Background: The role of genetics in the etiology of peanut allergy is unknown. For complex genetic traits, twin studies can provide information on the relative contribution of genetic factors to a disease, as the relative confounding effects of environmental factors are markedly decreased.

Objective: This study was performed to search for evidence that genetic factors influence peanut allergy by comparing the concordance rate for this allergy among monozygotic and dizygotic twins.

Methods: Twin pairs with at least one member with peanut allergy were ascertained through the Food Allergy Network by advertisements in the organization’s newsletters and Web site. Individuals with peanut allergy or parental surrogates were interviewed by telephone. A full atopic history was obtained, and peanut allergy and zygosity were determined using previously validated questionnaires. Heritability of peanut allergy was determined using univariate genetic model fitting by maximum likelihood using the Mx statistical modeling software package.

Results: Seventy-five twin pairs were recruited. Seventeen pairs were excluded because of unconvincing peanut allergy histories (9 pairs, including 4 of uncertain zygosity) or because one twin had reportedly never ingested peanut (8 pairs). The median age of the 58 remaining twin pairs was 5 years (range 1 to 58 years). Seventy individuals had peanut allergy. In addition to convincing histories of peanut allergy, 52 (74%) had been tested (skin prick testing with or without radioallergosorbent assay) and all had positive reactions to peanut. Twenty-nine of the 70 had experienced >1 reaction to peanut; 29 of 70 had multisystem reactions. Among the monozygotic pairs (n = 14), 9 were concordant for peanut allergy (pairwise concor-
dance, 64.3%) and among dizygotic pairs (n = 44), 3 were concordant for peanut allergy (pairwise concordance, 6.8%; $\chi^2 = 21.38, P < .0001$). Heritability of peanut allergy was estimated at 81.6% (95% confidence interval 41.6% to 99.7%) with model fitting using a population prevalence of peanut allergy of 0.4%.

Conclusions: The significantly higher concordance rate of peanut allergy among monozygotic twins suggests strongly that there is a significant genetic influence on peanut allergy. (J Allergy Clin Immunol 2000;106:536–6.)

Key words: Peanut, hypersensitivity, food allergy, genetics, twin studies

Peanut allergy affects 0.6% of the US population (0.4% of children) and represents a significant health concern because the allergy is long-lived, often severe, and potentially fatal. Despite the importance of this allergy, investigations concerning the genetic basis of this disorder have been limited to a single study suggesting a higher rate of peanut allergy among siblings compared with the general population in the United Kingdom (7% vs 0.5%) and a potential association with HLA class II genes. Although the high relative risk of peanut allergy among siblings suggests an important genetic component, this statistic is potentially subject to bias attributable to shared environmental risk factors.

Studies of concordance among monozygotic and dizygotic twins represent another step in determining the genetic influence on complex phenotypes such as peanut allergy. This approach obviates much of the aforementioned bias since twin pairs are generally exposed to a similar environment, allowing the estimation of genetic and environmental causes of familial resemblance. The procedure is predicated on the fact that monozygotic twins share all their genes in common, whereas dizygotic twins share on average only half of their genes. Under the assumptions of equal environment for both twin types, random mating, and no genotype-environment correlation or interaction, a greater similarity between monozygotic versus dizygotic twins is attributed to accumulated effects of several genes (additive genetic effects). Under a simple linear model, environmental influences shared by the twins (also called shared or common environment [eg, parenting style and eating habits]) will contribute to twin similarity in both monozygotic and dizygotic twins. Unique environmental influences (also called specific environment [eg, separate peer groups]) do not affect familial resemblance, but may be a significant part of the total variance of a trait. Thus the nature and extent of...
TABLE I. Concordance rates for peanut allergy

<table>
<thead>
<tr>
<th></th>
<th>Monozygotic</th>
<th>Dizygotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordant</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Discordant</td>
<td>5</td>
<td>41</td>
</tr>
<tr>
<td>Pairwise concordance rate *</td>
<td>64.3%</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

*χ² = 21.38; P < .0001.

Methods

Subjects

Volunteers were recruited through advertisements in newsletters and on the Internet Web site of the Food Allergy Network, a lay organization providing education and community service for families with children who have food allergies. The advertisement called for twins in whom one or both siblings had peanut allergy. Subjects or parental surrogates (for individuals younger than 18 years) were interviewed by telephone. The interview included demographic information and questions regarding family history of peanut allergy, personal atopic history, characteristics of peanut allergy, and zygosity. Twin pairs were excluded from analysis if zygosity was uncertain, if the diagnosis of peanut allergy did not fulfill the criteria below, or if a twin was never knowingly exposed to peanut. The study was approved by the institutional review board of the Mount Sinai School of Medicine.

