
Skin test results in related and unrelated persons with allergic rhinitis

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Background: First degree relatives of patients with allergic rhinitis are at increased risk of having the disorder. It is not yet clear whether or not two such related persons with allergic rhinitis are more likely to be skin test positive to the same specific allergenic extracts than unrelated persons with allergic rhinitis.

Objective: To determine whether or not first degree relatives (parent and child or full siblings) with allergic rhinitis are more likely to be skin test positive to the same allergen extracts than unrelated persons with the disease.

Methods: A retrospective chart review of Allergy Clinic patients was performed. Skin test results for 12 common aeroallergen extracts were compared in 32 pairs of genetically related subjects and 32 pairs of age-matched and sex-matched unrelated subjects, all with allergic rhinitis. The percent of concordant results (both members of a pair skin test positive or both negative) and discordant results (one member of a pair positive and the other negative) were calculated and compared for related and unrelated groups. Also, the expected rates of positive concordance (both skin tests positive) based on the prevalence of skin test positivity in the two groups were calculated and compared with the corresponding observed rates.

Results: Results were concordant in 242 of 384 skin tests (63%) in related pairs versus 233 of 384 skin tests (61%) in unrelated pairs ($P = .28$, not significant). The expected and observed rates of positive concordance were not significantly different in the related ($P = .38$) or unrelated ($P = .49$) groups. When the groups were subdivided into parent-child pairs and sibling pairs, a similar lack of significant differences between the groups was found.

Conclusions: It is concluded that first degree relatives, both with allergic rhinitis, are no more likely to be skin test positive to the same allergen extracts than unrelated persons with this disease. Further, it seems appropriate to advise patients with allergic rhinitis that their first degree relatives who also have the disorder will not necessarily have the same specific allergies.

Ann Allergy Asthma Immunol 1996;77:43-46.

INTRODUCTION

Being genetically related to someone with allergic rhinitis increases the likelihood of developing this condition.¹ It

is not yet clear whether related persons with allergic rhinitis are likely to be allergic to the same allergens. IgE responsiveness to a few allergens has been linked to specific HLA types in population studies.^{2,3} Such associations would be logical in that HLA Class II molecules are required for immune responsiveness to any antigen. This association, however, has not held up for the same allergens in family studies,^{4,5} and no such association has been demonstrated for the vast majority of allergens. While we know that being genetically related to someone with allergic rhinitis increases the patient's chance of having this condition and, by definition, positive skin tests, we do not

know whether the two will have positive skin tests to the same allergenic extracts. The current study attempts to answer the question by comparing skin test results in related and unrelated individuals to a dozen common allergenic extracts.

MATERIALS AND METHODS

A retrospective chart review was performed. All charts of current Naval Medical Center San Diego Allergy Clinic patients were reviewed for two members of the same family (parent and child or two siblings) who had both been diagnosed with allergic rhinitis. The diagnosis was made by one of three board certified allergists based on the presence of chronic nasal symptoms (some or all of the following: nasal congestion, rhinorrhea, sneezing, nasal itching, itchy eyes, and watery eyes) and the presence of positive skin tests that correlated with the history in terms of season or exposure. Parents in parent-child pairs and parents of sibling pairs were contacted to inquire about genetic relationships and all but full first degree relatives were excluded (ie, half-siblings and adopted children were excluded). These subjects constituted the related group. The remaining clinic charts were then sampled randomly to find unrelated (control) subjects also with allergic rhinitis and the same age and sex as the related pairs.

All subjects had been prick skin tested using lancets to at least the following 12 inhalant allergenic extracts: Bermuda grass, rye grass, oak, olive tree, Russian thistle, sage, *Alternaria*, *Hormodendrum*, cat, dog, *Dermatophagoides farinae*, and *Dermatophagoides pteronyssinus* (1:20 wt:vol, except cat 10,000 BAU/mL and mites 5,000 AU/mL, Bayer Allergy Products, Spokane, WA). The results were

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The Chief, Bureau of Medicine and Surgery, Navy Department, Washington, DC, Clinical Investigation Program sponsored this study #S-94-039, as required by HSETCINST 6000.41A. The views expressed in this article are those of the author and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

Received for publication October 26, 1995.

Accepted for publication in revised form January 24, 1996.

recorded at 15 minutes. Results that were both greater than 3 mm of wheal and 10 mm of erythema were recorded as positive.

The percent of concordant results (+/+ or -/-) as well as discordant results (+/-) among pairs (related or unrelated control) were calculated for each allergenic extract as well as for all 12 extracts together. The hypothesis that frequencies of concordance are independent of genetic relation (ie, not higher in related persons) was tested by a one-tailed Fisher's exact test.

