

Short communication

Hay fever – a Finnish nationwide study of adolescent twins and their parents

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Background Like other atopic diseases, hay fever is known to cluster in families. This clustering is due either to effects of a shared family environment or to genetic inheritance. By comparing the occurrence of hay fever among monozygous (MZ) and dizygous (DZ) twin pairs, we were able to estimate the contribution of genetic and environmental factors in the development of hay fever.

Methods A questionnaire mailed to a nationwide sample of 2483 families with 16-year-old twins furnished data for the cumulative incidence of physician-diagnosed hay fever among these adolescents and their parents. **Results** Among the 1765 twin pairs with data available for analysis, hay fever was reported for 14.1% of boys (95% CI=12.4–15.8%) and 10.0% of girls (95% CI=8.6–11.4%). The MZ twin pairs (probandwise concordance rate=60.3%, 95% CI=52–68%) were significantly more concordant for hay fever than were DZ twin pairs (31.5%, 95% CI=26–36%). Genetic factors accounted for 74–82% of the interindividual variability in liability to hay fever, variation in shared family environment for 7% at most, and unique (individual) environment for 18%.

Conclusions Familial occurrence of hay fever is mainly due to genes predisposing to the trait. Environmental exposures shared in common by family members but varying between families appear to account for at most a modest proportion of the variability in risk of developing hay fever.

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Atopic susceptibility is characterized by exaggerated IgE-mediated immune responsiveness to various exogenous substances. It can be manifested in positive skin-test reactions or in elevated total or specific serum IgE, and is an important predisposing factor for asthma, atopic eczema, and allergic rhinitis.

Allergic rhinitis is among the most common of the allergic disorders, and is characteristically a disease of the young, reaching its peak incidence in adolescence (1–3). Boys are more often affected than girls until adolescence, but thereafter the sex difference gradually disappears. Hay fever is regarded as a clinical subtype of allergic rhinitis: seasonal rhinitis triggered by outdoor pollen and often accompanied by conjunctivitis; its prevalence starts to decline in young adulthood (1). In Finland, with four distinct seasons, the pollen season lasts from March to August. The most important sensi-

tizing pollens (alder, birch, timothy, and cocksfoot) are prevalent throughout the entire country.

About half of all subjects with allergic diseases have a positive family history (4). For hay fever, a positive family history increases the risk in offspring up to threefold, compared to the risk in children of unaffected parents (4–7). This clustering is due either to genes predisposing to hay fever or to environmental factors shared by the family members, or both. To distinguish between biologic and cultural inheritance, twin or adoption studies are needed (8). In the traditional twin study design, higher concordance among monozygous (MZ) twin pairs than dizygous (DZ) twin pairs suggests genetic influence in the development of a trait. Statistical genetic modeling of twin data, in addition to estimating heritability, can distinguish between variation in shared and individual environment.

Previous twin studies have found evidence of genetic effect in serum IgE levels (9–12), skin test reactivity (12), and bronchial hyperreactivity (12), as well as in the development of asthma (2, 13–18) and atopic eczema (2, 18). Heritability estimates for hay fever have varied between 33% and 70% (2, 15, 18), possibly due to differences in the composition of the samples by age and sex, differences in exposure to environmental triggers, and differences in the gene pool of the populations. To study the development of hay fever among Finnish adolescents, we assessed familial risk of hay fever and estimates of different components of variation in the liability to hay fever among 16-year-old twins.

Material and methods

Data collection, zygosity determination, and statistical methods have been described in detail earlier and will be only briefly given here (17).

Data collection

The Finnish Twin Cohort Study is a project for the study of genetic and environmental determinants of chronic diseases and risk factors (19). The number of twins identified from Finland's Central Population Registry from 1974 onward is practically identical with the number of twins born in Finland (19).

