Etiological Relationships in Atopy: A Review of Twin Studies

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The genetics of asthma and atopy has been studied frequently in twin populations from various parts of the world. However, emphasis has been put on univariate analysis of questionnaire data, whereas clinical and intermediate traits only sporadically have been studied, especially in multivariate settings. This review focuses on multivariate twin studies of atopy and related traits. We conclude that the genetic liability to most atopic traits is significantly correlated but that trait-specific genes also play a role. Previous studies have estimated the genetic correlation between upper and lower respiratory allergic symptoms, that is, asthma and hay fever, to be between .47 and .95. Furthermore, atopic traits share a portion of their genetic determinants with other complex disorders like obesity and behavioral traits. A correlation of about .3 and .34 has been reported between genes associated with asthma and obesity, and between genes associated with asthma and depression, respectively. We emphasize that multivariate methods applied to twin studies, especially when genetic marker information is available, provide a valuable framework within which complex etiological mechanisms underlying atopy can be disentangled.

Atopy is a multifactorial disorder, which is defined by an individual tendency to become sensitized and produce IgE-antibodies towards common environmental allergens like pollen, animal dander, house dust mite (HDM), and fungi (Mygind et al., 1996). In the majority of cases atopy is accompanied by symptoms from the skin and respiratory tract. Typical manifestations are asthma, hay fever, atopic eczema, and urticaria. Structured definitions of these phenotypes are presented by Bousquet et al. (2001) and Bateman et al. (2008); these are the definitions used in the present review.

Several objective tests are available that measure various characteristics of the atopic syndrome such as serum IgE, skin test reactivity, eosinophils, exhaled nitric oxide, airway obstruction, and airway responsiveness. These intermediate phenotypes are related both to the clinical atopic symptoms and to one another due to reasons that are still incompletely understood.

Twin studies have been fundamental for establishing the substantial contribution of genetic factors in the etiology of atopic disease (Los et al., 2001). In particular, the risk of disease in a co-twin of an affected monozygotic (MZ) twin is increased 5 to 10 times compared with 2 to 4 times in a co-twin of an affected dizygotic (DZ) twin, relative to the general population. These findings are consistent with genetic influences on disease susceptibility and most studies, irrespective of the country of origin and the age of the study cohorts, report heritability estimates on the order of 70% (Los et al., 2001). However, the majority of these studies have been concerned with questionnaire data whereas studies of clinical and intermediate phenotypes are sparse. Furthermore, the interrelationships between atopic diseases and objective markers of atopy have only rarely been studied in twins.

At the heart of the multivariate classical twin design is the ability to estimate the degree to which the same genetic and environmental factors influence different traits (Posthuma et al., 2003). If there is an overlap of genes for two traits it is expected that the cross-twin cross-trait correlation in MZ twins will be higher than in DZ twins for these traits. Using this information cannot only widen our understanding of atopic co-morbidity it can also enhance gene-mapping efforts (Ferreira, O'Gorman, et al., 2006; Harris et al., 1998). In this review we focus on twin studies that have examined covariation between atopic traits and give suggestions on how information from these studies can guide future research.

Criteria for Identification of Research Papers Used in This Review

We performed a search in Medline combining the words twin, twin study, and heritability with allergy, asthma, atopy, skin prick test, airway responsiveness, hay fever, eosinophil, nitric oxide, eczema, and IgE.

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Studies which reported on the resemblance between twins for any atopic trait were identified. Related articles were identified and the reference list of each article was examined.

Relationship Between Atopic Diseases

Upper and Lower Respiratory Symptoms

It has been suggested that upper and lower respiratory allergic symptoms constitute a continuum of liability with asthma being the more severe manifestation (Linneberg et al., 2002; Lundblad, 2002). In fact, the emergence of the 'one-airway-one-disease' dogma is based partly on the observation that up to 90% of subjects with allergic asthma also have symptoms of rhinitis (Leynaert et al., 2000), and up to 60% of subjects with allergic rhinitis have asthma (Leynaert et al., 2000). An even stronger motivation for regarding these conditions as two different expressions of the same underlying disorder is that the majority of patients with asthma have inflammatory changes in their noses (Fokkens & Braunstahl, 2005). Likewise, asymptomatic inflammatory changes in the lungs often accompany rhinitis, indicating that co-morbidity is perhaps even more substantial than would be expected if figures were based on clinical symptoms alone (Braunstahl et al., 2003).

