethidium bromide. DNA bands were visualised using the gel documentation system (Bio-Rad, USA). A PCR product of 1µl was used for the sequencing reaction (Big Dye Terminator v3.1 cycle sequencing kit) according to the manufacturer’s instructions and was analysed using the ABI 3500 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

**Statistical Analysis**

Genotype and allele frequencies were computed and analysed for deviation from the Hardy–Weinberg equilibrium (HWE). Fisher's exact test (two-tailed) was used to compare allele frequencies between ASD subjects and the controls. The differences in genotype distributions were evaluated using Pearson's χ2 test. LD pattern was plotted for the genotyped SNPs using
Haploview 4.2, and haplotype analysis was performed using unphased 3.1.7. Power was calculated using online sample size estimator (http://osse.bii.a-star.edu.sg/calculation2.php). We also compared the allele frequencies of the SNPs in the south Indian population to that of the global population by using the ENSEMBL genome browser (https://asia.ensembl.org/index.html).

**Results**

Genotype distributions of the studied SNPs were within the Hardy–Weinberg equilibrium (p ≥0.05). There were no significant differences in genotype and allele frequencies of OXTR- SNPs between ASD participants and controls (Table 2). Thereby, they fail to support the role of OXTR in the pathogenesis of ASD participants in the population under study. No significant difference was observed in the LD pattern plotted for the subjects and controls (Fig.2). Further, haplotype analyses also failed to yield any significant association, similar to the findings of previous studies (Table 3). We also observed a high frequency for minor alleles under investigation when compared to other ethnicities (Fig.3-6, supplementary image). Power estimated for rs2254298, rs53576, rs2254295 and rs60902022 were -2.50%, -4.40%, -7.20%, and -7.30% respectively.
Table 2: SNPs in *OXTR* gene showing genotype and allelic association with ASD

<table>
<thead>
<tr>
<th>SNPs</th>
<th>Subjects</th>
<th>Genotype, n (%)</th>
<th>P value*</th>
<th>Allele, n (%)</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P value$^$</th>
<th>HWE P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2254295</td>
<td>ASD</td>
<td>TT (0.82)</td>
<td>TC (0.18)</td>
<td>CC (0)</td>
<td>T</td>
<td>C</td>
<td>0.66</td>
<td>0.8333</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90</td>
<td>20</td>
<td>0</td>
<td>200(0.91)</td>
<td>20(0.09)</td>
<td>0.661</td>
<td>0.294</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>TT (0.79)</td>
<td>TC (0.21)</td>
<td>CC (0)</td>
<td>T</td>
<td>C</td>
<td>0.204</td>
<td></td>
</tr>
<tr>
<td>rs60902022</td>
<td>ASD</td>
<td>TT (0.57)</td>
<td>TC (0.36)</td>
<td>CC (0.06)</td>
<td>T</td>
<td>C</td>
<td>0.72</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63</td>
<td>40</td>
<td>7</td>
<td>166(0.75)</td>
<td>54(0.25)</td>
<td>0.726</td>
<td>0.848</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>TT (0.54)</td>
<td>TC (0.38)</td>
<td>CC (0.09)</td>
<td>T</td>
<td>C</td>
<td>0.503</td>
<td></td>
</tr>
<tr>
<td>rs2254298</td>
<td>ASD</td>
<td>TT (0.82)</td>
<td>TC (0.18)</td>
<td>CC (0)</td>
<td>T</td>
<td>A</td>
<td>0.78</td>
<td>0.8739</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90</td>
<td>20</td>
<td>0</td>
<td>200(0.91)</td>
<td>20(0.09)</td>
<td>0.784</td>
<td>0.294</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>TT (0.79)</td>
<td>TC (0.21)</td>
<td>CC (0)</td>
<td>T</td>
<td>A</td>
<td>0.226</td>
<td></td>
</tr>
<tr>
<td>rs53576</td>
<td>ASD</td>
<td>TT (0.32)</td>
<td>TC (0.44)</td>
<td>CC (0.25)</td>
<td>G</td>
<td>A</td>
<td>0.99</td>
<td>0.9974</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35</td>
<td>48</td>
<td>27</td>
<td>118(0.54)</td>
<td>102(0.46)</td>
<td>0.989</td>
<td>0.198</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>TT (0.31)</td>
<td>TC (0.45)</td>
<td>CC (0.24)</td>
<td>G</td>
<td>A</td>
<td>0.278</td>
<td></td>
</tr>
</tbody>
</table>