Data were collected by questionnaires mailed to twins born in 1975 through 1978 and to their parents within 2 months of the 16th birthday of the twins. Parents were sent a family questionnaire about the childhood of the twins, and each parent also a personal questionnaire on his or her own health including a question on hay fever. A total of 2483 families were contacted, and 2023 (81%) questionnaires on twins' childhood returned. Individual response rates were 93% for girls, 87% for boys, 86% for mothers, and 82% for fathers. Twin zygosity was determined by a validated questionnaire method (20). Uncertainty about zygosity remained for 118 twins, who were therefore excluded from the analyses. Hay fever in the twins was defined on the basis of the parental response on the family questionnaire as to whether the first-born twin, the second-born twin, neither, or both of the twins had been diagnosed with hay fever. This question was left unanswered in 140 questionnaires, and these twins were omitted from the analyses. The final twin sample size was 1765 pairs. The mother and the father were asked whether they had ever been diagnosed by a doctor as having hay fever. Hay fever status data were available for both parents in 1695 families.

Statistical analysis

Standard univariate twin analyses were used to describe patterns of familial aggregation of hay fever. As descriptive statistics, probandwise concordance rates were computed, and tests of homogeneity of prevalence rates across twin types performed. Twin similarity was assessed by the probandwise concordance rate (21), and tetrachoric correlations were computed from pairwise contingency tables. Additionally, the parents' similarity for hay fever was analyzed. The risk of hay fever in the offspring was assessed after stratification of the twin data on parental hay fever status. The effect of parental hay fever status on the occurrence of hay fever in their offspring was examined for each parent separately and independently of the other parent.

Model fitting was carried out to estimate the components of variance in the liability to hay fever. From data on twins reared together, it is possible to model four separate parameters: an additive genetic (A) component and effects due to dominance (D), common (C), and unique (E) environmental components. Common environmental effects are those shared by both twins or all family members, whereas unique environmental effects are not correlated between family members and represent exposures unique to each individual. One can fit models based on the different combinations of these parameters: AE, ACE, ADE, and CE, but effects due to dominance and common environmental effects cannot be simultaneously modeled (21, 22). Chi-square (χ^2) goodness-of-fit statistics were used to assess how well a model fit the data. Analyses including confidence intervals for the variance component estimates were carried out with Mx (version 1.40), a statistical program for genetically informative data sets (22).

Results

At the age of 16, the cumulative incidence of hay fever was 14.1% in boys (95% CI=12.4–15.8%) and 10.0% in girls (95% CI=8.6–11.4%) with the same sex difference found in all zygosity groups. No differences appeared in the cumulative incidence between different zygosity groups (Table 1). The MZ twin pairs (probandwise concordance rate=60.3%, 95% CI=52–69%) were significantly more concordant for hay fever than were DZ twin pairs (31.5%, 95% CI=26–37%), whereas no difference appeared in concordance rates between opposite-sex (29.7%, 95% CI=23–37%) and like-sex (33.6%, 95% CI=26–42%) DZ twin pairs. Thus, the risk of an MZ twin's having hay fever was fivefold and that of a DZ twin threefold if the

Table 1. Descriptive statistics for twins

Zygosity	No. of pairs	No. of twins with hay fever	Cumulative incidence (%)	No. of concordant pairs	No. of discordant pairs	Probandwise concordance rate (%)	r^a	CI 95% ^{a)}
Monozygous female	335	71	10.6	19	33	53.5	0.77	0.63–0.90
Monozygous male	222	65	14.6	22	21	67.7	0.87	0.77–0.97
All monozygous	557	136	12.2	41	54	60.3	0.82	0.73–0.90
Like-sex dizygous female	273	50	9.2	8	34	32.0	0.53	0.28–0.78
Like-sex dizygous male	293	81	13.8	14	53	34.6	0.48	0.26–0.69
All like-sex dizygous	566	131	11.6	22	87	33.6	0.49	0.32–0.65
Opposite-sex dizygous female		65	10.1					
Opposite-sex dizygous male		90	14.0					
All opposite-sex	642	155	12.1	23	109	29.7	0.41	0.24–0.57
All dizygous	1208	286	11.8	45	196	31.5	0.45	0.33–0.56
TOTAL	1765	422	12.0	86	250			

^{a)} r (correlation coefficient) with 95% CI (95% confidence interval).

