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CORRESPONDENCE

Dyspnoea perception during clinical remission of atopic asthma

To the Editor:

I read with interest the paper by VAN DEN TOORN *et al.* [1] reporting dyspnoea perception during clinical remission of atopic asthma. The authors found that there was no difference in dyspnoea perception between remission patients and asthmatics, and they suggested that physical and psychological factors may play a role in the apparent absence of symptoms.

Recently, VAN DER WOUDE *et al.* [2] showed that there was no difference in the perception of dyspnoea or an increase in reactivity of the airways during methacholine provocation as compared to placebo during maintenance treatment with long-acting β_2-agonists at a high dose. We have previously reported that inhalation of short-acting β_2-agonists decreases dyspnoea, but increases perception of dyspnoea induced by a resistive load in asthma [3].

With respect to the difference in results, I suggest that both a local and a central effect on perception of asthma are important. The perception of asthma involves a number of higher neural centres in the central processing of sensations related to chest wall mechanics, the effort of breathing, bronchoconstriction and airway sensitivity. Therefore, future studies containing all variables related to dyspnoea may provide an answer to dyspnoea perception in asthma.

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References

1. Van den Toorn LM, Overbeek SE, Prins JB, Hoogsteden HC, De Jongste JC. Dyspnoea perception during clinical remission of atopic asthma. *Eur Respir J* 2002; 19: 1047–1050.
2. van der Woude HJ, Aalbers R. Unaltered perception of dyspnoea during treatment with long-acting β_2-acting agonists. *Eur Respir J* 2001; 18: 269–271.
3. Jang AS, Choi IS. Increased perception of dyspnea by inhalation of short acting β_2 agonist in patients with asthma of varying severity. *Ann Allergy Asthma Immunol* 2000; 84: 79–83.

Cooperative effect of adenosine deaminase and ABO-secretor genetic complex on susceptibility to childhood asthma

To the Editor:

In a cohort of asthmatic children, we have recently shown that the ABO-secretor genetic complex influences susceptibility to asthma in children [1].

Since previous studies have shown an association of asthma with adenosine deaminase (ADA) genotype [2], we have searched for possible interactions between the two systems concerning their effects on susceptibility to asthma in children.

The sample study has been described in a previous paper [1] and was composed of 165 children, 109 males and 56 females, aged from 1 month–15 yrs. The criterion for inclusion in the study was the occurrence of two or more episodes of wheezing in the last 6 months, irrespective of aetiology/pathogenesis of the attack.

A consecutive series of 362 newborn infants from the same Caucasian population in Rome, Italy, was used as the control sample.

ADA phenotype was determined by starch gel electrophoresis according to the method of SPENCER *et al.* [3]. ABO and secretor phenotypes were determined according to a standard laboratory procedure [1].

Table 1 shows the distribution of secretor-ABO-ADA joint genotype in asthmatic children and in the control population.

The proportion of nonsecretor/O subjects with the

Table 1. – Cooperative effect of adenosine deaminase (ADA) and secretor-ABO complex on susceptibility to asthma in children

	Nonsecretor/O		Other phenotypes	
	ADA*1*1	ADA*2 carriers	ADA*1*1	ADA*2 carriers
Asthmatics	28 (17.5)	3 (1.9)	115 (71.9)	14 (8.8)
Controls	33 (9.5)	5 (1.4)	260 (74.9)	49 (14.1)
OR	2.02	1.30	0.85	0.58

Data are presented as n (%) unless otherwise stated. OR: odds ratio.

Table 2. – Cooperative effect of adenosine deaminase (ADA) and secretor-ABO complex on susceptibility to asthma in children: three way contingency table analysis by a log linear model

	G	df	p-value
a *versus* b *versus* c interaction	0.012	1	NS
Cumulative effect of a and b on c	8.436	3	0.05

a: secretor/ABO complex genotype; b: ADA genotype; c: disease status (asthmatic/healthy); G: 2ln likelihood ratio (G distribution is similar to that of Chi-squared); df: degrees of freedom.

ADA*1/*1 genotype was much higher in asthmatic children than in controls. On the contrary, the proportion of subjects with other phenotypes of secretor-ABO complex carrying the ADA*2 allele was much lower in asthmatic children than in controls. The other two phenotypic categories showed a similar proportion in asthmatic children and controls.

The lack of three-way interaction among secretor/ABO complex, ADA and disease (table 2), suggests that ADA does not influence the effect of the secretor-ABO complex and *vice versa*, thus indicating that there was not an epistatic effect. On the contrary, the analysis suggests a cooperative effect of the genetic factors on susceptibility to asthma.

The Chi-squared test of independence (table 3) indicated that most of the difference between asthmatics and controls was due to the difference in the proportion of phenotypic categories nonsecretor/O with ADA*1/*1 phenotype (highest susceptibility to asthma) and other phenotypes of the secretor-ABO complex carrying the ADA*2 allele (lowest susceptibility to asthma). The odds ratio between these phenotypic categories was equal to 2.97.

