

Is intrinsic asthma a hereditary disease?

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Although studies of families, inbred populations and twins have established that asthma has a hereditary basis, little evidence has shown that intrinsic asthma has an increased familial occurrence. To document this issue, we compared the prevalence of asthma in families of intrinsic asthmatics, extrinsic asthmatics and non-asthmatics. The intrinsic asthma group included those with negative skin tests to common aero-allergens ($n = 117$). The extrinsic asthma group included those with one or more positive skin tests ($n = 164$). The non-asthmatic group ($n = 224$) was recruited at a check-up center. The siblings of each subject completed a standardized questionnaire on history of asthma. The results showed that asthma was more prevalent ($P < 0.001$) in siblings of intrinsic asthmatics (8.9%) than in siblings of the non-asthmatic group (2.4%). The prevalence of asthma in siblings of intrinsic and extrinsic asthmatics was similar. In conclusion, both intrinsic and extrinsic asthma have an increased family occurrence.

Key words: extrinsic asthma; genetics; heredity; intrinsic asthma; occurrence.

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Asthma is a reversible obstructive respiratory disease whose prevalence among the general population usually varies between 1 and 7% (3). In clinical practice, two forms of asthma are commonly distinguished. Extrinsic asthma, in which an exogenic causal factor is involved, generally begins at an early age and affects boys more often than girls (8). Intrinsic asthma, in which no exogenic factor can be identified, begins later and strikes men and women equally (8). Family (4, 11, 12), large twin (6), and inbred population (10) studies suggest that regardless of its clinical presentation, asthma has an increased family occurrence.

Some evidence that intrinsic asthma occurs in families has been reported (1, 10, 12, 13). However, no study including a large group of non-asthmatics and asthmatics classified as extrinsic or intrinsic on the basis of skin tests to common aero-allergens has been performed.

Our purpose was to determine whether or not intrinsic asthma occurs in families by comparing the prevalence of asthma in siblings of intrinsic asthma patients with its prevalence in siblings of extrinsic asthma patients and non-asthmatic subjects.

METHODS

Asthmatics were consecutively enrolled from patients 25 to 65 years old attending the Department of Chest Diseases and Clinical Immunology of our hospital. Asthma was identified by the 1978 ATS standardized questionnaire (history of asthma attacks) and by a medical evaluation by the same doctor (F.P.). All asthmatics underwent skin tests by intradermal injection of 0.02 ml of 1/10,000 w/v concentrations of the following allergens: house dust, house dust mite, and cat and dog danders (Institut Pasteur, Paris) and by prick

Table 1.
Clinical characteristics of subjects
(asthmatics and non-asthmatics) and their siblings

Group	Intrinsic	Extrinsic	Non-asthmatics
Subjects			
<i>n</i>	117	164	224
age*	51.5±10.6	44.5±10.8	41.1±8.6
age at onset of asthma	38.5±15.8	24.9±16.2	
Siblings			
<i>n</i>	273	412	550
age*	48.6±15.1	41.8±13.6	40.0±12.6

* values are mean ± SD (year)

tests using 1/20 w/v concentrations of grass and parietaria pollen extracts (Laboratoire des Stallergènes, France). Prick tests were performed using the Stallerpoint® device. Codeine phosphate (9% solution) was used as a positive control and considered positive if ≥ 4 mm. A negative control test was performed using the diluent to discard false positive results. A study by Eriksson has shown that a limited number of allergens suffice for identifying most of the atopic patients among adult asthmatics (7) and for performing an efficient screening method. Intradermal tests were considered as positive if the diameter of the wheal was ≥ 6 mm; prick tests were considered positive if wheal diameter was ≥ 3 mm and if the negative control test was negative. Asthmatics who had one or more positive skin tests were included in the extrinsic group while those who had negative skin tests were included in the intrinsic group. Asthmatic from the intrinsic and extrinsic groups were asked about the age at onset of asthma. The number of siblings in the subject's family was also established during the initial interview.

The non-asthmatic group was recruited consecutively from 25- to 65-year-old adults undergoing check-up examinations at a Public Health Center in Marseille. In France, all adults affiliated to the social security (i.e. 95% of the general population) are invited, on a 5-year basis, to have such an examination. These subjects were interviewed and examined

by the same physician. Asthmatic subjects, i.e. subjects with a history of asthma, attacks and a medical evaluation suggesting asthma, were discarded.

The subjects from the three groups (intrinsic asthmatics, extrinsic asthmatic and non-asthmatic subjects) were asked to have their brothers and sisters complete the same standardized questionnaire as their asthmatic sibling and mail it back to the hospital. This questionnaire particularly asked the following questions: "Have you ever had asthma?" and "Was asthma diagnosed by your doctor?" If they responded "Yes" to both questions, the diagnosis of asthma was accepted. For the sake of clarity, in this paper the term "prevalence" stands for cumulative prevalence.

Statistical analysis

Analysis of variance and the chi-square (χ^2) test with two degrees of freedom (2df) were used to compare means and proportions within the three groups. A *P* value < 0.05 was considered significant. When statistically significant differences were detected between the three groups, two by two comparison procedures using the orthogonal contrast method (9) or the chi-square (χ^2 , 1df) test (correction of Yates for small samples) were performed to determine where the difference was.

RESULTS

Table 1 lists the clinical characteristics of patients or non-asthmatics whose siblings all completed the questionnaire. Overall, 85% of the studied families, in each group, provided complete responses from their siblings. On the average intrinsic asthmatics were 7 years older than extrinsic asthmatics and asthma attacks started 13.6 years later in the former group than in the latter. Siblings of the intrinsic group were 6.8 years older than their extrinsic group counterparts. Among the individuals from the non-asthmatic group, asthmatics were discarded, leaving a group of 224 subjects.