A few twin studies have looked at the relationship between upper and lower respiratory symptoms. Results are shown in Table 1.

These studies are remarkably similar in respect to their estimates of phenotypic correlations regardless of age-group and geography, however the explanations for these correlations tend to differ more between studies. Duffy and colleagues studied self-reported asthma and hay fever in Australian adults and found that the genetic liability to asthma and hay fever were moderately correlated both in males and in females (Duffy et al., 1990). Furthermore, correlations for environmental factors were also substantial especially among males. Lichtenstein and Svartengren studied self-reported asthma and hay fever in children from the Swedish Twin Registry (Lichtenstein & Svartengren, 1997) and noted an even stronger genetic correlation between the traits. In fact, they were not able to rule out complete pleiotropy, whereas environmental correlations approached zero. One questionnaire study from the Danish study of 11,231 young adult twin pairs gave results that were consistent with the Australian study (Thomsen et al., 2006a). Furthermore, a clinical study of 575 subjects from the same Danish population suggested a highly shared genetic liability between wheeze and rhinitis (Thomsen et al., 2006b). Lastly, Nystad and colleagues looked at the relationships between self-reported atopic diseases and self-reported symptoms of the same diseases, that is, asthma versus wheeze and hay fever versus rhinitis (Nystad et al., 2005). Their study showed that genetic effects mainly explained the co-occurrence of diseases and symptoms but that genetic factors accounted for a greater variation in reported diseases than in symptoms of the same diseases. This means that

Table 1
Correlation Between Upper and Lower Respiratory Allergic Symptoms

Study (1° author)	Country	Age group (years)	Number (pairs)	r^1	ρ_A^2	ρ_E^3	Genetic model[4]	Definition of symptoms
Duffy et al. (1990)	Australia	18–88	3808					
Males				.56	.52	.53	ADE	Questionnaire, self-reported ever asthma/wheeze and hay fever
Females				.55	.65	.33	AE	
Lichtenstein & Svartengren (1997)	Sweden	7–9	1480	.54	.90	.00	AE	Questionnaire, parent-reported ever asthma/wheeze and hay fever
Thomsen et al. (2006a)	Denmark	12–41	11,231	.57	.57	.58	AE	Questionnaire, self-reported ever asthma and hay fever
Thomsen et al. (2006b)	Denmark	20–49	256	.64	.95	.25	AE	Clinical, interview-based history of wheeze and rhinitis
Van Beijsterveldt & Boomsma (2007)	Netherlands	5	8633	.48	.47	.73	AE	Questionnaire, parent-reported ever physician-diagnosed asthma and hay fever

Note: [1]Phenotypic (within-subject) correlation
[2]Additive genetic correlation
[3]Environmental correlation
[4]Variance components model under which the genetic and environmental correlations were derived. A, additive genetic variance; D, dominance genetic variance; E, unique environmental variance.

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diseases and symptoms do not necessarily reflect the same underlying disorder, which perhaps explains why different studies of the same but yet slightly differing phenotypes report different covariance structures for these phenotypes.

Respiratory Symptoms and Skin Manifestations

Varying with the severity of disease, up to 50% of subjects who suffer from atopic dermatitis in childhood go on to develop asthma and/or hay fever later in life (Gustafsson et al., 2000). Also, both acute and chronic urticaria are accompanied by asthma and/or hay fever in a considerable proportion of cases (Mygind et al., 1996). In asthma, hay fever, and atopic dermatitis there is an imbalance between Th2 and Th1 cells, which favors IgE synthesis (Mygind et al., 1996), however in atopic dermatitis, an allergic reaction seems not to be the major cause of symptoms (Mygind et al., 1996). In urticaria, histamine release from mast cells is the primary cause of symptoms. However, type I allergic reactions and IgE-mediated histamine release is one among many reactions that can lead to urticaria (Mygind et al., 1996).

