

EDITORIAL

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Using twin studies to determine genetic and environmental components of allergy and asthma

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For many years, the best opportunity to study the genetics of asthma was through studies of twins. Twin studies were useful as they offered the unique opportunity to examine groups consisting of pairs of individuals for whom both the *in utero* environment and genetics were identical [monozygotic twins (MZ)] with groups consisting of pairs of individuals for whom the *in utero* environment was identical but only 50% of their genetic makeup was common [dizygotic twins (DZ)]. In the earliest studies of asthma genetics, these features of twin studies were used to assist in determining the respective influence of genes and environment and the studies generally concluded that the environment exerted a stronger effect than genetics.

The influence of genetics was indicated by the concordance for asthma [1, 2], as well as serum IgE and skin reactivity [3] always being higher for MZ than DZ twins. Analyses in twin and other studies also suggested that the environment exerted a greater influence than genetics on total IgE level [4, 5], skin reactivity [6–8] and RAST responses [9]. For airway responsiveness (AR), concordance has been reported as being greater in MZ than DZ twins [3], but this has not been shown in all studies [10, 11]. In a more recent Norwegian asthma genetics study of 3334 twin pairs, a stronger genetic influence was found for disease diagnosis than for symptoms [12]. These and many other twin studies [13] have suggested that genes influence susceptibility for asthma and atopy and probably also for the level of AR. Conversely, the high levels of discordance for asthma between MZ twins pointed to a stronger influence of environment over genetics for the development of asthma.

With the advent of the modern era of genetics with its ability to characterize individual genes at the DNA level, rapid advances have been made in knowledge and the emphasis for asthma genetic studies has shifted away from twin studies. Over 5000 studies involving asthma

genetics have now been published, and a long list of genes and genotypes for which findings have been replicated has been established [14, 15]. Candidate genes for which findings have been replicated in two or more studies now number 79 and replication in six or more studies has now been recorded for 25 genes, but these lists continue to grow rapidly [14, 15]. Owing in part to the large number of genotypes that appear to influence asthma, none of the genotypes discovered to date exerts an effect that can explain more than a few percent of the variability of any asthma-related phenotype within populations [16]. To complicate this issue, exceptionally rare polymorphisms can be very common in particular ethnic groups [17], so that each ethnic group will need to have each asthma-related gene screened for polymorphisms to determine genetic influences. Hence, DNA studies cannot be used to determine either an individual's or a group's general genetic susceptibility to asthma, or to compare the overall relative contribution of genetics and environment. The highly complex and polygenic nature of asthma genetics does, therefore, impose limits on how much DNA studies can achieve.

Thus, twin studies still have relevance, as they have the advantage of being able to more globally assess genetic relationships between phenotypes and interrelationships between genetics and environment. As indicated by the authors of the present study of Thomsen et al. [18] in the current edition of this journal, few previous studies had examined the genetic and environmental relationships between asthma and atopic disease using statistical approaches that include variance components analysis. The authors were able to contrast the level of genetic association with the degree of environmental correlation. Using this more sophisticated approach for data analysis, the study demonstrates how twin studies can be used to make a significant contribution to future research into asthma genetics. Broad correlations were found between the major phenotypic factors [18]. These results were in common with several previous studies, but the correlations themselves were stronger than had been previously shown most likely due to the more refined statistical

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approach. Of particular interest are the findings that quantify relationships between different phenotypic attributes. Traits with the strongest genetic correlations were wheeze and rhinitis, wheeze and AR, and rhinitis and skin prick tests (SPTs). These relationships are plausible since they are also the most physiologically related variables. Genetic correlations between AR and other phenotypes including SPTs and rhinitis were less prominent, and again, these results are logical as several previous studies have suggested that AR is inherited separately from atopy and other phenotypes. The data on environmental correlations are also of interest. A high degree of environmental sharing was found between SPT results and both rhinitis and wheeze, most probably reflecting the common aetiological background of these traits. The environmental correlation between wheeze and rhinitis was much lower. In general, the authors noted that around three quarters of the phenotypic correlation between any pair of traits could be attributed to genetic factors shared between the traits, and that the remainder of the correlation was due to environmental factors.

In classic twin studies, the assumption is usually made that environmental sharing is the same for MZ and DZ twins, so that differences between MZ and DZ twins are related to genetics. The validity of this assumption is difficult to determine. For example, parents of MZ twins and the MZ twins themselves may inadvertently produce a family lifestyle that is more similar for these twins than would be the case for DZ twins. As pointed out by the authors of the current study [18], this would lead to overestimation of the genetic contribution of MZ compared with DZ twins. There is no easy way to compare similarity of local environment for twin pairs, so this issue remains unresolved. In addition, both MZ and DZ twins are more likely to share their environment than non-twin siblings. These factors need to be kept in mind in studies comparing the two different kinds of twin pairs.

In summary, molecular studies into asthma genetics have contributed a great deal to current knowledge and received greatest attention in recent years, but more traditional twin studies still have an important place in research into asthma genetics. By using more sophisticated statistical methodologies such as those used by Thomsen et al. [18], the strength of the genetic factors that underline disease processes can be defined and, unlike molecular genetic studies, an overall estimate of genetic vs. environmental effects can also be made.

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