EDITORIAL

Genetic and environment in asthma: the answer of twin studies

G.H. Koppleman**, H. Los**, D.S. Postma**

Twin studies have been widely used to estimate the genetic contribution to diseases. In this issue of the European Respiratory Journal, Skadhauge et al. [1] present the results of a large Danish population-based twin study on asthma. In this study, the heritability in liability to asthma, i.e. the proportion of variance due to genetic factors, is estimated to be 0.77 for males and 0.68 for females. In other studies, the heritability of asthma is estimated to be between 0.36 and 0.75 [2–4] (table 1). Thus, the results of this Danish study are consistent with those of other twin studies and add to the body of evidence indicating that the genetic contribution to asthma is considerable. In addition, the results of this study suggest individual specific, unshared, environmental factors to be important as well. In this editorial, the assumptions and methods of twin studies will be assessed, and the role of genetic and environmental factors in asthma reviewed.

Genetic studies using the twin-design have four major assumptions [8]: 1) monozygous (MZ) and dizygous (DZ) twins are samples of the same gene pool; 2) twins are representative of the general population; 3) self-reported zygosity is correct in questionnaire-based studies; and 4) the environment for both MZ and DZ twins is similar.

The first and second assumptions are valid, provided that representative or complete samples are taken from the population. The second assumption, the representativity, may not be totally valid because MZ and DZ twins differ from each other and from singletons with respect to their intrauterine environment [9]. The shared intrauterine environment may have an adverse effect on the growth and organ maturation of the foetus. However, this most likely does not influence the development of asthma since the prevalence of asthma is comparable in twins and singletons [1, 2, 4]. The third assumption has been tested [10, 11]. In general, self-reported zygosity questions are adequate in 95–98% of cases. Finally, the fourth assumption of an equal environment may not be valid in the case of asthma. For instance, it has been shown that MZ twins have more similar smoking patterns than DZ twins [12]. It is unknown whether or not this higher similarity in MZ twins is also the case for other environmental factors, such as exposure to indoor allergens and viruses. A higher similarity in environment for MZ twins compared to DZ twins may lead to an overestimation of the heritability of asthma.

The method for diagnosing asthma is a self-reported questionnaire in most large-scale twin studies. Subjects in these studies are not tested clinically. This method may lead to an under- or overestimation of asthma prevalence [13, 14]. Overestimation could occur, for instance, if asthma is diagnosed by questions on wheeze. Small children in particular may wheeze during the course of a respiratory infection but not have asthma [15]. Therefore, studies on the genetics of asthma are currently directed at measurable clinical components of asthma, e.g. airway hyperresponsiveness (AHR), reversibility and variability of airway obstruction. If it were known which of these components of asthma have a high genetic contribution, these components could then be selected for genetic studies to find genes that regulate these components. As an example, one twin study of reasonable size on AHR has been published, in which the heritability of AHR to methacholine was 0.66 [16]. Clearly, more studies are needed.

In general, statistical analyses of twin studies are complicated. In the study of twins, phenotypic similarities and differences are compared between MZ and DZ twins. MZ twins share 100% of their genetic information and DZ twins share on average 50%. If a trait is influenced by genetic factors, MZ twins should resemble each other to a greater extent than DZ twins, and the correlations between MZ and DZ twin pairs may be used to estimate the relative size of genetic and environmental influences.

In biometric modelling, one goes a step further. Since these biometric analyses are not frequently presented in pulmonary journals, some assumptions and methods will be addressed before discussing the results of these analyses in the study of asthma. In biometric modelling, a quantitative genetic analysis can be performed with dichotomous variables (e.g. asthma/not asthma). To permit these analyses, the first assumption is that disease status is determined by an unobserved continuous variable called the liability. If the liability falls above a threshold individuals are classified as affected. The second assumption is that the distribution of the liability is normal [17]. The variance of the distribution of the liability is composed of multiple environmental and genetic influences. The environmental component can be dissected in influences shared by both twins and influences not shared. Furthermore, the genetic component consists of an effect of individual alleles on the trait (additive effect) or interaction between alleles at the same locus (dominance effect) [8]. The last possible source of genetic effects, i.e. interaction of alleles at different loci (epistasis) cannot be discriminated from dominant genetic effects in twin studies, which is a limitation of this design. Thus, the observed phenotypes P1 of twin 1 and P2 of twin 2 of a twin pair, will be linear functions of the underlying additive genetic influences (A-twin

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1, A-twin 2), dominant genetic influences (D-twin 1, D-
twin 2), shared environmental influences (C-twin 1, C-
twin 2) and specific environmental influences (E-twin 1,
E-twin 2). These functions are calculated in a path model
by specialized computer programs (fig. 1). The results of
these calculations are then compared to those of known
models, including a model in which the disease is caused
by environmental factors alone, and a model in which the
disease is caused by genetic factors, or combinations of
these models. In this way, the best fitting model is calcu-
lated, i.e. the model that describes the data best. For more
background information, the reader is referred to the book
by NEALE and CARDON [18].

By applying the above mentioned methods, SKUDHAUGE
et al. [1] found evidence for the liability for asthma in a
model consisting of additive genetic factors and non-
shared environmental influences, with modest evidence of
effects of a shared environment. Interestingly, other large-
scale twin studies in different countries in the world came
to the same conclusion [2, 4, 7]. The question that arises
is: how do these findings relate to current evidence on the
role of genetic and environmental factors in asthma?