Two questionnaire studies of twins have looked at the co-occurrence of respiratory symptoms and atopic skin manifestations. The first was a Swedish study that gave bivariate heritabilities for the associations between asthma, hay fever, eczema, and urticaria in 7- to 9-year-old children (Lichtenstein & Svartengren, 1997). Diagnoses were based on parent-report. Genetic correlations between asthma and eczema, and between hay fever and eczema were .35 and .73, respectively. Furthermore, genetic correlations between asthma and urticaria, and between hay fever and urticaria were .48 and .45. The genetic correlation between eczema and urticaria was .48. Environmental correlations between traits were generally small suggesting that the co-occurrence of skin and respiratory symptoms was due mainly to mutual genetic factors.

The second study was conducted in the Danish Twin Registry among young adults who were asked about the lifetime occurrence of asthma, hay fever, and flexural eczema (Thomsen et al., 2006a). Results suggested a 3.8 (2.7–5.3)-fold increased risk of skin symptoms in MZ co-twins of twins with respiratory symptoms; the magnitude of the increase was smaller in DZ twins [Relative Risk = 1.7 (1.2–2.6)]. These cross-disease risks translated into genetic correlations between asthma and eczema, and between hay fever and eczema, respectively of .43 and .37. Furthermore, environmental correlations between the same traits were .33 and .22 consistent with some overlap in environmental risk factors.

Relationship Between Atopic Diseases and Intermediate Phenotypes

Airway hyperresponsiveness (AHR) is a hallmark of asthma. However, studies of subjects with asthma show that not all suffer from AHR (Cockcroft & Davis, 2006). Furthermore, a small part of subjects who have AHR are asymptomatic indicating an incomplete overlap between the two (Backer et al., 1991). AHR has also been shown to be significantly associated with rhinitis (Ciprandi et al., 2004). It is however less clear why some subjects with rhinitis have AHR but not asthma. One possibility is that AHR is a marker of severity in subjects with rhinitis (Cirilli et al., 2005). Another is that AHR in rhinitis patients is a subclinical form of asthma (Ulrik et al., 2000). This is consistent with the finding that subjects with rhinitis and concomitant AHR are at greater risk of developing asthma compared with subjects who only have rhinitis (Porsbjerg et al., 2006).

A clinical study of Danish adult twins showed that the genetic liability to asthma symptoms and AHR correlated .70 whereas the genetic correlation between rhinitis and AHR was only .43 (Thomsen et al., 2006b). On the contrary, genetic risk factors for positive skin prick test were highly correlated with genetic risk factors for rhinitis (.92) but less so with asthma symptoms (.64). In other studies positive skin prick test has been shown to be a determinant of AHR in subjects who have rhinitis without concomitant asthma (Mete et al., 2004). We therefore propose that the inheritance of asthma is closely related to the inheritance of AHR, whereas the presence of AHR in nonasthmatic subjects with rhinitis is mediated by a genetic similarity between rhinitis and positive skin prick test.

Relationship Between Intermediate Phenotypes

Airway Hyperresponsiveness and Atopy

AHR and positive skin prick test are central features of atopic disease. Causes for their interrelationship have, however, been subject to different explanations. A reason for this is perhaps that AHR possibly has a different meaning in subjects with asthma than in subjects with rhinitis (see above). Another reason is that different indicators can measure both traits, such as for example different airway challenge tests, serum IgE, and skin test reactivity.

AHR occurs in a transient form following acute airway inflammation that usually involves eosinophils and mast cells (Cockcroft & Davis, 2006). A second and more persistent component of AHR appears related to the chronicity of the underlying disease (asthma) and the chronic effects of airway inflammation (airway remodeling; Cockcroft & Davis, 2006). Atopic sensitization marks the alteration of a subject's responsiveness to an allergen and involves many of the same components that play a role in the inflammation of the airways such as, for example, recruitment of mast cells and eosinophils. Whether this pathophysiological connection arises because of shared genetic determinants is, however, less clear.