The prevalence of asthma differed significantly ($P < 0.001$) between the three groups of siblings. As shown in Fig. 1, the prevalence of asthma was similar in siblings of extrinsic (6.8%) and intrinsic (8.0%) asthmatics but the prevalence of asthma in these two groups was higher than in siblings of control subjects (2.4%).

One or more siblings of 18 subjects in the intrinsic group, 45 in the extrinsic group and 116 in the non-asthmatic group failed to complete the questionnaire. The clinical characteristics of these subjects with incomplete family responses were not different from those of their

counterparts with complete family responses. Within the three groups with incomplete family responses, the relative prevalence of asthma among the siblings who did answer questions did not differ from the relative prevalence of asthma in the three groups of siblings with complete family responses.

DISCUSSION

The results of this study show that the prevalence of asthma among siblings of intrinsic asthmatics was higher than among siblings of non-asthmatic subjects but not different from among siblings of extrinsic asthmatics. The higher prevalence of asthma among siblings of intrinsic asthmatics than among siblings of the non-asthmatics supports the hypothesis that intrinsic asthma has an increased family occurrence. Conceivably, siblings of asthmatic patients might have been more prone to answer "yes" to questions related to asthma than siblings of non-asthmatic subjects. However, this response bias is unlikely because only relatives whose asthma was diagnosed by a doctor were considered as asthmatics. That the results from groups whose whole family did not respond were similar to those whose whole family responded further argues against this bias. In siblings from the non-asthmatic group, the prevalence of asthma may have been underestimated, since the fact that no asthma diagnosis was given by a doctor is no guarantee for not having asthma. If no family member has asthma, a patient would be less inclined to see a doctor for respiratory symptoms. The large difference in prevalence rate of asthma in siblings from the asthmatic and non-asthmatic groups is not likely to be accounted for by this potential bias. The prevalence of asthma in siblings was based upon the response to a questionnaire which included: "Have you ever had asthma?" and "Was asthma diagnosed by your doctor?" The criteria might have missed some individuals when the diagnosis of asthma may have been called other things (e.g. recurrent bronchitis) but such a misclassification would have occurred similarly in the three groups as well.

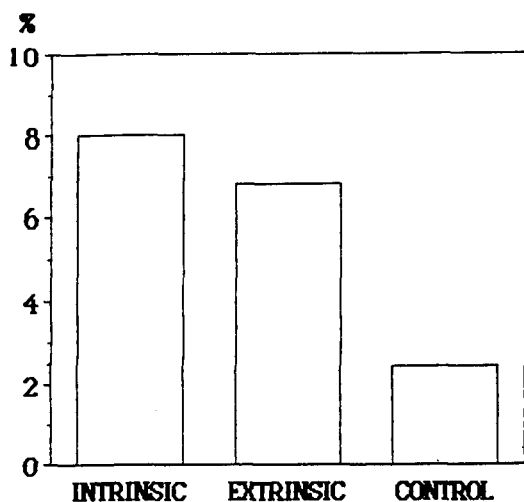


Fig. 1. Prevalence of asthma among siblings of the three groups (overall comparison of the three provided $P < 0.001$).

We restricted the study in the three groups to subjects 25 to 65 years old because the age distribution is known to influence the cumulative prevalence of asthma. We deliberately decided not to study the distribution of asthma in offsprings of the groups because it would have been necessary to get data not only on asthma but also on atopy in the subjects' spouses.

Up to now few studies had provided conclusive evidence that intrinsic asthma runs in families. In their first family study Sibbald & Turner-Warwick (13) claimed that only extrinsic asthma had a hereditary basis because they observed a higher prevalence of asthma among siblings of "polar" extrinsic than among "polar" intrinsic asthmatics (10.5% and 2.4%, respectively). "Polar" was used by these authors to define asthmatics as "intrinsic" or "extrinsic" according not only to skin tests but also to the clinical features of the disease. However, since their study did not include a non-asthmatic group, the possibility of familial transmission of intrinsic asthma could not be dismissed. In a subsequent study including a control group (12), they suggested, by studying a rather limited group, a higher prevalence of asthma in relatives of intrinsic (and extrinsic) asthmatics than in control subjects. In Schwartz's data (11), there appeared to be no difference in the incidence of the atopic diseases, including asthma, in relatives of patients with allergic or non-allergic asthma, and in both groups the prevalence was significantly higher than among the relatives of controls. However, in this study performed in 1947 the classification into allergic or non-allergic asthma was only based on a history suggesting that allergens played or did not play a role in their condition. In the Discussion section of his paper, Schwartz reviewed studies assessing the heredity of asthma. Among the many studies reviewed, only Adkinson's (1) seems relevant. Adkinson in 1920 studied 400 cases of asthma, classified according to cutaneous reactivity into extrinsic and intrinsic. The prevalence of a family history of allergic diseases (unfortunately, the paper does not bring any substantiation of the different diseases)

was similar in asthmatics with positive (52%) and negative (41%) skin tests to common allergens. The author concluded that there was no difference from the point of view of heredity between extrinsic and intrinsic asthma.

In conclusion, intrinsic and extrinsic asthma both have an increased family occurrence, probably through a genetic mechanism. Also, these two forms of asthma have common pathological changes, increased bronchial hyper-reactivity, hypereosinophilia and increased total IgE level (2). High IgE level as well as specific IgE appear to be under the same gene control, located on chromosome 11q (5). In addition, a large part of the intrinsic group might be allergic to allergens not (yet) identified by the physician. All these facts raise the issue of true differences between intrinsic and extrinsic asthma.

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