### Genetic factors

Major susceptibility genes for asthma and atopy have
not been determined to date [19]. Several reports indicate
a possible role for mutations in a gene on chromosome 11
coding for the β-chain of the high-affinity immunoglobu-
lin (Ig)E receptor in atopy or asthma, however, the picture
is not clear as these mutations do not seem to play a role
in either asthma or atopy in other populations [20]. The
gene coding for the β2-adrenergic receptor has been stud-
ied in more detail. Current data indicate that two common
polymorphisms in this gene do not play a role in the cau-
sation of asthma. They may, however, modify asthma into
a more severe phenotype expressed as more nocturnal com-
plaints, higher use of inhaled corticosteroids in patients
with these mutations and a reduced effect of
β-mimetics [21].

### Environmental factors

Environmental risk factors in asthma are: active or pas-
sive smoking, exposure to allergens [22], viral respiratory
infections, and possibly diet and air pollution [23]. Intu-
ively, most of these environmental factors appear to be
largely shared. However, the twin studies suggest that not
the shared, but the unshared individual-specific environ-
ment appears to be important. It is a challenge for re-
searchers to assess which factors have these specific effects
and to what extent the timing of exposure is relevant. It is

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**Table 1. – Results of twin studies of asthma**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Number of twin-pairs</th>
<th>MZ correlation*</th>
<th>DZ correlation*</th>
<th>Probandwise concordance MZ/DZ</th>
<th>Heritability</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish</td>
<td>6996</td>
<td>0.65</td>
<td>0.25**</td>
<td>0.60–0.75</td>
<td>Adult population-based study. Correlations calculated by DUFFY et al. [2]</td>
<td></td>
</tr>
<tr>
<td>Australian</td>
<td>3808</td>
<td>0.65</td>
<td>0.24**</td>
<td></td>
<td>“Asthma or wheezing” by questionnaire.</td>
<td></td>
</tr>
<tr>
<td>Finnish</td>
<td>13888</td>
<td>0.43</td>
<td>0.25**</td>
<td>0.13/0.07</td>
<td></td>
<td>Hospitalization, medication or cause of death/adult population based study. Questionnaire (ever wheezing with shortness of breath, wheezing without a cold or parental reported asthma)</td>
</tr>
<tr>
<td>Swedish</td>
<td>434 M</td>
<td>0.62</td>
<td>0.26**</td>
<td>0.60–0.75</td>
<td>Adult population</td>
<td></td>
</tr>
<tr>
<td></td>
<td>456 F</td>
<td>0.41/0.18**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norwegian</td>
<td>257</td>
<td>0.75</td>
<td>0.21**</td>
<td>0.45/0.12**</td>
<td>0.75</td>
<td>Population-based study of twins aged 18–25 yrs.</td>
</tr>
<tr>
<td>Finnish</td>
<td>171</td>
<td>0.76</td>
<td>0.45</td>
<td></td>
<td></td>
<td>Population-based study of twins aged 16 yrs</td>
</tr>
<tr>
<td>Danish</td>
<td>1929 M</td>
<td>0.76</td>
<td>0.48/0.19**</td>
<td></td>
<td></td>
<td>Population-based study of twins aged 12–26 yrs.</td>
</tr>
<tr>
<td></td>
<td>2131 F</td>
<td>0.71</td>
<td>0.47</td>
<td>0.42/0.26**</td>
<td></td>
<td>Age 12–26 yrs</td>
</tr>
<tr>
<td></td>
<td>1867 M</td>
<td>0.81</td>
<td>0.37</td>
<td>0.51/0.16**</td>
<td></td>
<td>Age 27–41 yrs</td>
</tr>
<tr>
<td></td>
<td>2110 F</td>
<td>0.65</td>
<td>0.15</td>
<td>0.38/0.09**</td>
<td></td>
<td>Age 27–41 yrs</td>
</tr>
</tbody>
</table>

MZ: monozygous; DZ: dizygous; M: male; F: female. *: correlation is tetrachoric correlation; **: statistically significant differences between MZ and DZ pairs.

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**Fig. 1. – Path diagram depicting genetic and environmental effects.** Twin 1 and twin 2 are the first and second twin pair with phenotype P1 and P2, respectively. A: additive genetic effects; C: shared environmental effects; E: nonshared environmental effects; D: dominant genetic effects. a, c, d and e are path coefficients, which are measures of variance of these genetic and environmental effects. Monozygous (MZ) twins share 100% of their genes, and therefore the correlation is 1 for additive and 1 for dominant effects. In dizygous (DZ) twins, these correlations are 0.5 for additive, and 0.25 for dominant effects. (Reproduced with permission from [18].)
of major interest to learn and understand how these factors interact with each other and with genetic factors.

In summary, what answers do twin studies give to the question of which genetic and environmental factors cause asthma? Firstly, twin studies have indicated the considerable genetic component of asthma. This component most likely consists of genes of additive effect. Secondly, twin studies have shown that individual specific environmental factors may be important as well. To understand the genetics of asthma further, we recommend directing the twin approach at measurable components of asthma, such as airway hyperresponsiveness, reversibility and variability in airway obstruction. Since we currently do not know which genes lead to susceptibility to asthma, the next challenge will be to study the interaction of these genes and specific environmental factors in the development of asthma.

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