

Findings on the atopic triad from a Danish twin registry

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SUMMARY

OBJECTIVE: To estimate to what extent the same genetic and environmental risk factors influence asthma, hay fever and eczema.

DESIGN: From the nationwide Danish Twin Registry, twin cohorts born between 1953 and 1982 were contacted for a questionnaire survey, and a total of 29 183 twin individuals (86%) responded. Subjects were classified as cases when responding affirmatively to three questions about the lifetime occurrence of asthma, hay fever and eczema. Variance components twin analysis was conducted using maximum likelihood methods.

RESULTS: The phenotypic (within-subject) correlations in liability between the different diseases were 0.57 (95%CI 0.54–0.59) for asthma and hay fever, 0.40 (95%CI 0.36–

0.42) for asthma and eczema, and 0.33 (95%CI 0.29–0.36) for hay fever and eczema. Decomposition of these correlations into their genetic and environmental contributions showed that shared genes explained between 70% and 85% of the correlation between the different diseases. The remaining parts were explained by environmental factors shared between the diseases.

CONCLUSION: To a large extent, atopic diseases share a common genetic background, although disease-specific genes also play a considerable role. These results can prove informative when counselling families with atopy, and may furthermore be used to guide the search for pleiotropic genes of importance for these diseases.

KEY WORDS: asthma; hay fever; eczema; twin study

ASTHMA, hay fever and atopic dermatitis (eczema) often occur simultaneously. In particular, a history of eczema is a well-established risk factor for both hay fever and asthma.¹ Varying with the severity of disease, up to 50% of subjects who suffer from eczema in childhood go on to develop asthma and/or hay fever later in life.² Furthermore, hay fever is often associated with asthma.³ Long-term follow-up of individuals with hay fever has shown that their risk of asthma is increased by up to ten times.⁴

Co-morbidity between these diseases can potentially be caused by common aetiological relationships, i.e., a common genetic or environmental background. For example, it is likely that eczema and hay fever are precursors for asthma because they share a common aetiology.⁵ However, previous studies—most prominently the European Community Respiratory Health Survey (ECRHS) and the International Study of Asthma and Allergies in Childhood (ISAAC)—have shown that these relationships vary considerably between different geographical regions.^{6,7} This diversity must be kept in mind when comparing results because a

substantial variation in genetic and environmental risk factors between different populations may influence their generalisability.

The classical twin study is a powerful way to examine the aetiological relationships underlying common diseases.⁸ The rationale behind the classical twin study is that identical twins share not only all their genes, but also their upbringing and early environment. On the other hand, besides their upbringing and early environment, fraternal twins share only 50% of their genes. Hence, if identical twins resemble each other more than fraternal twins in terms of disease, genetic factors are assumed to contribute to the development of that disease.⁸ The classical twin study can be extended to include two or more diseases simultaneously. The information obtained from such a study can be used to estimate to what extent the same genetic (pleiotropy) and environmental factors influence these diseases.⁸ We studied a large population-based sample of Danish young adult twins and used the classical twin study to estimate to what extent the same genetic and environmental factors influence asthma, hay fever and eczema.

METHODS

Sample

The study population was recruited from the nationwide Danish Twin Registry and comprised twin cohorts born between 1953 and 1982.⁹ In these cohorts, zygosity was established in 1991 using four questions of similarity and mistaken identity, which have a frequency of misclassification of less than 4%.¹⁰ In 1994, a total of 34 076 twin individuals were sent a questionnaire with items aimed at identifying multiple phenotypes including asthma, hay fever and eczema. Affected subjects were identified on the basis of affirmative responses to the questions 'Do you have, or have you ever had, asthma?' 'Do you have, or have you ever had, hay fever?' and 'Do you have, or have you ever had, eczema in the folds of your elbows or knees?'.¹¹ The participation rate was 86%, comprising 29 183 subjects (12 356 twin pairs and 4471 single responders). Among these, a total of 11 231 twin pairs had complete data on zygosity and atopic status: 3563 identical twin pairs, 4159 fraternal twin pairs of the same sex, and 3509 fraternal twin pairs of opposite sex.