Definition of peanut allergy

Peanut allergy as previously defined is present when an individual has a reaction within 60 minutes of an isolated ingestion of peanut or peanut-containing products. Reactions were convincing if peanut ingestion resulted in one or more symptoms in at least one of the following organ systems (skin—hives, edema; respiratory—wheezing, throat tightness, repetitive coughing, shortness of breath; or gastrointestinal tract—vomiting, diarrhea). These criteria had a high rate of validity (95%) with positive test results for peanut-specific IgE antibodies and determination of acute reactions to peanut by questionnaire (90%). Positive peanut allergy histories were not confirmed by oral food challenges because convincing histories would have made challenges unethical for most participants and for practical reasons because most patients were not readily available because of distance. Additional information regarding the peanut allergy was obtained by questioning subjects about confirmatory tests for peanut-specific IgE antibody and about all episodes in which peanut was ingested (including accidental ingestions). A twin was considered not to have peanut allergy if he or she had ingested peanut without reactions.

Definition of zygosity

Parental surrogates or adult twins were asked whether the twin pair was identical or fraternal as determined by them, their physician(s), or both. They were also asked a series of specific questions about similarities in physical features as previously published to ascertain zygosity. If responses were discrepant, no conclusion about zygosity was made. The determination of zygosity through questionnaire is highly reliable (95%).

Data analysis and statistics

Difference in concordance between monozygotic and dizygotic twins was tested using pairwise concordance rates. Concordant pediatric-aged twins were ascertained simultaneously by parental report, and were therefore treated as doubly ascertained, concordant twins pairs. Contingency table analysis using the χ² distribution was performed for pairwise rates. The significance threshold was set at P < .05. To estimate heritability, univariate genetic models were fitted to contingency tables using maximum likelihood estimation with Mx statistical modeling. First, a model was fitted allowing for additive genetic (A) as well as common (C) and specific (E) environmental factors to account for the observed variance (the ACE model). The significance of the additive genetic and shared environmental variance was tested in the CE and AE models, respectively. Alternative models were compared by likelihood ratio tests (high, significant values indicate a poor fit in comparison with the ACE model). Confidence intervals (CIs) were calculated for the standardized parameter estimates for the full ACE model and its submodels. An ascertainment correction was used to account for the absence of concordant unaffected pairs. Population prevalence data were included to obtain unbiased CIs.

Results

Seventy-five twin pairs were recruited. Of these, 58 pairs (14 monozygotic and 44 dizygotic) provided adequate histories and zygosity information for analysis. Seventeen pairs were excluded because of unconvincing peanut allergy histories (9 pairs including 4 of uncertain zygosity) or because one twin had never ingested peanut (8 pairs). The median age of the 58 remaining twin pairs was 5 years (mean 7.9 years; range 1 to 58 years). There were 4 adult pairs (> age 17), all of whom were discordant for peanut allergy (2 dizygotic, 2 monozygotic pairs). All of the twin children were ascertained simultaneously through their parent.

Seventy individuals had peanut allergy. In addition to convincing histories of peanut allergy, 52 had been tested (skin prick testing with or without radioallergosorbent assay) and all had positive reactions to peanut. Twenty-nine of the 70 had experienced ≥ 1 reaction to peanut; 29 of 70 had multisystem reactions. Thirty-five of the pairs had other siblings (48 total) and none reported peanut allergy. Four parents of twin pairs reported peanut allergy (3 mothers, 2 with concordant monozygotic females and 1 with discordant male/female twins; and a father with discordant male/female twins).

The distribution of twin pairs by zygosity and concordance, and the pairwise concordance rates are shown in Table 1. Among discordant twins, there were 5 male monozygotic pairs, 4 female monozygotic pairs, and 3 male/female dizygotic pairs. Among discordant pairs, there were 3 male and 2 female monozygotic pairs, 15 male and 5 female dizygotic pairs, and 21 male/female pairs. The pairwise concordance rates were significantly different (χ² = 21.38; P < .0001).
TABLE II. Standardized parameter estimates and confidence intervals for fitting genetic models to data on peanut allergy, using the population prevalence for children or for the total population

<table>
<thead>
<tr>
<th>Model</th>
<th>a²</th>
<th>CI a²</th>
<th>c²</th>
<th>CI c²</th>
<th>e²</th>
<th>CI e²</th>
<th>LR χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>0.816</td>
<td>0.416-0.997</td>
<td>0.167</td>
<td>0.000-0.561</td>
<td>0.017</td>
<td>0.002-0.077</td>
<td>18.99</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AE</td>
<td>0.983</td>
<td>0.926-0.998</td>
<td>—</td>
<td>—</td>
<td>0.019</td>
<td>0.002-0.074</td>
<td>0.428</td>
<td>.513</td>
</tr>
<tr>
<td>CE</td>
<td>—</td>
<td>—</td>
<td>0.816</td>
<td>0.688-0.897</td>
<td>0.187</td>
<td>0.103-0.312</td>
<td>18.985</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total population prevalence: 0.06</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE</td>
<td>0.872</td>
<td>0.450-0.997</td>
<td>0.109</td>
<td>0.000-0.524</td>
<td>0.019</td>
<td>0.002-0.084</td>
<td>0.175</td>
<td>.676</td>
</tr>
<tr>
<td>AE</td>
<td>0.982</td>
<td>0.920-0.998</td>
<td>—</td>
<td>—</td>
<td>0.018</td>
<td>0.002-0.080</td>
<td>0.002</td>
<td>0.985</td>
</tr>
<tr>
<td>CE</td>
<td>—</td>
<td>—</td>
<td>0.798</td>
<td>0.667-0.887</td>
<td>0.202</td>
<td>0.113-0.333</td>
<td>18.985</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