A clinical study of 381 Australian twin pairs 8 to18 years of age estimated cross-twin cross-trait risks

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for AHR by hypertonic saline challenge and skin test positivity to common aeroallergens (Clarke et al., 2000). The MZ to DZ twin odds ratio was 3.1 (1.2–8.1) consistent with – but not proof of – some degree of genetic similarity between the two traits. Another large Australian study of adult twin pairs and their families ascertained through a proband with asthma examined genetic similarities between AHR and atopy (Ferreira et al., 2006a). Genetic liabilities to AHR by the histamine test and skin test positivity to any allergen among 11 tested were correlated .35. Furthermore, environmental risk factors were correlated .67 indicating that, to a great extent, the same environmental factors — possibly exposure to HDM — influence both traits. Further analyses of AHR and serum total IgE in that sample were consistent with the findings among an Australian nontwin sample studied by Palmer and colleagues, which indicated that AHR and atopy in large part represent distinct genetic entities (Palmer et al., 2000).

A Danish study of adult twins found a genetic correlation between AHR by methacholine and atopy by skin test positivity of .59 indicating a stronger genetic relationship between these traits than would be expected based on the findings from Australia (Thomsen et al., 2006b). Conversely, a smaller degree of environmental resemblance was noted (environmental correlation, .41).

Other Intermediate Phenotypes

Harris and colleagues (2004) analyzed the relationship between exhaled nitric oxide (a marker of airway inflammation) and airway responsiveness in adult twins. Results indicated that the traits were correlated primarily because of common genetic influences. In particular, cross-twin cross-trait correlations in MZ and DZ twins, respectively, were .23 and .04.

Ferreira, O'Gorman, et al. (2006) studied relationships between intermediate traits in Australian twins. Results were consistent with moderate to high genetic similarities between serum total IgE and eosinophilia, and between AHR and airway obstruction, whereas airway obstruction and IgE were genetically dissimilar, as were FEV1 and HDM sensitivity.

Relationship Between Atopic Diseases and Other Traits

Obesity

Increased body weight is associated with self-reported asthma both in children and adults, and especially among females (Camargo et al., 1999; Chen et al., 2002; Figueroa-Munoz et al., 2001). Furthermore, some studies report an association between obesity and objective markers of asthma, such as airway responsiveness and atopy although results are conflicting (Huang et al., 1999; Schachter et al., 2001). Finally, some studies have evaluated asthmatic patients who have undergone either surgical or medical weight loss and shown an improvement in symptoms of asthma, asthma severity, use of medication, and several measures of pulmonary function in those patients following treatment (Hakala et al., 2000; Macgregor & Greenberg, 1993). Much speculation has arisen as to the mechanisms that cause asthma and obesity to be associated. In particular, genetics, immune mechanisms, lung mechanics, lack of physical activity, diet, and endocrine factors have been suggested to act in a developmental context to link the two disorders (Weiss, 2005).

A study of 1384 twin pairs from the University of Washington Twin Registry estimated the extent to which genetic factors were shared between asthma and obesity and found a genetic correlation of .29 (Hallstrand et al., 2005). Moreover, a study of 11,302 young adult twin pairs from the Danish Twin Registry found a genetic correlation of .28, however, only in females (Thomsen et al., 2007). These results seem to concur well with several molecular genetic studies, which highlight that pleiotropic effects are present (Tantisira & Weiss, 2001). In particular, these suggest basic functions of metabolism, autonomic nervous system activity, and immune mechanisms in common. Furthermore, several inflammatory products in obese people, such as TNF-α, IL-6, leptin, C-reactive protein, and nitric oxide are suspected directly to influence the development of asthma suggesting that phenotypic effects also play a role (De Winter-de Groot et al., 2005; Lee & Pratley, 2005; Weiss, 2005).

Behavioral Traits

There is evidence to suggest an association between a range of psychological disorders and asthma. Anxiety disorders have been associated with asthma and other studies show a link between depression and asthma (Goodwin, 2003; Goodwin, Jacobi, et al., 2003). There are several alternative explanations for these observations. One possibility is that psychological disorders cause asthma or conversely, that asthma causes psychological disorders. A third possibility is that psychological disorders and asthma are associated because of a shared genetic or environmental background. However, to date only a few twin studies have looked into these possibilities.