Statistical analysis

Odds ratios (ORs) were calculated to obtain measures of the increased risk of a particular atopic disease in a subject given the presence of either the same or another disease within the subject, or in the subject's twin. These estimates can be used to crudely assess, for example, what a subject's own risk of asthma would be if the subject's twin brother or sister had hay fever, relative to when the brother/sister is unaffected. According to biometrical genetic theory, a higher cross-disease risk in identical twins compared with fraternal twins signals, but is not proof of, a genetic relationship between the diseases.⁸

Correlations in liability between twin pairs for the different diseases were calculated under the assumption of the multifactorial threshold model. This model assumes that: 1) many factors (genetic and environmental) contribute to the development of the disease; 2) each member of a twin pair is assumed to have individual liability, the pair of liabilities for a twin pair being assumed to be normally distributed; and 3) as the number of causal factors for the disorder increases in an individual, the liability for the disease increases. When a threshold is reached, the burden of liability becomes so great that disease results.⁸ The threshold then represents the population prevalence of that disease and is equivalent to a Z value of the (standard) normal distribution.¹² Age and sex were incorporated into the threshold model, allowing them to impact on the liability thresholds according to their degree and direction of association with the different atopic diseases.

Latent factor models of genetic and environmental

effects were fitted to the observed data. These models assumed that the individual susceptibility to developing the different diseases was a linear function of genetic and environmental influences. Genetic influences were partitioned into additive genetic effects (loci contributing additively to disease risk, A) and non-additive genetic effects (interacting alleles, either from the same locus, genetic dominance, or from separate loci, epistasis, D). Environmental influences were divided into shared environmental effects (environmental factors that increase the resemblance between members of the same family, C) and non-shared, random environmental effects (influences unique to an individual, E).⁸ For most human traits, it is reasonable to assume that all four sources of variance (A, D, C and E) act simultaneously. However, components C and D are not identified under the same model in studies that include only twins reared together.¹³ Therefore, the likelihood of the data was determined under two different saturated models that included components A, C and E or A, D and E.

According to biometrical genetic theory, components A and D are correlated 1.0 in identical twins and respectively 0.5 and 0.25 in fraternal twins. The C component is by definition correlated 1.0 across both identical and fraternal twin pairs, whereas the E component is uncorrelated between twins.⁸ Fixing the appropriate variance components to 0 subsequently fit nested sub-models. The difference in log-likelihood between the saturated and the nested models provided an estimate of the significance of the contribution of the individual variance components to disease susceptibility. As components C and D turned out not to contribute significantly to the individual susceptibility to disease, models that included only components A and E were used to estimate the magnitude of genetic and environmental sharing between the diseases. These parameters were expressed as respectively genetic and environmental correlations between diseases, and were estimated as the additive genetic or the

Table 1 Prevalence of atopic diseases in a sample of 11 231 twin pairs aged 12–41 years

Zygosity	Pairs <i>n</i>	Age years	Asthma <i>n</i> (%)	Hay fever <i>n</i> (%)	Eczema <i>n</i> (%)
MZ	3 563	25.1	394 (5.5)	788 (11.1)	528 (7.4)
Males	1 626	25.3	174 (5.4)	348 (10.7)	179 (5.5)
Females	1 937	25.0	220 (5.7)	440 (11.4)	349 (9.0)
DZ-ss	4 159	26.8	424 (5.1)	943 (11.3)	532 (6.4)
Males	2 050	26.8	204 (5.0)	478 (11.7)	198 (4.8)
Females	2 109	26.9	220 (5.2)	465 (11.0)	334 (7.9)
DZ-os	3 509	27.3	409 (5.8)	825 (11.8)	451 (6.4)
Males			199 (5.7)	405 (11.5)	161 (4.6)
Females			210 (6.0)	420 (12.0)	290 (8.3)
All DZ	7 668	27.1	833 (5.4)	1768 (11.5)	983 (6.4)
Total	11 231	26.4	1227 (5.5)	2556 (11.4)	1511 (6.7)

MZ = identical twins; DZ-ss = fraternal, same sex twins; DZ-os = fraternal opposite sex twins.

