

Sensitization to four common inhalant allergens within 302 nuclear families

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Summary

The coincidence of allergic sensitization was investigated in 302 school-aged children and their parents. Specific sensitization to four common inhalant allergens (grass and birch pollens, cat dander, *Dermatophagoides pteronyssinus*) was ascertained by means of skin-prick tests (SPT) carried out on the complete family unit at the beginning of a 22-month follow-up period. The same test procedure was then repeated on the children twice at 11-month intervals to provide cumulative prevalences of sensitization. A clinical history of atopy in the children (hay fever or asthma; $n=47$), which was derived from an interview, is associated with sensitization (positive SPT in 89%). For three allergens (grass and birch pollens, cat dander) sensitization occurs significantly more frequently in the children of mothers who are sensitized to the same allergen (odds-ratios (ORs), 2.5–4.1). Additionally, in three of the four explanatory models related to a single antigen, maternal sensitization to one of the complementary allergens is of importance (ORs, 2.7–3.7). In contrast to this finding, none of the paternal sensitizations has statistical significance. Based on a reaction to at least one of the four allergens, the child's relative risk to be sensitized is increased in case of maternal (OR, 2.88; $P=0.001$) but not of paternal (OR, 1.06; $P=0.83$) sensitization. In conclusion, our data indicate that the maternal status is more predictive than that of the father with regard to the child's risk of sensitization.

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Introduction

In studies on the inheritance of atopy, the disorders have been defined using either the clinical history or total IgE measurement [1,2]. No reports have been prepared using population-based data about the specific immunologic response against environmental allergens within family groups. This seems surprising since recent immunogenetic studies assume such an antigen specificity of inheritance to exist [3,4] and, as far as we know, only studies of twin pairs regarding specific sensitization in first degree relatives have been published to date [5,6]. In order to investigate relationships between parents and their children, we analysed skin-prick test (SPT) data from 302

unselected nuclear families for a coincidence of sensitization to four common inhalant allergens within the two generations.

Materials and methods

Population

A population of 463 families with a total of 704 children aged 7–16 years from the area of Freiburg city and one community in the Black Forest was randomly selected in October 1987. The study population had been living in the region for years, thus providing stable macro-environmental conditions for this period. It was possible to carry out three consecutive examinations with 421 families, each during the same season (winter/spring) and 11 months apart [7]. The first investigation included a standardized SPT of the children as well as one of their

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parents. In the second and third survey only the children were tested. Of the 421 families those with SPT results of the mother and the father were included in the analysis ($n = 302$). For the sake of a uniform comparison only the youngest child of each family was taken into account in the following section of this report (age: mean = 10.6 yr, s.d. = 2.0 yr; gender: 49.7% boys).

Atopic history

To ascertain the initial medical history regarding bronchial asthma ('for your child/your husband/you has a doctor ever diagnosed asthma?') and hay fever ('for your child/your husband/you has a doctor ever diagnosed hay fever?') a standardized face-to-face interview was conducted with the child's mother. If asthma or hay fever had been diagnosed, the child was classified as having 'clinical signs of atopy'.

Skin-prick test procedure

Four purified and immunochemically characterized aeroallergens (ALK, Denmark) were applied to the forearm (distance between allergens about 30 mm) in a standardized order with the aid of an uncoated Phazet® needle. Extracts from grass pollens (mixture of the six most common species), birch pollens, *Dermatophagoides pteronyssinus* and cat dander were used (concentration, 10 Histamine Equivalent in Prick testing). As control solutions histamine hydrochloride (10 mg/ml) and sodium chloride (9 g/l) were applied. The reactions were recorded after 15 min [7]. The largest and the orthogonal diameter of a weal were measured by means of a transparent ruler and the arithmetic mean calculated. Sensitization was defined as a weal diameter exceeding the negative control by ≥ 2 mm. The tests were carried out by the same two nurses during the whole study under the supervision of a physician.