Wamboldt and colleagues (1998) studied the association between atopy and behavioral symptoms in middle childhood in a small twin sample (207 pairs) ascertained through the Colorado Department of Health Statistics. A behavior problem score was derived from the Child Behavior Checklist (CBCL) whereas atopy was scored on the basis of a doctor's diagnosis of allergy and asthma. 'Atopy' was weakly (r = .11 to .21) but significantly correlated with most behavioral traits in the CBCL. The authors concluded that additive genetic effects accounted for a large proportion (77–89%) of the observed phenotypic correlations between atopy and internalizing, externalizing, and total problem score, respectively. The alternative explanation of a purely phenotypic causation was not specifically tested in that study.

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Another study by Wamboldt et al. (2000) analyzed the relationship between atopic disorders and depression in 3843 adult twin pairs, 33 to 60 years of age from the Finnish Twin Cohort. Data were collected by questionnaire. The Beck Depression Inventory was used to assess depressive symptoms and these were subsequently correlated with a total 'atopy' score made up of questions on the lifetime occurrence of asthma, hay fever, and eczema. The results were consistent with some genetic covariance between atopic disorders and depressive symptoms. In particular, additive genetic effects correlated .34.

Conclusions

The genetics of asthma and atopy has been studied frequently in twin populations from various parts of the world. However, emphasis has been on univariate analysis of questionnaire data, whereas clinical and intermediate traits only sporadically have been studied, especially in multivariate settings. Multivariate studies provide a valuable framework within which causes for covariation between traits can be disentangled (Posthuma et al., 2003). However, in spite of advances in computational and statistical tools multivariate analysis is still a cumbersome and timely procedure.

The few but interesting results that come from this area tell us that pleiotropy is a common phenomenon in atopic disease. In particular, upper and lower respiratory allergic symptoms correlate highly with respect to genetic risk factors. Furthermore, the genetic liability to respiratory symptoms correlates well with the genetic liability to skin symptoms like atopic eczema. Generally, studies find that asthma share more of its genetic determinants with hay fever than with eczema. However, among these results there seems to be tendency for smaller studies to invoke genetic explanations for atopic comorbidity, whereas larger studies also emphasize the role of trait-specific genes, that is, that some genes are important for each condition, in which other genes are associated with atopic disease or inflammation in general (Barnes, 2000; Nishimura et al., 2001).

Analysis of intermediate phenotypes generally recognizes the role of environmental causes for covariation. For example, Ferreira, O'Gorman, et al. (2006) found that among Australian adults the co-occurrence of multiple intermediate phenotypes were to large extent attributable to environmental factors, although some genetic overlap between traits was noted too. Furthermore, Strachan and colleagues (2001) studied a large clinical sample of adult female twins from the St Thomas UK Adult Twin Registry. They found that MZ twins often differed in respect to clinical signs of allergic disease such as pattern of skin test positivity and serum IgE. Results were consistent with a clinical study of Australian twins discordant for asthma by Duffy et al. (1998) who observed that DZ twins differed more than MZ twins in respect to skin test positivity to outdoor allergens like pollen, whereas skin test positivity to indoor allergens like HDM were of similar magnitude in DZ and MZ twins. These findings suggest that pollen allergy in asthmatics develops as a result of an underlying atopic predisposition shared with asthma, whereas indoor allergens like HDM are more likely direct environmental causes of asthma. Subsequent immunoblotting analysis of individual IgE-binding components from HDM and grass pollen in this Australian sample furthermore showed that MZ twins who were both sensitized to the same allergen differed considerably in their specific responses towards allergen determinants, consistent with a substantial role of environmental or epigenetic modifying factors (Sluyter et al., 1998; Tovey et al., 1998). Genetic control of overall atopy is therefore far stronger than that controlling sensitization to individual allergens. Thus, in spite of substantial genetic influences on atopic susceptibility associations between different clinical manifestations equally likely reflect acquired phenotypes rather than common or linked genotypes (Strachan et al., 2001).