Table 2 Risk of a particular atopic disease in a co-twin of an affected twin relative to a co-twin of an unaffected twin

	Asthma OR (95%CI)	Hay fever OR (95%CI)	Eczema OR (95%CI)
Identical twins			
Asthma	20.69 (15.08–28.38)		
Hay fever	4.30 (3.20–5.56)	14.28 (11.40–17.90)	
Eczema	3.81 (2.72–5.32)	2.87 (2.17–3.78)	32.98 (24.66–44.11)
Fraternal twins			
Asthma	4.24 (2.97–6.06)		
Hay fever	2.00 (1.46–2.73)	3.10 (2.49–3.85)	
Eczema	1.73 (1.16–2.58)	1.40 (1.02–1.93)	5.63 (4.20–7.56)

OR = odds ratio; CI = confidence interval.

random environmental covariance between two diseases divided by the square root of the product of the additive genetic or the random environmental variances of those two diseases, respectively.¹²

A *P* value <0.05 was considered statistically significant. The statistical package Mx was used for the analyses.¹⁴ The protocol was evaluated and approved by the Danish National Committee on Biomedical Research Ethics.

RESULTS

The mean age of the population was 26.4 years (range 12–41) and 52% were females. The overall cumulative prevalence of the three diseases was: asthma (5.5%), hay fever (11.4%) and eczema (6.7%) (Table 1).

The diseases were significantly associated within the same individual: asthma-hay fever, OR 8.81 (95% confidence interval [CI] 7.58–10.23), asthma-eczema, OR 4.82 (95%CI 4.01–5.79), and hay fever-eczema, OR 3.25 (95%CI 2.79–3.78). The risk of a particular atopic disease was dramatically increased in a subject if the subject's twin brother or sister was affected, either by the same disease or by another. The effect was more pronounced in identical twins compared with fraternal twins, indicating that the three diseases were genetically related (Table 2).

Univariate variance components analysis showed that additive genetic factors accounted for 71% of individual susceptibility to asthma, 71% of susceptibility

to hay fever and 82% of susceptibility to eczema, whereas the rest was ascribable to non-shared environment. In both males and females, the same genes influenced susceptibility to each of the three diseases (asthma *P* = 0.18, hay fever *P* = 0.08 and eczema *P* = 0.63).

The results of bivariate variance components analysis are shown in Table 3. In particular, asthma was more strongly correlated with hay fever than with eczema, whereas hay fever and eczema were least alike. Phenotypic (within-subject) correlations between the different diseases were 0.57 (95%CI 0.54–0.59) for asthma and hay fever, 0.40 (95%CI 0.36–0.42) for asthma and eczema and 0.33 (95%CI 0.29–0.36) for hay fever and eczema. Decomposition of these correlations into their genetic and environmental contributions showed that shared genes explained between 70% and 85% of the correlation between the different diseases, whereas the remaining parts were explained by environmental factors shared between the diseases.

DISCUSSION

This study showed that the risk of a particular atopic disease was higher in a subject if the subject's sibling already had a history of any other atopic disease. Biometrical analysis indicated that these observations were to a large extent ascribable to genetic pleiotropy, whereas environmental risk factors shared between

Table 3 Correlations between atopic diseases

	Correlation* OR (95%CI)	$\rho_A^\dagger$ OR (95%CI)	$\rho_E^\ddagger$ OR (95%CI)	Proportion of phenotypic correlation due to [§]	
				Genetic factors %	Environmental factors %
Asthma-hay fever	0.57 (0.54–0.59)	0.57 (0.54–0.63)	0.58 (0.54–0.65)	70	30
Asthma-eczema	0.40 (0.36–0.42)	0.43 (0.36–0.50)	0.33 (0.23–0.49)	81	19
Hay fever-eczema	0.33 (0.29–0.36)	0.37 (0.31–0.42)	0.22 (0.14–0.32)	85	15

* Phenotypic (within-subject) correlation.