The secretor gene (FUT2) and the ABO system act in concert to build up oligosaccharide structures in exocrine secretions, including secretions in the respiratory tract. Specific oligosaccharide epitopes are necessary for recognition and adherence of microorganisms to the cell membrane, suggesting that genetic variation in these systems may influence susceptibility to viral and bacterial respiratory infections [4].

In purine metabolism, the classical function of the ADA enzyme is considered to be the regulation of intra- and extracellular levels of adenosine. Recently, it has been demonstrated that ADA is present on the surface of many cell types, including lymphocytes and neurons, where it can act as an ectoenzyme [5]. A costimulatory role has been observed for ADA bound with CD26 on the lymphocyte surface, while ADA bound with adenosine 1 receptors (A1R) on the neuronal surface seems to act as a direct local modulator of adenosine action on A1R, and also as a cell adhesion molecule thus having a role in neural development and plasticity processes [5].

Table 3. – Cooperative effect of adenosine deaminase (ADA) and secretor-ABO complex on susceptibility to asthma in children: Chi-squared test (X^2) of independence (asthmatics *versus* controls)

	X^2	df	p-value
a *versus* b *versus* c *versus* d	8.621	3	0.045
a *versus* (b+c) *versus* d	8.452	2	0.015
a *versus* d	7.640	1	0.006

a: nonsecretor/O-ADA*1*1; b: nonsecretor/O-ADA*2 carrier; c: other phenotypes-ADA*1*1; d: other phenotypes-ADA*2 carrier; df: degrees of freedom.

Since the ADA*2 allele is associated with lower ADA enzymatic activity, the negative association of the ADA*2 carrier genotype with the disease could indicate a role of decreased local and/or systemic adenosine levels in the pathogenesis of asthma. The suppressive effects of adenosine on lymphocyte function suggests that the ADA*2 allele could, in part, protect against higher immune reactivity.

Four adenosine receptors (A1, A2a, A2b and A3) have been discovered on the surface of many different cell types [6]. In the respiratory system, the bronchoconstrictor effects of adenosine are well known [7]. Thus, ADA polymorphism could modulate adenosine receptor activity in the respiratory tract with effects on the signal transduction pathway of adenosine and other mediators.

Based on the different roles of the ABO-secretor complex and ADA in the functional integrity of the respiratory tract, it is likely that the effects of the two systems on susceptibility to asthma follow different pathways: the ABO-secretor complex acting on the bacterial-viral infective component and ADA on the cellular reactivity component. Thus, *a priori*, an epistatic interaction was unlikely and our analysis has confirmed the expectation.

At present the genetic analysis of multifactorial disorders is a central problem in medical genetics and there is a general consensus on the necessity of a nonreductionist approach [8]. The analysis of single genetic factors, based on a mendelian perspective, cannot solve the problem. It would be more productive to define a set of genes functionally related to the disease and to study simultaneously genetic and environmental factors involved in the susceptibility to the disease. A comprehensive approach will help to evaluate gene-to-gene and gene-to-environment interactions and will help in the understanding of pathogenic mechanisms.

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References

1. Ronchetti F, Villa MP, Ronchetti R, *et al.* ABO-secretor genetic complex and susceptibility to asthma in childhood. *Eur Respir J* 2001; 17: 1236–1238.
2. Ronchetti R, Lucarini N, Lucarelli P, *et al.* A genetic basis for heterogeneity of asthma syndrome in pediatric

ages: adenosine deaminase phenotypes. *J Allergy Clin Immunol* 1984; 74: 81–84
3. Spencer H, Hopkinson D, Harris H. Adenosine deaminase polymorphism in man. *Ann Hum Genet* 1968; 32: 9–14.
4. Kauffmann F, Frette C, Pham QT, Nafissi S, Bertrand JP, Oriol R. Association of blood group-related antigens to FEV1, wheezing and asthma. *Am J Respir Crit Care Med* 1996; 153: 76–82.
5. Franco R, Valuenzela A, Lluis C, Blanco J. Enzymatic and extraenzymatic role of ectoadenosine deaminase in lymphocytes. *Immunol Rev* 1998; 161: 27–42.
6. Dalziel HH, Westfall DF. Receptors for adenine nucleotides and nucleosides: subclassification, distribution and molecular characterization. *Pharmacol Rev* 1994; 46: 449–466.
7. Polosa R, Holgate ST. Adenosine broncoprovocation: a promising marker of allergic inflammation in asthma? *Thorax* 1997; 52: 919–923.
8. Sing CF, Haviland MB, Reilly SL. Genetic architecture of common multifactorial diseases. Ciba Foundation Symposium 197. USA, John Wiley and Sons, 1996; pp. 211.