

Genetic factors in childhood asthma

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ABSTRACT The prevalences of asthma and atopy were examined in the families of 77 asthmatic and 87 control children attending a London general practice. The prevalence of asthma in first degree relatives of asthmatic children was found to be significantly higher than in relatives of control children, and this difference was more pronounced for relatives of atopic probands than for relatives of non-atopic probands. Among the relatives of asthmatics, atopic asthma was more common than non-atopic asthma, irrespective of the atopic status of the proband. However, among the relatives of control children, neither the prevalence of asthma nor the atopic status of the asthmatic relatives was influenced by the atopic status of the proband. These findings support the hypothesis that asthma and atopy are inherited independently. Although atopy itself does not predispose to asthma, it may enhance a genetic susceptibility to the condition, thus increasing the likelihood that the latter will be expressed.

Two forms of asthma can be distinguished: *atopic asthma* in which patients give a positive immediate reaction on skin prick testing, and *non-atopic asthma* in which patients give no positive reactions.

Although family and twin studies have established that asthma has an hereditary basis^{1,2} no evidence has been presented to show whether or not both the atopic and the non-atopic forms of the disease can be inherited. However, it has been shown that the prevalence of asthma is higher in relatives of atopic asthmatics than in relatives of non-atopic asthmatics.³ Therefore, if there is a genetic basis in both forms, the heritability of atopic asthma is likely to be greater than that of non-atopic asthma.

Current studies suggest that this difference in heritability might arise from an increase in the susceptibility to asthma of patients who inherit a predisposition to both asthma and atopy. Pepys⁴ has shown that the prevalence of asthma in first degree relatives of asthmatics increases with the number of positive skin tests in the probands, indicating that atopy may enhance the manifestation of asthma. However, the prevalence of hay fever and eczema in these relatives was more strongly associated with the atopic status of the probands than was the prevalence of asthma, sug-

gesting that asthma may be inherited independently of atopy.

In the present study, family study methods have been used to investigate the hypotheses that atopic and non-atopic asthma are both heritable, and that asthma may be inherited independently of atopy. Patients have been selected from a general practice population, since the findings of previous investigations may have been biased by studying hospital outpatients who were likely to have had a more severe form of asthma than occurs in the general population.

Methods

The study group consisted of 164 children, aged 1-12 years, and their families attending a general practice in Roehampton, South-West London. The data were collected in the course of a survey of asthma and wheezy bronchitis, carried out between 1967-76.⁵⁻⁷

The first child from each family recruited in the original survey was designated the proband for the purposes of the present study. Probands were grouped according to their history of lower respiratory illness as follows.

Children in whom wheeze had occurred *only* in association with symptoms suggestive of respiratory infection were diagnosed as suffering from wheezy bronchitis and have been excluded from

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the present study. The clinical relationships between these children and those with asthma has been discussed by Horn *et al.*,⁷ while the genetic relationship has been reported by Sibbald *et al.*¹⁵

Children in whom wheezy episodes occurred in response to allergens, exercise, or emotion, as well as with symptoms suggestive of respiratory infection, were diagnosed as having asthma. On auscultation there was high-pitched wheezing over most parts of the lungs.

The control group consisted of children with no history of wheezy illness. Although the majority had experienced one or more episodes of bronchitis, wheeze had never been detected on auscultation.

The asthma and control groups were each subdivided into atopic and non-atopic groups dependent on the proband's skin prick test response to pollens, house dust mite, animal danders, and moulds. The criterion for a positive response was a weal of 2 cm or more in diameter in the absence of any equivalent reaction in the control solution. Children with one or more positive reactions were designated atopic, while those with no positive reactions were designated non-atopic.

The age, sex, and personal history of hay fever and eczema were recorded for every proband. The history of asthma in the parents and siblings of probands was obtained through interview with one or more members of the family and from scrutiny of medical records. Estimation of the prevalence of atopy, as shown by the presence of positive skin tests, was carried out in all accessible relatives. Complete information was available for the 30 (34%) of the control children (applicable to table 3).