† Additive genetic correlation.

‡ Environmental correlation.

§ Percentage of the phenotypic correlation attributable to genetic and environmental factors, respectively, shared between the diseases.

the diseases also played a role. In particular, around three quarters of the correlation in liability between asthma, hay fever and eczema was attributable to the same genetic background, while the rest was due to environment sharing.

These results expand upon two earlier twin studies, one in children and one in adults, which have found that genetic susceptibility to one atopic disease is highly shared with genetic susceptibility to another.^{15,16} In particular, a Swedish study of 7- to 9-year-old twins found that genetic factors were strongly correlated between asthma, hay fever and eczema, but that the overlap between environmental risk factors was small.¹⁵ An Australian study of adults reported comparable findings for asthma and hay fever.¹⁶

The genetic architecture underlying atopic diseases is complex. In particular, the combined action of multiple genes plus environmental factors makes the prediction of disease state for a given genotype difficult. This complexity has previously been underlined in that a number of genes seem to be important for each of the atopic conditions, whereas other genes are associated with atopic disease or inflammation in general.¹⁷ Our study showed that pleiotropy is important in atopy. This information can be used to enhance gene-mapping efforts. In particular, disregarding such information about genetic covariation between different diseases can lead to loss of power in detecting genetic linkage.¹⁸ Multivariate genetic linkage analysis of twin data will undoubtedly provide an attractive means by which to study the genetics of atopy.¹⁹

Self-reported measures of disease have some inherent difficulties. For example, in this study we rely partly on recollection of past episodes of disease, which may bias prevalence estimates downwards.²⁰ This is important if disease episodes lie primarily in early childhood or if episodes are mild. However, the question regarding asthma has proven to have a high specificity, and is hence suitable for excluding false-positive cases.²¹ Although this may apply, at least partly, to hay fever and eczema, it must be kept in mind that objective verification of disease is lacking in this study. We nevertheless believe that the increased power provided by the large sample size is preferable in this setting compared with a more precise study of a smaller sample.

Critics argue that several assumptions of twin studies are unjustified and that results are therefore misleading.^{22,23} In particular, twins are said to be 'special', in terms of both their intrauterine environment and their upbringing, which means that results from twin studies cannot be generalised to the population as a whole.^{22,23} Furthermore, the power of the classical twin study to detect effects of shared environment is usually low, especially when studying small sample sizes.²⁴ For this reason, results of twin studies can be erroneously taken as evidence that genetic factors alone can explain familial aggregation of disease.²⁵ This is particularly important as studies from recent decades have sug-

gested that the worldwide increase in the prevalence of atopic disease is due mainly to environmental influences.²⁶ Lastly, variance components twin analysis usually assumes that genetic and environmental sources of variance act additively to produce phenotypic variance,⁸ i.e., one assumes no interaction or correlation between genes and the environment. Ignoring these effects, if they are in fact present, can lead to biased estimates. However, it is important to note that our finding of a substantial genetic impact on the susceptibility to atopic disease does not preclude considerable geographical differences in genetic and environmental risk factors, nor that environmental risk factors are important for the overall increase in the prevalence of atopic disease over the last decades.

In conclusion, this study indicates that to a large extent the different atopic diseases share a common genetic background, although disease-specific genes also play a considerable role. Relatives with a high degree of genetic similarity resemble each other more than do relatives who have a smaller proportion of their genes in common for the different atopic diseases. These results can prove informative when counselling families with atopy, and may also be used to guide the search for pleiotropic genes of importance for these diseases.