Table 2. Effect of parental hay fever on hay fever of twin offspring

	Hay fever status of offspring					
	Sons			Daughters		
	With hay fever (n)	Without hay fever (n)	Cumulative incidence (%)	With hay fever (n)	Without hay fever (n)	Cumulative incidence (%)
Mothers (n)						
With hay fever	67	295	18.5	51	281	15.4
Without hay fever	131	1469	8.2	103	1689	5.7
Rate ratio (95% CI)	2.26 (1.72–2.97)	1.0		2.67 (1.95–3.66)	1.0	
Test for homogeneity of rate ratios over sex:	$\chi^2=0.62, P=0.43, d.f.=1$					
Combined rate ratio estimate (95% CI) ^{a)} :	2.43 (1.97–2.98)					
Fathers (n)						
With hay fever	51	219	18.9	36	280	11.4
Without hay fever	147	1545	8.7	118	1690	6.5
Rate ratio (95% CI)	2.17 (1.62–2.91)	1.0		1.75 (1.23–2.49)	1.0	
Test for homogeneity of rate ratios over sex:	$\chi^2=0.89, P=0.35, d.f.=1$					
Combined rate ratio estimate (95% CI) ^{a)} :	1.98 (1.58–2.47)					

^{a)} Differences in rate ratios in sons and daughters were not significant; therefore, rate ratios over combined data were calculated.

cotwin had hay fever compared to the study population considered as individuals (Table 1). Mothers reported hay fever (18.0%, 95% CI=16.2–19.8%) more often than did fathers (14.7%, 95% CI=13.1–16.4%). In 4.3% of the families ($n=73$), both parents had hay fever. The tetrachoric correlation for hay fever between the spouses was 0.24 (95% CI=0.15–0.35), indicating that parents were

somewhat more similar for hay fever than would be expected on the basis of random association alone. The risk of hay fever was calculated separately for sons and daughters of affected parents. As no difference was found in risk by sex, the data for boys and girls were pooled (Table 2). If the mother had hay fever, the risk of her twin offspring's having hay fever was 2.4-fold (95%

Table 3. Comparison of alternative genetic models fit to Finnish twin data on hay fever

Model	Components of variance estimates and 95% confidence intervals ^{a)}			Goodness-of-fit tests			
	Additive genetic effects (A)	Common (shared) environment (C)	Unique environmental effects (E)	χ^2	d.f.	P value	AIC ^{b)}
ACE ^{c)}	0.74 (0.45–0.89)	0.07 (0.00–0.31)	0.18 (0.12–0.28)	0.80	3	0.85	–5.20
AE	0.82 (0.74–0.89)	–	0.18 (0.11–0.26)	1.13	4	0.89	–6.87
CE	–	0.59	0.41	23.1	4	<0.01	15.10
E	–	–	1.0	160.2	5	<0.01	150.2

^{a)} Confidence intervals computed only for models with adequate fit. ^{b)} Akaike's information criterion (AIC) is global measure of goodness-of-fit. ^{c)} Variance component estimates in ACE model add up to 0.99 instead of 1.0 due to rounding.

CI=2.0–3.0) that of a twin with an unaffected mother. The risk imposed by a father with hay fever was 2.0-fold (95% CI=1.6–2.5) that of a twin with an unaffected father (Table 2).

Model fitting of the twin pair data gave two equally well-fitting models (Table 3). In both of the models, the proportion of total variance due to genetic effects was high (in ACE, 74%; in AE, 82%), whereas, in both models, the unique environmental effects accounted for 18% of the liability to hay fever. Thus, the effect of shared environment on hay fever in the less parsimonious ACE model was quite small (7%). The CE model excluding genetic effects fit the data significantly less well, and the model comprising only unique environmental effects (E) could be rejected on the basis of chi-square statistics.

Discussion

Analysis of our data on Finnish adolescent twins and their parents showed familial aggregation of hay fever, which was mainly accounted for by the variation in genetic liability instead of shared family environment.

In respect to hay fever, the twins represent Finnish 16-year-olds well. The twins of the nationwide cohort were all studied at the same age, and the response rate was high. The occurrence of hay fever among the twins was well in keeping with that among adolescent singletons in Finland (23). In addition, no difference in hay fever occurrence was found between our first-born twins and second-born twins (24), and there are no known causes of twinning affecting occurrence of hay fever.