HWE: Hardy–Weinberg equilibrium

*P value by Pearson's $\chi^2$ test

$^\$P value by Fisher's exact test
<table>
<thead>
<tr>
<th>Haplotype</th>
<th>rs2254295</th>
<th>rs60902022</th>
<th>rs2254298</th>
<th>rs53576</th>
<th>Case frequency</th>
<th>Control frequency</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>T</td>
<td>T</td>
<td>G</td>
<td>G</td>
<td>0.3444</td>
<td>0.3084</td>
<td>0.5279</td>
</tr>
<tr>
<td>H2</td>
<td>T</td>
<td>T</td>
<td>G</td>
<td>A</td>
<td>0.3386</td>
<td>0.3077</td>
<td>0.6429</td>
</tr>
<tr>
<td>H3</td>
<td>T</td>
<td>T</td>
<td>A</td>
<td>A</td>
<td>0.004559</td>
<td>0</td>
<td>0.3126</td>
</tr>
<tr>
<td>H4</td>
<td>T</td>
<td>C</td>
<td>G</td>
<td>G</td>
<td>0.1189</td>
<td>0.1617</td>
<td>0.4393</td>
</tr>
<tr>
<td>H5</td>
<td>T</td>
<td>C</td>
<td>G</td>
<td>A</td>
<td>0.1026</td>
<td>0.1151</td>
<td>0.6706</td>
</tr>
<tr>
<td>H6</td>
<td>C</td>
<td>T</td>
<td>G</td>
<td>G</td>
<td>0</td>
<td>0.004464</td>
<td>0.704</td>
</tr>
<tr>
<td>H7</td>
<td>C</td>
<td>T</td>
<td>A</td>
<td>G</td>
<td>0.05411</td>
<td>0.06117</td>
<td>0.8319</td>
</tr>
<tr>
<td>H8</td>
<td>C</td>
<td>T</td>
<td>A</td>
<td>A</td>
<td>0.01285</td>
<td>0.04151</td>
<td>0.2081</td>
</tr>
<tr>
<td>H9</td>
<td>C</td>
<td>C</td>
<td>G</td>
<td>G</td>
<td>0.004559</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>H10</td>
<td>C</td>
<td>C</td>
<td>A</td>
<td>G</td>
<td>0.01437</td>
<td>0</td>
<td>0.4868</td>
</tr>
<tr>
<td>H11</td>
<td>C</td>
<td>C</td>
<td>A</td>
<td>A</td>
<td>0.005014</td>
<td>0</td>
<td>0.972</td>
</tr>
</tbody>
</table>
Figure-2: Linkage disequilibrium pattern (r2) of OXTR SNPs in ASD patients and controls in south Indian population
Figure-3: Graphical representation of global allele frequencies of SNP- rs2254298 with present study. (Source: 1000 Genome Phase 3-Ensemble Genome Browser)

Figure-4: Graphical representation of global allele frequencies of SNP- rs53576 with present study. (Source: 1000 Genome Phase 3-Ensemble Genome Browser)
Figure-5: Graphical representation of global allele frequencies of SNP- rs2254295 with present study. (Source: 1000 Genome Phase 3-Ensemble Genome Browser)

Figure-6: Graphical representation of global allele frequencies of SNP- rs60902022 with present study. (Source: 1000 Genome Phase 3-Ensemble Genome Browser)
Discussion

The greatest scientific support researchers can provide to families of children with ASD is finding a proper therapeutic strategy. Many strategies are currently being adopted and recently OT based treatments have been showing promising results. However, uncertain outcomes of single-dose and long-term treatments have hampered its large-scale therapeutic use [43]. Such discrepancies may have possibly stemmed from the varying genotypes of persons with ASD undergoing treatment, affecting overall treatment efficiency. OXTR is one of the most extensively studied genes due to its association with social behaviour in persons with and without ASD [40]. Owing to the strength of evidences provided by the numerous association studies often conducted on two common SNPs in the OXTR gene- rs2254298 and rs53576, and based on the observed ethnic discrepancies in association status between populations, we investigated these two significant SNPs along with two other SNPs, rs2254295 and rs60902022 in its vicinity, in south-Indian subjects. To the best of our knowledge, this is the first study to study the association of OXTR genetic variants with ASD in a south Indian population.