Statistical analysis

The children's data provided information about the lifetime prevalence of asthma or hay fever and the cumulative prevalence of specific sensitization over an average period of 22 months resulting from three tests. The parental data included the lifetime prevalence based on diagnoses and the SPT results in the first survey. Only the results of children with natural parents were analysed. The sensitizations of the mothers, fathers and both parents were cross-tabulated with the child's SPT and atopic history. The reference group comprised families without any parental sensitization. Using logistic regression models, the relative risks of the mother's and father's

Table 1. Comparison of the sub-population with skin-prick test for both parents and the whole study population

Variable	Families with skin-prick tests for both parents ($n = 302$)	All families ($n = 421$)
Age, median (yr)		
mother	38	38
father	41	41
Asthma (%)		
mother	4.6	5.9
father	5.3	5.0
Hay fever (%)		
mother	14.9	13.8
father	11.6	11.4
Educational level (%)		
high school	34.8	33.0
technical college	21.2	20.0
manual training	37.4	38.5
unskilled	6.6	8.6

sensitizations were estimated under control of the child's gender [8,9]. The significance of the relative risks (estimated as odds-ratio(OR)) derived from the regression models were tested by applying χ^2 .

Results

The prevalence of atopic diseases in the population of 302 families was about 5% for paternal as well as maternal asthma and about 14% for maternal compared with 11% for paternal hay fever (Table 1). In the case of the offspring, an atopic history of asthma or hay fever was reported for 15.6% of the 302 children. A positive SPT to one of the four allergens was observed in 161 of the 604 parents (26.7%) whereas, in the case of the children, the cumulative prevalence was 39.4%. This prevalence was increased in children with atopic history (89.4%) compared with the subjects without such a history (30.2%).

Compared with the offspring of unsensitized parents, the children of mothers and fathers with a sensitization were more frequently reactive (Table 2). This applied to the four single allergens and to the reaction to at least one of the four allergens.

Multivariate analyses of antigen-specific associations of sensitization were carried out using logistic regressions (Table 3). A child's sensitization to grass and birch pollens and cat dander was significantly more frequent if the mother showed a reaction to the same (ORs, 2.5, 2.8 and 4.1, respectively) or to any other of the three

Table 2. Cumulative prevalence of the child's sensitization and clinical signs of atopy stratified for the parents' sensitization to the same four allergens. Relationships between the child's and the parents' status are differentiated for the specific sensitizations

	Cumulative prevalence for the children (<i>n</i> (%))			
	Predictor: parental sensitization to the respective allergen			
	Mother alone	Father alone	Both	None
<i>Grass pollen</i>				
Sensitization	13 (39.4)	14 (33.3)	4 (57.1)	32 (19.9)
Clinical signs	8 (24.2)	7 (16.7)	2 (28.6)	21 (13.0)
<i>Birch pollen</i>				
Sensitization	14 (35.9)	8 (22.2)	3 (33.3)	23 (14.3)
Clinical signs	8 (20.5)	7 (19.4)	1 (11.1)	21 (13.0)
<i>Cat dander</i>				
Sensitization	9 (37.5)	4 (26.7)	—	21 (13.0)
Clinical signs	7 (29.2)	2 (13.3)	—	21 (13.0)
<i>Dermatophagoides pteronyssinus</i>				
Sensitization	7 (33.3)	12 (33.3)	0	28 (17.4)
Clinical signs	3 (14.3)	8 (22.2)	0	21 (13.0)
<i>At least one of four</i>				
Sensitization	36 (65.5)	26 (39.4)	8 (40.0)	49 (30.4)
Clinical signs	13 (23.6)	11 (16.7)	2 (10.0)	21 (13.0)

complementary allergens (ORs, 2.7, 3.7 and—not significant—1.6, respectively). For none of the four allergens was a significant association between the child's and the father's sensitization to the same allergen or any complementary allergen observed.

The risk for a positive SPT was increased approxima-

tely threefold for children of mothers sensitized to at least one of the four allergens (OR, 2.88; Table 3). In contrast, an increased risk did not show up in the case of the father being sensitized (OR, 1.06). To analyse whether the higher maternal compared with the paternal risk with regard to specific sensitizations was caused by maternal

Table 3. Odds-ratios (*P*-values) of the parent's specific sensitization for the child's sensitization to the same allergen and of the complementary parent's sensitization to at least one of the four allergens. Risk estimation is based on logistic regression models (*n* = 302), each under mutual control of the independent variables and the child's gender

