

# No association between asthma or allergy and the CCR5 $\Delta$ 32 mutation

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Arch Dis Child 2002;86:426–427

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Accepted  
21 February 2002

**Aims:** To investigate whether the presence of the CCR5 $\Delta$ 32 allele was associated with atopy or asthma.

**Methods:** A total of 118 children with asthma, 145 children with non-asthmatic, but allergic phenotype, and 303 children without allergic or asthmatic disorders were studied.

**Results:** There were no significant differences in the frequency of CCR5 $\Delta$ 32, or in the distributions of genotypes between the groups. The relative eosinophil blood count was slightly lower in patients with heterozygous genotype, than in patients with wild type genotype.

**Conclusion:** No association was found between the susceptibility of allergy or asthma and the functional deficient CCR5 $\Delta$ 32 allele.

Asthma is a pulmonary disease characterised by increased bronchial responsiveness to a variety of stimuli. Chemotactic cytokines, or chemokines, are small signalling proteins which are deeply involved in the physiology and pathophysiology of acute and chronic inflammatory processes, by attracting and stimulating specific subsets of leukocytes. Several studies have shown that chemokines and their receptors are implicated in asthma.<sup>1</sup>

A common 32 base pair (bp) deletion mutation in the CC chemokine receptor 5 gene (CCR5 $\Delta$ 32), which causes truncation and loss of CCR5 receptors on lymphoid cell surfaces has been described.<sup>2</sup> Two recent studies in the *Lancet* have reported controversial results about the prevalence and role of the CCR5 $\Delta$ 32 mutation in asthmatic individuals. Hall *et al* have reported an association of the CCR5 $\Delta$ 32 allele with reduced risk of asthma in Scottish children,<sup>3</sup> while Mitchell *et al* found no significant association for atopy or asthma/wheeze in families from Western Australia and Southern England.<sup>4</sup>

Given the potential importance of CCR5 in allergic inflammation, we determined the prevalence of the CCR5 $\Delta$ 32 mutation in three groups of Hungarian children.

## METHODS

A total of 118 asthmatic children (aged 3–18 years, mean 10.1 (SD 3.5) years), 145 non-asthmatic, allergic children (aged 1–18 years, mean 5.4 (SD 3.8) years), and 303 children of comparable age without atopic or allergic disorders were enrolled in the study.

The asthmatic children attended the Allergic Outpatient Consultation of the Budai Children's Hospital. All the asthmatic children had specialist physician diagnosed asthma with the following characteristics: (1) recurrent breathlessness and expiratory dyspnoea requiring treatment; (2) physician diagnosed wheeze; and (3) reversibility of the wheezing and dyspnoea by bronchodilator treatment, measured as forced expiratory volume in one second (FEV<sub>1</sub>) by a spirometer (Piston).

The non-asthmatic allergic children attended the Allergic Outpatient Consultation of Heim Pál Pediatric Hospital. All the allergic children had specialist physician diagnosed allergy with the following criteria: (1) clinical signs of severe allergy (including allergic rhinitis, atopic dermatitis, food allergy, and urticaria); and (2) atopy (defined as described elsewhere<sup>5</sup>).

The control children were selected from patients in the Heim Pál Pediatric Hospital who met all of the following criteria:

(1) no symptoms and history of allergic diseases; and (2) total serum IgE below the general population mean for their ages.

Informed parental consent was obtained for each patient and the study was approved by an institutional review committee.

White blood cell counts and eosinophil cell counts were measured by Coulter MAXM Analyser. Genotyping of CCR5 was carried out as described previously.<sup>6</sup>

CCR5 $\Delta$ 32 allele frequencies were calculated by allele counting. Hardy–Weinberg equilibrium was tested by using a  $\chi^2$  goodness of fit test. The technique of  $\chi^2$  decomposition was used to test for differences in CCR5 $\Delta$ 32 distributions between the different phenotypes. Analysis of variance was used to estimate the impact of the polymorphism on quantitative traits. The power calculation was performed by StatMate software (GraphPad Software Inc., San Diego, California).

## RESULTS

Table 1 presents the distribution of CCR5 $\Delta$ 32 genotypes and the allelic frequencies in the three groups. The results were overall in Hardy–Weinberg equilibrium. The allelic frequency in the controls (11.2%) was in good agreement with that found in a previous study of Hungarian newborns (11.6%). There were no significant differences in the frequency of CCR5 $\Delta$ 32, or in the distribution of genotypes between the groups. In contrast to the results of Hall and colleagues,<sup>3</sup> there were several homozygous carriers for the  $\Delta$ 32 allele among the asthmatic patients (3.4%).

