LETTERS TO THE EDITOR

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 adenosine 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.[1] In some strains of rat[2] or guinea pig,[3] 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.[4] These results suggest that 5HT may play an important role as mediator of adenosine 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 *Msp*I restriction polymorphism of HTR2 on chromosome 13q[5] 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.[5] The *Msp*I genotypes of HTR2 are the same in controls as in both types of asthma and in eczema and rhinitis. Nor is atopy (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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Assocation between genotypes of HTR2 and respiratory and skin disorders

Symptoms	No of cases	Mean age (y) [SD]	Male/ female	Serological criteria		HTR2 (MspI)	
				IgE (IU/ml)	RAST	AA+AB*	BB*
Control	100	37 [9]	50/50			32+48	20
Eczema	100	25 [8]	60/40	>400 or	>1 positive	33+45	22
Allergic asthma	100	53 [11]	55/45	>400 or	>1 positive	29+52	19
Intrinsic asthma	100	59 [12]	40/63	<400 and	all negative	32+39	29
Allergic rhinitis	100	43 [9]	40/60	>400 or	>1 positive	33+47	20
Non-atopic	215	50 [16]	98/117	<400 and	all negative	69+94	52
Atopic	285	42 [15]	147/138	>400 or	>1 positive	90+137	58

* 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).

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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.[1] 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.

Affected and unaffected offspring

(a) AS × AA couples (nuclear families, n = 165; offspring, n = 356)

Proband	Offspring				
	AS	AA	Total	χ^2	p
Mother (86)	114	65	179	13·413	p<0·001
Father (79)	94	83	177	0·684	0·30<p<0·50

(b) AT × AA couples (nuclear families, n = 86; offspring, n = 180)

Proband	Offspring				
	AT	AA	Total	χ^2	p
Mother (58)	74	42	116	8·826	0·001<p<0·01
Father (28)	39	25	64	3·063	0·05<p<0·10

The mendelian proportion was tested by the χ^2 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 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.[2]

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