Also calculated were the overall percentages of subjects in each group (related and unrelated) who were skin test positive to each extract and to the 12 extracts grouped together. This percentage estimates the probability that any one member of a group would have a positive skin test. Squaring this number estimates the probability that two members of a group would both have positive skin tests based on chance alone. This expected probability was then compared with the observed percentage of pairs who were actually both skin test positive. Using the normal approximation to the binomial distribution, a z (standard normal) value was determined by dividing the difference in the observed and ex-

pected values by the standard deviation. If such a value falls outside the interval ± 1.96 , the observed value is taken as different from the expected value with less than 5% chance of being wrong.⁶

RESULTS

Thirty-two pairs of genetically related subjects (13 parent-child pairs and 19 sibling pairs) and 32 pairs of age-matched and sex-matched but unrelated subjects, all with allergic rhinitis, were studied. Ages ranged from 4 to 48 years. Mean age (in years) for: all subjects 14.4, parents 35.2, children in parent-child pairs 8.9, children in sibling pairs 9.1. In each group (related and unrelated) there were 38 males and 26 females (16 males and 10 females in the parent-child pairs, 22 males and 16 females in the sibling pairs). No attempt was made to assign race or ethnicity. No subject had been on immunotherapy. Results were concordant in 242 of 384 (63%) skin tests in related persons versus 233 of 384 (61%) skin tests in unrelated pairs ($P = .28$, NS) (Table 1). Results in related persons were 30% +/+ (48% of the concordant results) while in unrelated subjects the results were 21% +/+ (35% of the concordant results) ($P = .004$).

The mean number of positive skin tests for individuals in the related group was 5.8 versus 4.9 in the unrelated group ($P = .09$).

The expected rate of +/+ concordance based on the incidence of skin test positivity in the two groups is shown in Table 2. These expected rates were compared with the corresponding observed rates of +/+ concordance with z (standard normal) values. A significant difference was found between these expected and observed values only for a single allergen extract (oak; $z = 2.03$, $P = .046$) in the related group and none in the unrelated group. For all extracts combined, there was no significant difference between expected and observed rates of positive concordance for related ($z = .87$, $P = .38$) or unrelated ($z = .69$, $P = .49$) groups.

The groups were subdivided into parent-child pairs and sibling pairs, and these same comparisons were made between related and unrelated pairs and again no significant differences were found (data not shown).

DISCUSSION

While it is established that being genetically related to someone with aller-

Table 1. Percent of 32 Related Pairs and 32 Unrelated Pairs with Concordant or Discordant Skin Test Results*

	BER	RYE	OAK	OLI	RUS	SAG	ALT	HOR	CAT	DOG	DF	DP	Total
Related subjects													
Concordant skin test results													
both negative	0.28	0.13	0.56	0.50	0.31	0.47	0.31	0.38	0.22	0.63	0.09	0.09	0.33
both positive	0.28	0.44	0.22	0.09	0.31	0.13	0.38	0.34	0.28	0.00	0.47	0.66	0.30
both negative or both positive	0.56	0.56	0.78	0.59	0.63	0.59	0.69	0.72	0.50	0.63	0.56	0.75	0.63
Discordant skin test results													
one negative and one positive	0.44	0.44	0.22	0.41	0.38	0.41	0.31	0.28	0.50	0.38	0.44	0.25	0.37
Unrelated subjects													
Concordant skin test results													
both negative	0.38	0.25	0.59	0.56	0.34	0.63	0.41	0.47	0.31	0.69	0.06	0.03	0.39
both positive	0.13	0.22	0.03	0.06	0.16	0.13	0.13	0.16	0.25	0.06	0.59	0.66	0.21
both negative or both positive	0.50	0.47	0.63	0.63	0.50	0.75	0.53	0.63	0.56	0.75	0.66	0.69	0.61
Discordant skin test results													
one negative and one positive	0.50	0.53	0.38	0.38	0.50	0.25	0.47	0.38	0.44	0.25	0.34	0.31	0.39

* ber = Bermuda grass, rye = ryegrass, oak = oak tree, oli = olive tree, rus = Russian thistle, sag = sage, alt = Alternaria, hor = Hormodendrum, cat = cat dander, dog = dog dander, df = *Dermatophagoides farinae*, and dp = *Dermatophagoides pteronyssinus*.

Table 2. Comparison of Expected and Observed Positive Concordance Rates*

	BER	RYE	OAK	OLI	RUS	SAG	ALT	HOR	CAT	DOG	DF	DP	Total
Related subjects													
% of group positive (P)	0.50	0.66	0.33	0.30	0.50	0.33	0.53	0.48	0.53	0.19	0.69	0.78	0.48
% of pairs both positive (O)	0.28	0.44	0.22	0.09	0.31	0.13	0.38	0.34	0.28	0.00	0.47	0.66	0.30
P X P (E)	0.25	0.43	0.11	0.09	0.25	0.11	0.28	0.23	0.28	0.04	0.47	0.61	0.23
SQ RT [E X (1-E)/N] (SD)	0.08	0.09	0.05	0.05	0.08	0.05	0.08	0.07	0.08	0.03	0.09	0.09	0.07
(O-E)/SD (Z)	0.41	0.08	2.03	0.11	0.82	0.32	1.17	1.46	-0.01	-1.08	-0.04	0.53	0.87
Unrelated subjects													
% of group positive (P)	0.38	0.48	0.22	0.25	0.41	0.25	0.36	0.34	0.47	0.19	0.77	0.81	0.41
% of pairs both positive (O)	0.13	0.22	0.03	0.06	0.16	0.13	0.13	0.16	0.25	0.06	0.59	0.66	0.21
P X P (E)	0.14	0.23	0.05	0.06	0.17	0.06	0.13	0.12	0.22	0.04	0.59	0.66	0.17
SQ RT [E X (1-E)/N] (SD)	0.06	0.07	0.04	0.04	0.07	0.04	0.06	0.06	0.07	0.03	0.09	0.08	0.07
(O-E)/SD (Z)	-0.25	-0.21	-0.44	0.00	-0.13	1.46	-0.07	0.67	0.41	0.84	0.09	-0.05	0.69