References

- 1 Linna O, Kokkonen J, Lahtela P, et al. Ten-year prognosis for generalized infantile eczema. *Acta Paediatr* 1992; 81: 1013–1016.
- 2 Gustafsson D, Sjöberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis—a prospective follow-up to 7 years of age. *Allergy* 2000; 55: 240–245.
- 3 Guerra S, Sherrill D L, Martinez F D, et al. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002; 109: 419–425.
- 4 Torén K, Olin A C, Hellgren J, et al. Rhinitis increase the risk for adult-onset asthma—a Swedish population-based case-control study (MAP-study). *Respir Med* 2002; 96: 635–641.
- 5 Feijen M, Gerritsen J, Postma D S. Genetics of allergic disease. *Br Med Bull* 2000; 56: 894–907.
- 6 Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998; 351: 1225–1232.
- 7 Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996; 9: 687–695.
- 8 Neale M C, Cardon L R. *Methodology for genetic studies of twins and families*. Dordrecht, The Netherlands: Kluwer Academic, 1992.
- 9 Kyvik K O, Green A, Beck-Nielsen H. The new Danish Twin Register: establishment and analysis of twinning rates. *Int J Epidemiol* 1995; 24: 589–596.
- 10 Christiansen L, Frederiksen H, Schousboe K, et al. Age and sex differences in the validity of questionnaire-based zygosity in twins. *Twin Res* 2003; 6: 275–278.
- 11 Ferris B G. Epidemiology standardization project (American Thoracic Society). *Am Rev Respir Dis* 1978; 118: 1–120.
- 12 Posthuma D, Beem A L, de Geus E J, et al. Theory and practice in quantitative genetics. *Twin Res* 2003; 6: 361–376.

- 13 Keller M C, Coventry W L. Quantifying and addressing parameter indeterminacy in the classical twin design. *Twin Res* 2005; 8: 201–213.
- 14 Neale M C, Boker S M, Xie G, Maes H H. *Mx statistical modelling*. 5th ed. Richmond, VA, USA: Department of Psychiatry, Medical College of Virginia, 1999.
- 15 Lichtenstein P, Svartengren M. Genes, environments, and sex: factors of importance in atopic diseases in 7–9-year-old Swedish twins. *Allergy* 1997; 52: 1079–1086.
- 16 Duffy D L, Martin N G, Battistutta D, et al. Genetics of asthma and hay fever in Australian twins. *Am Rev Respir Dis* 1990; 142: 1351–1358.
- 17 Barnes K C. Evidence for common genetic elements in allergic disease. *J Allergy Clin Immunol* 2000; 106 (Suppl): S192–S200.
- 18 Allison D B, Thiel B, St Jean P, et al. Multiple phenotype modeling in gene-mapping studies of quantitative traits: power advantages. *Am J Hum Genet* 1998; 63: 1190–1201.
- 19 Ferreira M A R, O’Gorman L, Le Souëf P, et al. Robust estimation of experiment-wise *P*-values applied to a genome scan of multiple asthma traits identifies a new region of significant linkage on chromosome 20q13. *Am J Hum Genet* 2005; 77: 1075–1085.
- 20 Brogger J, Eagan T, Eide G E, et al. Bias in retrospective studies of trends in asthma incidence. *Eur Respir J* 2004; 23: 281–286.
- 21 Torén K, Brisman J, Järholm B. Asthma and asthma-like symptoms in adults assessed by questionnaires. *Chest* 1993; 104: 600–608.
- 22 Evans D M, Martin N G. The validity of twin studies. *Genescreen* 2000; 1: 77–79.
- 23 Freese J. Commentary: the analysis of variance and the social complexities of genetic causation. *Int J Epidemiol* 2006; 35: 534–536.
- 24 Martin N G, Eaves L J, Kearsley M J, et al. The power of the classical twin study. *Heredity* 1978; 40: 97–116.
- 25 Hopper J L. Why ‘common environmental effects’ are so uncommon in the literature. In: Spector T D, Snieder H, MacGregor A J, eds. *Advances in twin and sib-pair analysis*. London, UK: Greenwich Medical Media Ltd, 2000.
- 26 Nolte H, Backer V, Porsbjerg C. Environmental factors as a cause for the increase in allergic disease. *Ann Allergy Asthma Immunol* 2001; 87 (Suppl): S7–S11.

