Association between serotonin type 2 receptor (HTR2) and bronchial asthma in humans

Serotonin (5HT), a chemotransmitter synthesised by decarboxylation of the essential amino acid tryptophan, is localised in the respiratory tract as well as the nervous system, and promotes adenosis induced bronchoconstriction. Of the seven types of serotonin receptors, HTR2 is a unique receptor which mediates platelet agglutination, lung smooth muscle constriction, and various brain functions, via a G protein and adenylate cyclase activation mechanism.

Studies of inbred mice show a significant difference in airway responsiveness between nine inbred strains to 5HT. In some strains of rat or guinea pig, 5HT antagonists markedly reduce bronchospasm. Similarly a randomised double blind study of eight asthmatic patients found better pulmonary function after administration of ketanserin, a HTR2 blocker. These results suggest that 5HT may play an important role as mediator of adenosis induced bronchoconstriction and further that HTR2 might be a candidate gene for asthma in humans. We have therefore conducted a genetic association study between an MspI restriction polymorphism of HTR2 on chromosome 13q and asthma and atopic disorder in a Japanese population (n = 500).

As shown in the table the heterozygosity of this polymorphism in our population (0.48) is the same as that (0.48) in white populations. The MspI genotypes of HTR2 are the same in controls as in both types of asthma and in eczema and rhinitis. Nor is asymp (raised IgE levels) associated with this polymorphism. These data are not affected by differences in age and gender ratio in the subjects. We conclude that structural or functional variants of HTR2 are not major genetic determinants of bronchial asthma in humans.

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Evidence of maternal segregation distortion in the sickle cell and β thalassaemia traits

Haemoglobinopathies, especially sickle cell syndromes and β thalassaemia, are common in Brazil because of the ethnic composition of the population. As a result, a community programme for haemoglobinopathies has been developed by one of us (ASR) for genetic counselling purposes at the Blood Centre of State University of Campinas (UNICAMP) over the last 10 years. All the pedigrees analysed in the present study have come from this programme and were split into nuclear families, in which a parent was the proband, with complete ascertainment.

The mendelian proportion was tested by the χ² test in the progeny of 165 sickle cell trait (AS) and 86 β thalassaemia trait (AT) probands married to persons with normal haemoglobin (AA). The families were fully examined and even people who had died and abortions were registered. The progeny sample was predominantly composed of children (93% ≤ 15 years old) and all the AS and AT subjects were asymptomatic or slightly symptomatic.

The table displays the number of affected and unaffected offspring produced by AS and AT fathers and mothers.

The mortality rate and the abortion index of both were too low to be correlated with the excess of AS and AT subjects.

These data showed a statistically significant maternal segregation distortion favouring the transmission of haemoglobin S and β thalassaemia alleles. As expected, the mendelian proportion was confirmed in the offspring of male probands. However, the different patterns of maternal and paternal inheritance of the trait were confirmed by the heterogeneity test only for haemoglobins S.

Therefore, our results, if confirmed, may establish a new mechanism for maintaining the Hb S and β thalassaemia polymorphisms. However, in order to avoid misunderstandings or premature conclusions, we are at this time engaged in increasing our records of cases analysed. It is interesting to emphasise, however, that the segregation distortion favouring the transmission of some mutant alleles (retinoblastoma) was described by recent studies in humans.

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Association between genotypes of HTR2 and respiratory and skin disorders

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No of cases</th>
<th>Mean age (y)</th>
<th>Male/female</th>
<th>Serological criteria</th>
<th>HTR2 (MspI)</th>
<th>IgE (IU/ml)/RAST</th>
<th>AA + AB*</th>
<th>BB*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>100</td>
<td>37 [9]</td>
<td>50/50</td>
<td></td>
<td></td>
<td>32 ± 48</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>100</td>
<td>25 [8]</td>
<td>60/40</td>
<td>&gt;400 or &gt;1 positive</td>
<td>33 ± 45</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic asthma</td>
<td>100</td>
<td>53 [11]</td>
<td>55±4</td>
<td>&gt;400 or &gt;1 positive</td>
<td>29 ± 52</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrinsic rhinitis</td>
<td>100</td>
<td>59 [12]</td>
<td>40±6</td>
<td>&lt;400 and all negative</td>
<td>32 ± 39</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>100</td>
<td>43 [9]</td>
<td>40±6</td>
<td>&gt;400 or &gt;1 positive</td>
<td>33 ± 47</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-atopic</td>
<td>215</td>
<td>50 [16]</td>
<td>98±117</td>
<td>&lt;400 and all negative</td>
<td>69 ± 94</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic</td>
<td>285</td>
<td>42 [15]</td>
<td>147±138</td>
<td>&gt;400 or &gt;1 positive</td>
<td>90 ± 137</td>
<td>58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Genotypic polymorphism in HTR2 was defined as AA (absence of restriction site on both alleles), BB (presence of restriction site on both alleles), or AB (heterozygous).


Evidence of maternal segregation distortion in the sickle cell and beta thalassaemia traits.

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