Association of glutamine 27 polymorphism of β_2 adrenoceptor with reported childhood asthma: population based study

E Hopes, C McDougall, G Christie, J Dewar, A Wheatley, I P Hall, P J Helms

Department of Child Health, Medical School, University of Aberdeen, Aberdeen AB25 2ZD
E Hopes, *PhD student*
C McDougall, *medical student*
G Christie, *research fellow*
P J Helms, *professor*

Department of Medicine, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH
J Dewar, *research fellow*
A Wheatley, *PhD student*
I P Hall, *reader*

Correspondence to: Professor Helms
p.j.helms@abdn.ac.uk

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The prevalence of asthma in children has doubled over the past 25 years.[1] Two common polymorphisms exist in the β adrenoceptor at amino acids 16 (glycine for arginine) and 27 (glutamic acid for glutamine). Both are functionally relevant in cultured cells, with the glycine 16 form of the receptor showing enhanced downregulation and the glutamic acid 27 form showing attenuated downregulation after exposure to β agonists.[2] The glutamine 27 polymorphism is associated with raised IgE concentrations in families with a history of asthma, and with increased reactivity of the airways in people with asthma.[3 4] We measured the prevalence of these polymorphisms in a random population of children to identify their importance in the expression of reported asthma.

Subjects, methods, and results

We approached children between the ages of 5 and 15 years (mean 10.5 years) and an accompanying parent who were attending the accident and emergency department of the Royal Aberdeen Children's Hospital. Approval from an ethics committee and written consent were obtained from the parents and participating children, and 425 (97%) of 438 agreed to participate. After completing a brief questionnaire each child provided a mouth wash sample (10 ml of boiled distilled water).[1] From the resulting suspension of buccal epithelial cells DNA was extracted, and the β_2 adrenoceptor polymorphisms were identified using the polymerase chain reaction and an allele specific oligonucleotide assay.[3] Frequency tables and Pearson's χ^2 test were used for bivariate comparisons and logistic regression employed in the multivariate analysis.

Complete information including phenotype information on both parents and genotype information in children was available for 410 children with genotyping data in 419. The childhood prevalence of reported asthma (104 out of 425, 24%) was similar to that observed in a recent postal questionnaire study from the same population.[5]

Thirty nine were arginine 16 homozygotes, 179 were glycine 16 homozygotes, and 201 were heterozygotes. Ninety three were glutamic acid 27 homozygotes, 107 were glutamine 27 homozygotes, and 219 were heterozygotes for the two. The two polymorphisms were in partial linkage disequilibrium. The allelic prevalences of the β_2 polymorphisms in this child population were virtually identical with those found in a random sample of adults in Nottingham (unpublished data). Both polymorphisms were in Hardy-Weinburg equilibrium.

Genotype at position 16 was not associated with reported asthma. Both homozygosity and heterozygosity for the glutamine 27 polymorphism were associated with reported asthma (table), with a significant association between the presence of this allele and reported asthma ($\chi^2 = 4.38$, df = 1, P = 0.04). On logistic regression analysis and taking other known factors into account (sex, maternal asthma, reported hay fever, and eczema) the glutamine 27 allele conferred an independent increased risk of reported asthma (odds ratio 2.18, confidence interval 1.13 to 4.23, P = 0.02). Conversely, homozygosity for the glutamic acid 27 polymorphism had a lower risk (odds ratio 0.46, (0.24 to 0.89)). Of the 104 children with reported asthma, 47 were also reported to have coexisting hay fever or eczema, or both. When this subpopulation was included in a secondary analysis, the modifying effect of glutamic acid 27 was of a similar order ($\chi^2 = 9.56$, df = 4, P = 0.05).

Genotypes at position 27 and reported asthma

	No asthma	Reported asthma	Totals for position 27 genotypes
Glutamine 27 homozygote	83	24 (22%)	107
Glutamine and glutamate heterozygote	156	63 (30%)	218
Glutamate 27 homozygote	78	15 (16%)	93

Comment

The finding that the glutamic acid 27 polymorphism may be associated with a decreased prevalence of reported asthma in childhood is consistent with its effects on IgE concentration and non-specific bronchial reactivity.[3 4] Interestingly, this polymorphism was not associated with asthma in adult populations,[3] in whom IgE may be a less important determinant of the asthma phenotype. Whether the glutamine for glutamic acid polymorphism at position 27 determines the asthma phenotype in children or whether it is in linkage disequilibrium with another gene, perhaps in the nearby T helper 2 cytokine gene cluster on chromosome 5q, remains to be established.

Contributors: PJH coordinated and supervised the study and, in discussion with I P Hall, had the original idea for it. PJH and IPH are joint guarantors for the study. CMcD recruited the families, applied the questionnaire, obtained the mouth wash samples, and, together with JD, AW, and EH, performed the laboratory analyses under the supervision of IPH. GC contributed to the background review and data analysis. The paper was written jointly by PJH, EH, and IPH.

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