Interestingly, our case-control analysis did not yield a significant association for selected SNPs in OXTR. The South Asian Genome and Exome (SAGE) database, that contains comprehensive genomic information of south Asian individuals who have been-underrepresented in previous global sequencing projects like the 1000 Genome Project showed that the allele frequency of rs53576 was 0.58523. Similarly, allele frequency of 0.54928 was recorded for south Asians in the 1000 Genome project (1000 Genome South Asian (1000GSAS)) making rs53576 a common polymorphism in the South Asian population. The allele frequency of rs2254298 in SAGE and 1000 GSAS were 0.10511 and 0.10062 respectively. Similarly, allelic frequencies of rs2254295 in SAGE and 1000 GSAS were 0.10511 and 0.10062 and that of rs60902022 were 0.27273 and
0.25565 respectively. Thus, present study could not record any significant difference in its presence in the subjects nor controls [44]. Therefore, for the south Indian population, the selected SNPs – rs2254298, rs53576, rs2254295 and rs60902022– were not associated with ASD manifestation but instead presented themselves as a common polymorphism prevalent within the population.

There are considerable supporting evidence across populations showing lack of association of these intronic SNPs with ASD occurrence [36,37,46]. These include studies on high Functioning Autism [47] and a meta-analysis by Bakermans-Kranenburg and van Ijzendoorn [45]. However, the Caucasian population [25] showed a significant association with rs2254298 (p=0.03) in 57 Caucasian autism trios but not with rs53576. Observations made on the ambiguous allelic associations of rs53576 to pro or antisocial behaviours and non-consensus association patterns of rs2254298 were within and across ethnicities. However, both these SNPs were associated with global social impairments in ASD participants and controls [40]. Similarly observations also suggest that these genetic modifier alleles are not inherently risk-conferring for their impact on social abilities [22, 33].

Clinical implications

Different clinical studies have suggested that the administration of OT is beneficial for the improvement of autistic symptoms such as non-cooperation and a lack of trust, thus improving the social responsiveness and social reciprocity [48]. Interestingly, animal-based studies have shown that some OXTR polymorphisms present in the cis-Regulatory Elements (cis-REs) of the OXTR gene could influence OXTR density in particular brain regions contributing to individual differences in OXTR expression [49]. Long-term OT administration in persons with ASD carrying a T-allele at rs6791619 rather than the haplotype at rs237851–rs6791619–rs53576–
rs237884 showed improved Clinical Global Impression-Improvement scores. This provided direct evidence that OXTR SNPs were associated with the efficacy of OT treatments [15]. Therefore, the efficiency of OT administration might differ according to the OXTR gene polymorphisms.

**Strengths and limitations**

This study is the first to look for association of SNPs in OXTR in south Indian persons with ASD and for their probable contribution to ASD etiology. It has attempted to understand the association status of the commonly studied, yet controversial SNPs in OXTR to provide this first report. The study holds a scope of determining the dosage of OT administration based on the genetic make-up of the ASD individual. However, the current study is limited by lack of power and the cryptic population substructure of the recruited participants. Intelligence Quotient (IQ) assessment for both subjects and controls and also the measurement of severity of ASD was not included in the study. Ethnicity which was determined based on language but not caste, religion and population stratification was also considerable limitation for the present study.

**Conclusion**

This study revealed that among south Indians, the studied SNPs in the OXTR gene are unlikely to contribute to the susceptibility for persons with ASD. However, genome wide analysis would give us a broader idea about the involvement of other SNPs or possibly SNPs acting along with the selected SNPs contributing to ASD phenotypes. Further, there are many problems associated with studying an intronic variation. Studies on intronic SNPs usually stem from strong association peaks obtained on genome-wide linkage/association studies. Positive associations obtained so far with SNPs rs2254298 and rs53576 may not be directly related to disease risks, instead to risks conferring haplotype blocks linked to these intronic SNPs. Therefore, a family-
based haplotype analysis on intronic variants might yield better information on risk association. In our study, haplotype tests performed with different allelic combinations on rs2254298 rs53576, rs2254295 and rs60902022 failed to prove any form of association. The negative association found in our study could be due to the low sample size. More research on the functional, behavioural and hormonal aspects, in a significant sample size, in different ethnic populations would help us to obtain more conclusive scientific evidence on OXTR.

Conflict of interest: None declared

References


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