a²: Additive genetic variance component; c²: shared environmental variance component; e²: specific environmental variance component; LR χ², likelihood ratio χ²; A, additive genetic factors; C, shared environmental factors; E, specific environmental factors.

Likelihood ratio tests and standardized parameter estimates of the genetic models are presented in Table II. The variation in peanut allergy was explained for the most part by genetic factors with heritabilities of 82% and 87% in the ACE model using the population prevalence for children or the total population prevalence, respectively. A reduced AE model that fit the data equally well gave a heritability of 98%. If shared environment was included in the model, it explained 17% and 11% of the variation, respectively. Both the likelihood ratio tests and the CIs indicate that additive genetic factors are highly significant. Shared environmental factors, although not statistically significant, could account for up to 56% of the variation; however, the CIs also overlap 0%. The role of unique environmental factors (including measurement error) was very small, as suggested by the high concordance of monozygotic twin pairs.

DISCUSSION

In complex genetic traits, the phenotype is influenced by a variety of environmental and genetic factors. By comparing concordance rates between genetically identical (monozygotic) and nonidentical (dizygotic) individuals, twin studies have provided an approximation of the genetic component of a number of disorders, including atopic diseases. Previous twin studies have estimated a high degree of heritability in atopic diseases including asthma (87%), atopic dermatitis (74%), and allergic rhinitis (74% to 82%).

Before this study, the heritabilities of specific food allergies had not been determined. Peanut allergy was selected for this study because the phenotype is reasonably stable and the phenotype can be diagnosed with high accuracy based on the medical history. Because a significantly higher concordance rate for peanut allergy among monozygotic compared with dizygotic twins was found, the genetic component of this complex phenotype appears to be strong and comparable to other atopic diseases.

Heritability estimates indicate the contribution of heredity, versus environment, to the variance of a trait. When heritability approaches zero, environmental factors account for the variance of the trait, whereas as it approaches 1, the variation in the trait is related solely to heredity. The estimate of heritability for peanut allergy in this study was high, 82% to 87%, using the full model that considers genetic (A) and environmental (C, E) components. As shown in Table II, both models that allow for a genetic component to account for variance in peanut allergy (ACE and AE models) reveal high heritability (up to 98%). When genetic factors are not part of the model (CE), the model fits significantly worse than the full ACE model (likelihood ratio 18.99, P < .001), making such a model untenable and reflecting the importance of the genetic component to peanut allergy.

There are 2 inherent limitations in this study. The first limitation is that a population-based sample was not obtained. Because of the relatively low population prevalence rate of peanut allergy (0.006) and twinning (0.012), more than 1 million respondents would be needed to obtain the number of twin pairs used in this study. This made a population-based study impractical. Ascertainment through affected individuals, as was done in this study, prevents the extrapolation of certain results (incidence/prevalence) to the general population. This sampling method does provide, however, a close approximation of the genetic influence on disease. Although bias of ascertainment might result in the inclusion of a disproportionately large number of concordantly affected pairs, that bias could be expected to act similarly on monozygotic and dizygotic pairs.

The second limitation concerns the diagnosis of peanut allergy and determination of zygosity through questionnaires. Oral challenge with peanuts, the more definitive diagnostic approach to peanut allergy, was not ethically feasible. Previous studies have shown that the methods used to diagnose peanut allergy and determine zygosity have high rates of validity (90% to 95% and 95%, respectively). Reanalysis of the data with assumptions biasing the diagnostic accuracy against the correct diagnosis of peanut allergy and zygosity by removing 10% of the individuals with peanut allergy and reassigning 5% of monozygotic to dizygotic pairs still indicated a strong genetic influence on this phenotype (P = .0002).

In summary, we have shown a strong genetic influence on the complex trait of peanut allergy. Previous studies have shown a role for HLA class II genes in the determi-
nation of this phenotype, but further studies are needed to dissect the role of multiple genes likely to influence this and other food allergy diseases.

We thank Elving Anderson, PhD, Walter E. Nance, MD, PhD, and Neil Risch, PhD, for their helpful advice.

REFERENCES


