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EDITORIAL

Genetic and environment in asthma: the answer of twin studies

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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.

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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

Table 1. – Results of twin studies of asthma

	[Ref.]	Number of twin-pairs	MZ correlation*	DZ correlation*	Probandwise concordance MZ/DZ	Heritability	Comments
Swedish	[5]	6996	0.65	0.25**			Adult population-based study. Correlations calculated by DUFFY *et al.* [2]
Australian	[2]	3808	0.65	0.24**		0.60–0.75	"Asthma or wheezing" by questionnaire. Adult population.
Finnish	[3]	13888	0.43	0.25**	0.13/0.07	0.36	Hospitalization, medication or cause of death/adult population based study.
Swedish	[6]	434 M 456 F			0.62/0.26** 0.41/0.18**		Questionnaire (ever wheezing with shortness of breath, wheezing without a cold or parental reported asthma) twins aged 7–9 yrs.
Norwegian	[4]	257 0	0.75	0.21**	0.45/0.12**	0.75	Population-based study of twins aged 18–25 yrs.
Finnish	[7]	171 3	0.76	0.45	0.42/0.19**		Population-based study of twins aged 16 yrs
Danish	[1]	1929 M	0.76	0.36	0.48/0.19**		Population-based study of twins aged 12–26 yrs.
		2131 F	0.71	0.47	0.42/0.26**		Age 12–26 yrs
		1867 M	0.81	0.37	0.51/0.16**		Age 27–41 yrs
		2110 F	0.65	0.15	0.380.09**		Age 27–41 yrs

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

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 calculated, *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

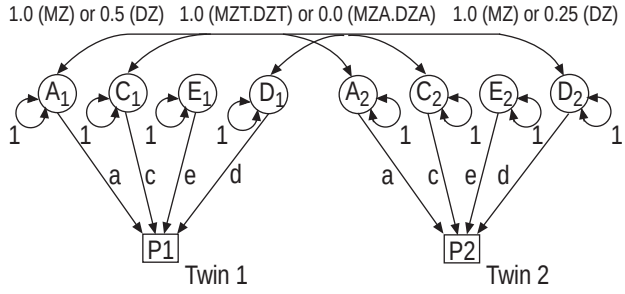

Fig. 1. – Path diagram depicting genetic and environmental effects. Twin 1 and twin 2 are the first and second twin pair with phenotype P1 and P2, respectively. A: additive genetic effects; C: shared environmental effects; E: nonshared environmental effects; D: dominant genetic effects. a, c, d and e 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].)

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 immunoglobulin (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 β_2-adrenergic receptor has been studied in more detail. Current data indicate that two common polymorphisms in this gene do not play a role in the causation of asthma. They may, however, modify asthma into a more severe phenotype expressed as more nocturnal complaints, 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 passive smoking, exposure to allergens [22], viral respiratory infections, and possibly diet and air pollution [23]. Intuitively, most of these environmental factors appear to be largely shared. However, the twin studies suggest that not the shared, but the unshared individual-specific environment appears to be important. It is a challenge for researchers to assess which factors have these specific effects and to what extent the timing of exposure is relevant. It is

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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