Based on the observed prevalence of CCR5 $\Delta$ 32 in our population, this study had an 80% power to detect a relative risk of 0.37 in the prevalence of asthma between carriers and non-carriers with a significance of  $p = 0.05$ . Hall and colleagues<sup>3</sup> reported an odds ratio of asthma in individuals with the CCR5 $\Delta$ 32 of 0.36. Therefore, our study with the same power and at the same level of significance should be able to detect significance differences in the proportion of patients with asthma between carriers and non-carriers if they exist in the population tested.

To determine the role of the CCR5 $\Delta$ 32 allele in asthma, some clinical and biological characteristics of the asthmatic patients were compared between the different genotypes. Among the 118 asthmatic there were 87 atopic (73.7%) and 31 non-atopic (26.3%) patients. There were no significant differences in the prevalence of the CCR5 $\Delta$ 32 allele or in the genotype distributions between atopic and non-atopic asthmatic

**Table 1** Genotype and allelic frequencies for CCR5Δ32 in the three groups of children

Population	WT/WT n (%)	WT/Δ32 n (%)	Δ32/Δ32 n (%)	Total n (%)	Allelic frequency of Δ32 % (SE)
Children with asthma	95 (80.5)	19 (16.1)	4 (3.4)	118 (100)	11.4 (2.1)
Non-asthmatic children with atopy	116 (80.0)	26 (17.9)	3 (2.1)	145 (100)	11.0 (1.8)
Children without atopy or asthma	240 (79.2)	58 (19.1)	5 (1.7)	303 (100)	11.2 (1.3)

patients (allele frequencies were 10.3% and 14.5%, respectively). The mean age of the patients at first diagnosis of asthma, total IgE concentration, white blood cell count, and absolute eosinophil cell count did not differ between the genotypes (data not shown). The relative eosinophil blood count was slightly lower in patients with heterozygous genotype than in patients with wild type genotype (3.9% SD 1.6% v 5% (SD 1.9%),  $p = 0.02$ ). In contrast, the relative eosinophil count was highest in patients with Δ32/Δ32 genotype (6% (SD 2.8%)), but because of the low number of patients with this genotype (four), the difference was not significant.

## DISCUSSION

In our investigation of 566 Hungarian children, we found no variation in the prevalence of CCR5Δ32 allele between the asthmatic, allergic, and control groups, suggesting that the CCR5Δ32 allele does not protect from asthmatic or allergic diseases, and does not even contribute to a reduced risk in allergic individuals from the development of asthma. Our findings are not in agreement with those of Hall and colleagues,<sup>3</sup> who found reduced prevalence for CCR5Δ32 in 98 Scottish asthmatic children, comparing them with 317 non-asthmatic children. In contrast, the results of Mitchell *et al* are comparable with ours.<sup>4</sup> Although comparison of these results is difficult because of the possible genetic and environmental differences in the populations, the CCR5Δ32 allele seemed to be protective against asthma in Scotland, but not in our study population.

## ACKNOWLEDGEMENTS

This study was supported by the following grants: OTKA (National Scientific Research Fund): T-016111, T032349, 022287/1997; Hungarian Ministry of Welfare: ETT 134/2001 474/96; János Bolyai Research Grant.

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## ARCHIVIST .....

### Special Educational Needs and Disability Act 2001

**T**he Special Educational Needs and Disability Act 2001 (SENDA) makes changes to the Education Act 1996 and the Disability Discrimination Act 1995 (DDA), changing the statutory framework for special educational needs and extending the DDA to education (Phillipa Stobbs. National Children's Bureau. Highlight No. 186; 2001)

The special educational needs provisions increase access to a place in a mainstream school, information and support available to parents, and parents' rights of appeal. From January 2002, a child with a statement of special educational needs must attend a mainstream school unless that is incompatible with the wishes of the parents or the efficient education of other children. Schools and local education authorities are required to take reasonable steps to prevent mainstream school placement interfering with the efficient education of other children.

The DDA changes introduce a "less favourable treatment duty" and a "reasonable adjustments" duty'. A school is held to discriminate against a child if, for a reason related to the child's disability, it treats the child less favourably than others to whom that reason does not apply and it cannot show that the treatment is justified. The reasonable adjustments duty requires the responsible body for the school to make reasonable adjustments to ensure that disabled pupils are not put at a substantial disadvantage. The provision of auxiliary aids and services, and physical adaptations to buildings are excluded from this duty but local education authorities and schools have a duty to plan to increase access for disabled pupils.