Results

The probands are described in table 1. There were significantly more children with atopy, hay fever, and eczema among asthmatic probands than control subjects. Similarly the proportion of probands with a positive family history of asthma was higher in the asthmatics than the controls. The sex ratio and mean age of the probands did not differ between groups.

The family history of asthma differed between asthmatic and control children (table 2). The overall prevalence of asthma was higher in relatives of asthmatic probands than controls, and this difference was more pronounced for relatives of atopic than for relatives of non-atopic probands. Furthermore, the prevalence of asthma was higher in parents than siblings in the families of asth-

matics, while the parents and siblings of controls were equally affected.

The distribution of atopic and non-atopic asthma among relatives is shown in table 3. In relatives of asthmatics, the prevalence of atopic asthma exceeded the prevalence of non-atopic asthma irrespective of the atopic status of the proband. In contrast, the prevalences of atopic and non-atopic asthma were equal in relatives of atopic and non-atopic controls.

Table 1 Clinical characteristics of the probands

Proband	Number (% total)	Males No (%)	Hay fever No (%)	Eczema No (%)	Family history of asthma No (%)	Mean age (yr)
Asthma						
Atopic	64 (83)†	42 (66)	25 (39)*	33 (52)*	25 (39)†	7.5
Non-atopic	13 (17)	9 (69)	0 (0)	0 (0)	4 (31)	5.4
Total	77	51 (66)	25 (32)†	33 (43)†	29 (38)†	7.1
Control						
Atopic	38 (44)	25 (66)	5 (13)	8 (21)	4 (10)	6.0
Non-atopic	49 (56)	24 (49)	0 (0)	8 (16)	5 (10)	5.4
Total	87	49 (56)	5 (6)	16 (18)	9 (10)	5.6

Excess as compared with control: *p < 0.05 and †p < 0.01.

Table 2 Prevalence of asthma in first degree relatives of probands

Proband	Prevalence (%) of asthma in			Significance Parents versus siblings
	Parents	Siblings	All relatives	
Asthma				
Atopic	23/128 (18)	11/124 (9)	34/252 (13)	p < 0.05
Non-atopic	4/26 (15)	1/26 (4)	5/52 (10)	SS
Total	27/154 (17)	12/150 (8)	39/304 (13)	p < 0.05
Control				
Atopic	2/76 (3)	2/53 (4)	4/129 (3)	SS
Non-atopic	5/98 (5)	2/75 (3)	7/173 (4)	SS
Total	7/174 (4)	4/128 (3)	11/302 (4)	NS

Significance

Asthma versus control Atopic p < 0.01
 Non-atopic SS
 Total p < 0.001

SS = sample too small for analysis, NS = not significant.

Table 3 Prevalence of atopic and non-atopic asthma in relatives of probands

Proband	Number of relatives at risk	Affected relatives		Row significance
		Atopic asthma	Non-atopic asthma	
		No (%)	No (%)	
Asthma				
Atopic	101	10 (10)	3 (3)	$\chi^2 = 3.78$, p < 0.10
Non-atopic	14	2 (14)	0 (0)	$\chi^2 = 2.00$, p > 0.10
Total	115	12 (10)	3 (3)	$\chi^2 = 5.78$, p < 0.10
Control				
Atopic	35	1 (3)	1 (3)	$\chi^2 = 0$
Non-atopic	69	2 (3)	2 (3)	$\chi^2 = 0$
Total	104	3 (3)	3 (3)	$\chi^2 = 0$

Table 4 Prevalence of atopy in first degree relatives of probands

Proband	Prevalence (%) of atopy in			Significance Parents versus siblings
	Parents	Siblings	All relatives	
Asthma				
Atopic	34/56 (61)	27/45 (60)	61/101 (60)	NS
Non-atopic	3/8 (37)	2/6 (33)	5/14 (36)	SS
Total	37/64 (58)	29/51 (57)	66/115 (57)	NS
Control				
Atopic	11/20 (55)	9/15 (60)	20/35 (57)	NS
Non-atopic	18/40 (45)	11/29 (38)	29/38 (42)	NS
Total	29/60 (48)	20/44 (43)	49/104 (47)	NS
Significance				
Asthma versus control	Atopic	NS		
	Non-atopic	NS		
	Total	NS		

Abbreviations as in table 2.