Atopic diseases share a small portion of their genetic determinants with other common chronic conditions such as obesity and psychological disorders. Several candidate regions are likely implicated in this. For example regions 5q23-34, 6p21-23, 11q13, and 12q13-14 are known to harbor genes that are important both in atopy and obesity (Beuther et al., 2006). These are the glucocorticoid receptor gene — which has also been associated with depression (van Rossum et al., 2006) — the tumor necrosis factor alpha gene complex, the low affinity immunoglobulin E receptor gene, and several genes encoding various cytokines such as STAT6, IFNγ, IL1A, and LTA4H. Furthermore, several inflammatory mediators, which are known to directly influence the risk of asthma, are produced in excess amounts in obese individuals (Lee & Pratley, 2005). This suggests that at least part of the correlation between asthma and obesity represents causal mechanisms that are independent of a common genetic background. Likewise, the genetic link between asthma and depression may be confounded by other factors. It is known that several other psychiatric traits like panic disorder, posttraumatic stress disorder, and suicidal behavior are associated with asthma (Goodwin, Jacobi, et al., 2003). Besides a possible role of genetic factors for this co-morbidity asthma may share a number of social and environmental risk factors with these traits (Goodwin, Wamboldt, et al., 2003). Therefore, it remains to be determined whether the relationship between psychological illness and asthma alludes to compromised immune functioning independently of a common genetic background.

Limitations

The present studies fall mainly into two categories; large registry-based questionnaire studies of disease

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phenotypes and smaller clinical studies of intermediate phenotypes. The questionnaire studies often focus on sample size with large numbers of individuals and therefore have high power to test genetic hypotheses, however they are often characterized by subjective, imprecise, and incongruent phenotypic definitions, which makes results difficult to generalize to the clinical setting. Clinical studies, on the other hand, reflect disease processes more accurately, but usually have smaller power that can lead to biased estimates of variance components.

Moreover, critics argue that several assumptions of twin studies are unjustified and therefore results can be misleading (Evans & Martin, 2000). In particular, it is assumed that environmental influences shared by twins are independent of zygosity (Hopper, 2000). If this is not true, for example if MZ twins are being treated more similarly by their parents than DZ twins, or if MZ twins seek to live in more similar environments compared with DZ twins, the genetic contribution to the traits under study can be overestimated (Hopper, 2000). There is evidence that these things indeed happen, but even so, it is generally acknowledged that these inconsistencies only have minor impact or no impact at all on the validity of twin studies (Martin et al., 1997).

Perspectives

Recent years have witnessed a growing tendency to incorporate genetic marker information into twin studies. Unfortunately twin studies of atopy have been very slow in picking up this trend in spite of ready accessibility to ideal sampling bases, that is, our large twin registries (Ahmadi et al., 2003; Evans et al., 2004; Ferreira et al., 2005).

Linkage analysis constitutes the backbone of genetic susceptibility locus mapping within families. Indeed, during the past decades a large number of linkage studies have suggested multiple candidate loci for atopy and related traits across the chromosome (Blumenthal, 2005; Cookson, 2002). The majority of these have applied univariate linkage methods. Univariate linkage methods are easy to apply and the interpretation of results is straightforward. However, univariate studies are often hampered by a large number of statistical tests owing to the fact that several different traits are analyzed independently within the same study. This leads to high Type-I error rates, which, unfortunately, often are ignored or overlooked (Ferreira, Visscher et al., 2006).

When traits share genetic determinants, as is the case for atopic diseases, univariate methods do not recognize the full power of the data. In fact, ignoring the correlational structure of such data can lead to loss of power to detect genetic linkage (Allison et al., 1998; Ferreira, 2004; Ferreira et al., 2005; Ferreira, O'Gorman, et al., 2006). To meet these terms multivariate linkage analysis applies. Multivariate linkage analysis, however, also has some disadvantages, primarily in terms of computational restrictions. These can be circumvented by for example analyzing correlated traits with univariate methods without loosing the ability to detect pleiotropic quantitative trait loci (Ferreira, Visscher et al., 2006).

Multivariate data sets can provide valuable insight into complex causal mechanisms and thereby ultimately increase our chances for discovering novel drug targets. We encourage use of genetic marker information with multivariate twin methods. In particular, a future closer collaboration between the different twin registries will facilitate studies that can help us better understand the etiological mechanisms underlying atopy.

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