Dependent variable: cumulative prevalence of sensitization to	Independent variables			
	Specific sensitization, mother	Specific sensitization, father	Any other sensitization, mother	Any other sensitization, father
Grass pollens	2.50 (0.011)	1.70 (0.12)	2.69 (0.009)	0.80 (0.61)
Birch pollens	2.81 (0.004)	1.34 (0.46)	3.72 (0.003)	1.26 (0.60)
Cat dander	4.12 (0.003)	2.51 (0.14)	1.62 (0.24)	0.95 (0.89)
<i>Dermatophagoides pteronyssinus</i>	1.82 (0.22)	1.62 (0.22)	2.98 (0.001)	0.76 (0.50)
At least one of four	—	—	2.88 (0.0001)	1.06 (0.83)

Table 4. Number of parental sensitizations (one and more than one) to one of the four allergens and frequencies of the child's sensitization to any or the same allergen ($n=282$)

Sensitization of the child	Parental sensitization									
	Mother alone						Father alone			
	None $n=161$		One Sensitization $n=28$		> One Sensitization $n=27$		One Sensitization $n=36$		> One Sensitization $n=30$	
	n	%	n	%	n	%	n	%	n	%
Any allergen	49	30	19	68	17	63	9	25	17	57
Same allergen as parent	—		$n=13$	68%	$n=15$	88%	$n=7$	78%	$n=15$	88%

'poly-sensitization', the number of sensitizations (one/more than one) of both parents were cross-tabulated with the children's reactivity (Table 4). In the sub-groups with more than one paternal sensitization, similar percentages for the child's sensitization to any allergen could be seen for mothers and fathers. However, in the case of fathers with only one sensitization ($n=36$), 25% of the children were sensitized, whereas for 28 'mono-sensitized' mothers, 68% of the children were reactive. In the four sub-groups referring to parental sensitization the children showed positive reactions to the same allergen(s) as the parent in 68–88% of the cases (Table 4).

As far as clinical signs of atopy are concerned, the prevalence was higher in each of the sub-groups of sensitized parents (Table 2). In multiple logistic regression none of these associations had any statistical significance (not shown).

Discussion

The primary aim of the study was to evaluate the hypothetical health effects of air pollution on the airways of children of school age and it was not directed at the importance of parental sensitization for their children's reactivity in SPT. However, the sequence of testing and the test procedure itself allowed an analysis of this relationship. Since the proportion of participating families was only 7.8% ($n=463$) of the target population of about 5900 families, a random sample of the non-responding population was interviewed regarding atopic diseases and social status. The comparison did not indicate a statistical difference between the participating families and the non-responders [10]. The analysed sub-population of 302 families where both parents were tested is not significantly different from the whole sample ($n=421$) regarding relevant variables (Table 1).

In this study, we observed associations of specific

sensitizations to four common inhalant allergens in 302 children and their parents. The associations gained significance for maternal but not for paternal status.

To our knowledge, no earlier investigation has addressed the coincidence of specific sensitization to aero-allergens in parents and their children within a population study. However, several studies on the prediction of atopy in general have demonstrated an increased risk for subjects with a positive family history [11,12]. Inheritance of atopy is further suggested by studies of twins, which find that there is a higher incidence of atopy in monozygous compared with dizygous twins [13]. The immunogenetic basis for the inheritance of atopy has been attributed to a recessive Mendelian trait in addition to a polygenic component regarding high total IgE [14]. In contrast, dominant inheritance of atopy caused by a gene locus on chromosome 11q has recently been suggested [15]. Studies on specific sensitization have moreover demonstrated that immune responsiveness to different aero-allergens depends on the presence of associated MHC class II haplotypes [3,4].

In numerous studies atopic diseases have been defined using history, clinical presentation or total serum IgE [2,13,16,17]. Only a few authors have reported antigen-specific associations in first degree relatives using SPT or measurement of specific IgE antibodies [5,6]. In the case of tree pollens, a significantly lower variance of IgE antibodies has been found in monozygous compared with dizygous twins [6]. However, in that paper negative results were reported for the three other allergens analysed. Another twin study found a higher concordance of positive skin tests in monozygous (6 of 8 pairs) compared with dizygous twins (1 of 7 pairs) [5]. In four of the five sensitized monozygous pairs concordant results occurred for specific allergens. Both studies might indicate a genetic effect on specific sensitization; however, even

under these favourable conditions, the phenotype could be explained only in part.