R É S U M É

OBJECTIF : Estimer dans quelle mesure ce sont les mêmes facteurs de risque génétiques et environnementaux qui influencent l’asthme, le rhume des foins et l’eczéma.

SCHÉMA : Deux cohortes provenant du Registre National Danois des Jumeaux, constituées de jumeaux nés entre 1953 et 1982, ont été contactées pour une enquête par questionnaire et au total 29 183 jumeaux (86%) y ont répondu. Les sujets ont été classifiés comme cas lorsqu’ils répondaient de manière affirmative aux trois questions concernant la survenue d’asthme, de rhume des foins ou d’eczéma pendant l’ensemble de leur vie. On a mené une analyse des variances des composantes des jumeaux en utilisant les méthodes de vraisemblance maximale.

RÉSULTATS : Les corrélations phénotypiques (au sein de chaque sujet) concernant le risque entre les différentes maladies a été de 0,57 (IC95% 0,54–0,59) entre l’asthme et le rhume des foins, de 0,40 (IC95% 0,36–0,42) entre

l’asthme et l’eczéma et de 0,33 (IC95% 0,29–0,36) entre le rhume des foins et l’eczéma. La décomposition de ces corrélations entre leurs composantes génétiques et environnementales a montré que les gènes communs expliquaient de 70% à 85% de la corrélation entre les différentes maladies. Les fractions résiduelles ont été expliquées par des facteurs environnementaux partagés entre les maladies.

CONCLUSION : Les maladies atopiques partagent dans une large mesure un arrière-plan génétique commun, bien que des gènes spécifiques à chaque maladie jouent également un rôle considérable. Ces résultats peuvent fournir des informations lorsque l’on accompagne des familles atteintes d’atopie et de plus, peuvent être utilisées pour guider la recherche de gènes pleiotropiques importants pour ces maladies.

R E S U M E N

OBJETIVO : Evaluar en qué medida los mismos factores de riesgo genéticos y medioambientales influyen sobre el asma, la fiebre del heno y el eccema.

MÉTODOS : Se contactaron cohortes de gemelos nacidos entre 1953 y 1982 del registro nacional danés de gemelos para una encuesta y se obtuvo respuesta al cuestionario de un total de 29 183 personas (86%). Los individuos se clasificaron como casos cuando respondieron afirmativamente a tres preguntas sobre la aparición de episodios de asma, fiebre del heno o eccema durante la vida. Los componentes de varianza del análisis de los gemelos se estudiaron mediante los métodos de máxima verosimilitud.

RESULTADOS : Las asociaciones fenotípicas (dentro de cada individuo) de predisposición entre las diferentes enfermedades fueron 0,57 (IC95% 0,54 a 0,59) para asma

y fiebre del heno, 0,40 (IC95% 0,36 a 0,42) para asma y eccema y 0,33 (IC95% 0,29 a 0,36) para fiebre del heno y eccema. La descomposición de estas relaciones en sus componentes genéticos y medioambientales demostró que genes comunes explicaban entre el 70% y el 85% de la relación entre las enfermedades. La proporción restante se explicó mediante factores medioambientales compartidos por las enfermedades.

CONCLUSIÓN : Las enfermedades atópicas comparten en gran medida un patrimonio genético común, aunque también cumplen una función considerable genes específicos de cada enfermedad. Estos resultados pueden resultar útiles en la orientación de las familias con atopía y pueden además utilizarse a fin de dirigir la búsqueda de genes pleiotropos, importantes para estas enfermedades.