Clinical diagnosis of allergic rhinitis is made mostly on patient history and evidence of allergic sensitization by skin tests or serum specific IgE determination. As seasonal rhinitis is less often

misdiagnosed than other forms of allergic rhinitis (25), and as it is the most prevalent form of noninfectious rhinitis among children and adolescents (26), mislabeling of hay fever is probably not as common among adolescents as among adults. Since the question on doctor-diagnosed hay fever has high specificity (94%) but relatively low sensitivity (33%) (27), cases with mild symptoms may have been undetected in our study. In model-fitting, such a random classification error, occurring similarly in MZ and DZ twins, would increase the estimate of the unique environmental variance component. Another limitation of our study is the absence of measured parameters of allergy, such as serum IgE and skin prick test reactivity, that would have allowed us to confirm the diagnosis of hay fever to some extent.

The estimate for genetic effects was higher among the adolescents of the present study (74–82%) than in the previous studies, most of which have included only adult twins. The lowest estimates for heritability were found among Swedish twins born around the turn of the century (2). In a recent Swedish study among 7–9-year-old children, heritability for hay fever was 33% in boys and 70% in girls (18). Among adults in Australia, the heritability estimate for hay fever was 60% (15). Among twins reared apart, concordance rates for hay fever were similar to those of twins reared together, indicating the importance of genetic factors (11).

There are several possible explanations of the greater impact of genes in the development of hay fever among adolescents than among adults. Firstly, those at genetically higher risk may express the disease at a younger age. Secondly, after they reach adulthood, individual environmental exposures between individual twins differ more and thus may affect the development of the disease to a greater

extent. Because most of the twins in this study lived together with their cotwin until the time of the study, exposures to risk factors for hay fever within a twin pair were uniform. Thirdly, compared to previous generations, expression of genes contributing to the development of hay fever may have been modified by environmental changes. This is supported by the increased occurrence of hay fever during the past decades, especially among children and young adults (23). Systematic underdiagnosis of parental hay fever may lead to overestimation of genetic effects among adolescents with no family history of hay fever. However, major underdiagnosis is unlikely, as hay fever occurrence in these parents is in agreement with data in other reports from Finland (28). Moreover, the number of adolescents with no family history of hay fever (50%) resembles such figures in previous family studies (4, 6). However, in comparison of the different twin studies, the effect of population genetic, geographic, or cohort variation cannot be excluded.

Variation in shared family environment accounted for less than 10% of total variability. Apart from the Swedish study on young twins (18), our results are consistent with previous studies in indicating that shared environmental factors appear to be of little importance (2, 11, 15). As young twins reared together share exposure to pollen, one would expect to see a larger component of shared environment in hay fever. However, as practically all Finnish families share exposure to common outdoor allergens, it cannot be a source of variation between the families. Other relevant environmental triggers may also be so ubiquitous that genetic variation must be the principal explanation of interindividual variance in disease occurrence. Compared to pollen exposure, there is more variation between families in such known risk factors for hay fever as social status of the parents, family size, and housing (1). According to the present analysis, these would account for a minor part of variation in liability to hay fever. In another analysis of the twins of our study, having a large number of older siblings was found to protect against hay fever, but such families were quite rare (7%) (24). Whatever the environmental factors responsible for the increase in hay fever, they do not appear to diminish the effect of genetic liability in disease variability.

We conclude that, among Finnish adolescents, familial accumulation of hay fever is mainly due to liability genes predisposing to the trait. Environmental factors may well be important in the development of hay fever, but, according to our results, these do not explain well the variation in hay fever occurrence between families and individuals. Our results also suggest that the expression of the

liability genes may have changed from that in the previous generations. Other differences between populations cannot, however, be ruled out. Comparison with similar studies among other age groups and other populations with different environmental exposures and prevalences of allergic diseases should throw light on the complex interplay of genes and environmental factors in the development of allergic disorders. It could also prove helpful in detecting factors responsible for the current increase in allergic diseases.

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