In the present study, higher cumulative prevalences of sensitization showed up in the case of children of reactive mothers and fathers compared with those of non-sensitized parents (Table 2). However, in the logistic regressions, the associations were stronger for mothers than for fathers. None of the paternal sensitizations was a significant risk for a sensitization in the offspring (Table 3), whereas in the case of the mothers, antigen-specific associations were obvious for three (birch and grass pollens, cat dander) of the four allergens. Additionally, in three of the four antigen-specific models, a maternal sensitization to one of the complementary allergens was of importance. Regarding *D. pteronyssinus* only non-specific maternal sensitizations had any statistical significance ($P=0.001$).

Our data again raise the old question of whether a cumulation of specific sensitization within families is more a consequence of genetic similarities or of an effect of equal antigen exposure resulting from living under the same environmental conditions. The higher prevalence of sensitization in children of reactive parents compared with the offspring of non-reactive parents (Table 2) underlines the primary role of genetic predisposition, since all families live within the same macro-environment. However, the importance of environmental factors (i.e. allergen exposure) for the sensitizations was not the objective of this study. Recently published results of a study of twins suggest that the degree of mite allergen exposure might be a predictive factor for the individual development of sensitization [18]. Another twin study directed at sensitization as well as at clinical atopy identified a higher concordance of atopy in monozygous, whether reared apart or together, than in dizygous twins reared apart or together [19]. Thus, although perhaps of lesser importance, allergen exposure might be a risk factor for specific sensitization and thereby complement information derived from genetic-related variables. The concept of allergen avoidance in high risk groups reflects this assumption. The associations of the child's and the parents' reactivity to the same allergen are of significance only where the mother is concerned (Table 3). Regarding sensitization to at least one of the four allergens no paternal risk can be seen (OR, 1.06). The discrepancy between maternal and paternal risk represents the sum of three statistical sub-results: firstly, the lower proportion of sensitized children in the case of 227 SPT-negative mothers (33%) compared with 216 SPT-negative fathers (39.3%); secondly, the higher proportion of sensitized children in the case of 27 mothers sensitized to more than one allergen (63%) compared with the corresponding 30 fathers (57%) and thirdly, the lower prevalence of

sensitization in the children of 'mono-sensitized' fathers (25%) compared with mothers reactive to only one allergen (68%; Table 4). The low association in the case of fathers with only one sensitization could be a finding by chance or a result of false-positive SPTs in those fathers. However, the latter would also be expected for mothers. The frequency of sensitization to the same allergen in parents and children is similar in the four parental subgroups with sensitization (Table 4). Therefore, it seems likely that the lack of significance for paternal sensitizations is a result of a relatively lower risk of paternal sensitization in general rather than a lacking antigen-specific concordance.

An 11-yr follow-up study starting at birth has found that maternal and paternal atopy involve an equivalent risk for development of atopy in the offspring [11]. However, other authors reported higher prevalences of clinical atopy in children of atopic mothers than in those of atopic fathers [16,17,20]. Based on one of these findings, it has been hypothesized that women with atopic asthma have a higher threshold and therefore transmit more predisposing genes to their children [17]. In addition to the threshold theory, intra-uterine events occurring in atopic mothers could be a further explanation for our finding. In a sample of 190 newborns, maternal atopy was highly significantly related to increased cord blood IgE, whereas paternal history of atopy was of no significance [21]. The author assumed that 'various humoral maternal and external factors may pass the placenta and influence *in utero* the IgE producing system of the fetus'. A biological contact to the child's immune system by this means is lacking for fathers. In post-natal life, also, the contact between child and mother might usually be closer than between child and father.

Since in several studies finding a higher maternal than paternal risk the analysed medical histories were reported exclusively by the mother the effect has been attributed in part to a reporting bias. Such an effect cannot be responsible for our finding based on objective measurement of sensitization in both generations.

In our epidemiological study only the sensitizations of the mothers are significant relative risks for positive SPT results to inhalant allergens in the offspring. Thus, our data indicate that the maternal status is more predictive regarding the child's risk of sensitization than that of the father. Based on logistic regressions, antigen-specific associations occur for maternal sensitization to three single allergens, and in three explanatory models other maternal sensitizations are statistically important. Hence, our findings are compatible with the hypothesis that genetic factors contribute not only to atopy in general but also to the susceptibility to producing specific IgE antibodies against environmental allergens [22].

The implication of the coincidence of specific sensitization in mothers and their offspring is that risk assessment regarding sensitization to common inhalant allergens has to consider genetic predisposition differentiated for maternal and paternal factors. Moreover, the biological origin of the discrepancy between the maternal and the paternal risk needs further investigation.

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