* P = proportion, O = observed rate, E = expected rate, SD = standard deviation, N = 32 (pairs), Z = standard normal deviate. See Table 1 for allergen extract legend.

gic rhinitis increases the likelihood of developing this condition,¹ it is less clear whether two such relatives with allergic rhinitis will be allergic to the same allergens. Specific immune responsiveness would seem most likely related to specific HLA II types. Indeed, correlations have been established in population studies between specific IgE antibodies to Amb a V and HLA DR2 and Lol p I and II and HLA DR3.^{2,3} When such associations were sought in family studies, however, they could not be established.^{4,5} Most such family studies have focused on the allergens where population studies had suggested a link.

The present study was initiated in a clinical setting where parents often assumed that they would have the same specific allergies as their children or that their children would have the same specific allergies. An attempt was thus made to answer the question: Are two related persons, both with allergic rhinitis, more likely to be skin test positive to the same allergen extracts than two unrelated persons with allergic rhinitis? The answer appears to be no. When looking at overall concordance rates (both members of a pair were skin test positive or were both negative to a given extract), the rates are not significantly different; 63% in related pairs versus 61% in unrelated pairs. The positive concordance rate (both skin test positive) is higher in the re-

lated group (30% versus 21% in the unrelated group); however, this appears to be due to the slightly higher overall rate of positive skin tests in the related group. Expected positive concordance rates were calculated based on the rate of positive skin tests for a given group, and the observed positive concordance rates were not statistically significantly different than these expected values. It must be concluded that there is no statistical evidence of a genetic influence on which specific allergen extracts yield positive skin test results in these patients with allergic rhinitis.

Many factors contribute to developing allergic rhinitis to a specific substance; inheritance of genes predisposing to atopic disease (and perhaps specifically allergic rhinitis), environmental exposure to the substance in an appropriate concentration (dose) and over an appropriate time, immune responsiveness, age of the subject, etc. If some heritable immune responsiveness played the major role in developing specific allergies, first degree relatives with allergic rhinitis would be expected to be more likely to develop skin test positivity to the same allergen extracts than unrelated persons with allergic rhinitis; however, this is not the case. Presumably the multitude of other factors contributing to the ultimate expression of a specific allergy

overwhelmed any genetic factor for specific immune responsiveness. If we were able to control for some of the other factors, for example, by testing siblings at the same age, perhaps genetic immune responsiveness would be more apparent. Also, most allergenic extracts are relatively crude mixtures of various components of the source material. These extracts usually contain several major and minor allergens capable of eliciting IgE-mediated responses in susceptible persons. A genetic influence on reactivity to specific allergens might be more apparent if these allergens were studied individually via immunoblotting and other in vitro techniques.

In a clinical setting, where patients are told "what they are allergic to" based on history and skin test results with allergen extracts, it would seem appropriate to advise patients with allergic rhinitis that their first degree relatives with allergic rhinitis will not necessarily have the same skin test results.

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CLINICAL FEATURES OF VOCAL CORD DYSFUNCTION

Much of the data on vocal cord dysfunction (VCD), a condition that frequently mimics asthma, is based on reports of one or a few patients. A more comprehensive overall clinical picture of this condition should help in earlier diagnosis and more appropriate management. Therefore these authors conducted a retrospective survey of all patients (N = 95) hospitalized at their institution from 1984 through 1991 with laryngoscopically proven VCD.

Fifty-three patients (56%) had VCD as well as asthma (which was documented either by bronchodilator response or response to inhaled histamine or methacholine). The VCD only group was significantly younger (mean age 34.3 yrs.) than the group with VCD and asthma and a control group with asthma alone, and was predominately female. Asthma had been misdiagnosed for an average of 4.8 years in the VCD group and almost all were receiving prednisone (average dose 29.2 mg/d) along with other asthma medication. Medical utilization was very high in this group averaging 9.7 ER visits and 5.9 hospital admissions per year.

The best historical discriminating factors were a lack of bronchodilator response and no sputum production in the VCD group. Pulmonary function showed a lack of airflow limitation and in 23% of asymptomatic subjects a truncation of the inspiratory limb of the flow-volume loop.

The authors point out that visualization of vocal cord closure during inspiration is essential to the diagnosis and should be done when the patient is symptomatic either spontaneously or with provocation of symptoms with methacholine or exercise.

—JGE

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