The family history of atopy was similar in asthmatic and control children (table 4). The prevalence of atopy in relatives did not differ significantly between groups of probands. However, there was a tendency for atopy to occur more frequently in the families of atopic probands than in the families of non-atopic probands. The parents and siblings of probands were equally affected in all groups.

Discussion

The findings of this study support those of previous investigations in showing that asthma clusters in families.^{1,8} The overall prevalence of asthma in the first degree relatives of asthmatics was found to be 13%, while that in the relatives of controls was only 4%. These figures agree well with those of Leigh and Marley¹ whose family data were collected by similar methods. They found a prevalence of 13.2% in the first degree relatives of asthmatics and a prevalence of only 1.5% in the relatives of controls. Although this familial aggregation of asthma may arise partly from shared family environments, twin studies have shown that shared genetic factors must also play an important role.^{2,9}

The increased prevalence of asthma in the relatives of both atopic and non-atopic asthmatics, as compared with the relatives of controls, suggests that both forms of asthma may be hereditary. Furthermore, the similarity between atopic and non-atopic patients in the distributions of asthma among their parents and siblings shows that, if they are hereditary, they may share a common genetic defect. Although the mode of inheritance cannot be decided accurately from the available

data, the evenness of the distribution of asthma among the relatives is compatible with either polygenic inheritance or dominance with incomplete penetrance.

Despite this similarity in their modes of inheritance, the increase in the prevalence of asthma in the relatives of asthmatic as compared with control patients was greater for atopic than non-atopic probands. Thus the hereditary component underlying atopic asthma may be greater than that underlying non-atopic asthma.

Within the families of asthmatics, there appeared to be no correlation between the type of asthma in first degree relatives and the atopic status of the proband. This is best illustrated by our findings that the prevalence of atopic asthma exceeded the prevalence of non-atopic asthma in relatives of both atopic and non-atopic probands. The absence of any strict association between atopy and asthma strongly suggests that asthma may be inherited independently of atopy. Additional support for this hypothesis comes from our observation that asthma was more prevalent in the relatives of asthmatics than in the relatives of controls, whereas the prevalence of atopy did not differ significantly between groups.

Although it has been established that atopy is at least partly hereditary,^{9,10} neither the prevalence nor the type of asthma in the relatives of controls were influenced by the atopic status of the proband. Thus atopy itself did not predispose to asthma.

If, as the results suggest, atopy and asthma are inherited independently and atopy itself does not predispose to asthma, it seems likely that the increased risk of asthma in relatives of atopic asthmatics must arise from an increased susceptibility to asthma of patients who inherit a predisposition to both asthma and atopy. Thus, the findings of this study support the hypothesis of Sibbald and Turner-Warwick³ that clinically different forms of asthma may have a common genetic defect, whose manifestation may be enhanced in the presence of atopy.

The control children used in this study were not strictly normal in that 62 (71%) had had one or more episodes of bronchitis. The prevalence of atopy (44%) and the sex ratio (1:29) in these probands were higher than are generally found in children of this age,^{11,12} suggesting that the control children may have possessed some genetic factors in common with the asthmatic children.

Development of positive skin prick tests may be age-dependent, reaching a maximum in early adulthood.¹¹ Since the majority of children in the

present study were young (see table 1), the prevalence of atopy among the probands and their siblings might have been underestimated. Therefore, the relationship between atopy and asthma should now be investigated in the families of adults to avoid any bias which may have been introduced by the youth of our probands.

We would like to acknowledge the financial support of the National Heart and Chest Hospitals. BS was supported by a research scholarship from the British Council.

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