

Genetic and environmental factors in the changing incidence of allergy

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Several studies have indicated that the incidence and prevalence of allergic diseases are increasing. Such data should not be regarded as mere statistical curiosities, but should be analysed to provide information on the factors contributing to allergy and its changing epidemiology. Extensive evidence has been accumulated that allergic diseases are polyfactorial. Data reported in the literature and particularly twin studies have also suggested polyfactorial control of individual allergy variables, such as total serum levels IgE and IgG4, specificity of antibody response, mediator release from inflammatory cells and target organ response. Markers of genetic susceptibility may identify individuals at risk for allergy, while identification of the environmental factors influencing the phenotypic expression of allergy can be useful in evaluating the cost–benefit ratio of taking preventive measures in such individuals.

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In order to discuss genetic and environmental factors involved in the changing incidence of allergic diseases, we shall address the following points.

- What is an allergic disease?
- Are allergic diseases really increasing?
- Are allergic diseases inherited or acquired?
- What is inherited in allergic diseases?
- Impact of genetic and environmental factors on preventing allergic diseases.

What is an allergic disease?

The concept of allergy – and of atopy, anaphylaxis and hypersensitivity – has been the subject of many interpretations and controversies since it was first described. At a clinical level, allergic diseases represent a heterogeneous group of conditions which are commonly classified by their possible role in the pathogenesis of a type I (IgE-mediated) hypersensitivity mechanism according to the classification of Coombs and Gell (1). It is evident, however, that the pathogenesis of conditions, such as asthma, rhinitis and urticaria-angioedema is multifactorial, and may not involve IgE antibody. Thus, the definition of an allergic disease must be given in all papers dealing with genetic and environmental aspects of these conditions. This will avoid, for example, the data on the genetics of

asthma being extrapolated to form the genetics of allergy as a whole, or the genetic and environmental influences on the IgE response being invoked to explain the more complex polyfactorial nature of diseases, such as urticaria or atopic dermatitis, where the role of IgE antibodies may be limited or absent.

The aim of this paper is not to give a definitive answer to the question “what are allergy and allergic diseases?”, but will accept the oversimplified theory that allergic diseases result from the combination of four different abnormalities. These are:

- an aptitude for allergen recognition and an amplified specific response
- increased polyclonal IgE and IgG4 production
- up-regulation of inflammatory cells, particularly mast cells and eosinophils
- hyperresponsiveness of target tissues and organs.

There seems to be a present consensus of opinion on the role of the CD4 T cell phenotype Th2 in influencing the first three of these abnormalities through the production of cytokines, such as interleukin-3 (IL-3), IL-4, IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF) (2–4). Neural influences appear to be very important in the development of the inflammatory component of allergic diseases and the hyperrespon-

siveness of target tissues (5). Moreover, bidirectional influences occur among all these reported abnormalities (Fig. 1).

It is important to outline the relative role of the four abnormalities outlined above in the pathogenesis of allergic diseases. In hay fever, the specific IgE response to grass allergens appears to be the major pathophysiological abnormality, while in intrinsic asthma, where no specific IgE antibodies are found, the eosinophilic inflammation and hyperresponsiveness of the bronchial tissues are typical findings. Total serum IgE levels have, however, been reported to be increased in this condition, in the absence of a detectable specific IgE response (6). If this type of evaluation is extended to other allergic diseases, it is interesting to note that increased polyclonal IgE production and eosinophilic inflammation appear to be common features of all allergic diseases, but the presence of specific IgE antibody is only an optional event, and the hyperresponsiveness is particular to the different tissues, such as the bronchi, nose, skin and eyes, depending on the precise allergic disease being considered.

Are allergic diseases really increasing?

In 1873, Blackley described the increasing prevalence of hay fever and factors which elicit or predispose an individual to an attack (7).

"... It would seem that hay fever has, of late years, been considerably on the increase. It is possible that the fact of my attention having been closely directed to the disorder, for some time past, has brought more cases under my notice than formerly, and that the increase has not really been so marked

as it has appeared to me to be. But even if some allowance be made for this probability, it will still appear that the disease was less frequently seen fifteen or twenty years ago than it is at the present time ..."

How has our knowledge of the prevalence of allergic diseases changed since these comments were made?

Data are now available on the increasing incidence of allergic diseases (8–10). These data represent the basis for description of the increasing importance of allergology and socio-economical implications (11). However, even in prospective studies evaluating the differences in prevalence of allergic diseases, carried out using the same diagnostic procedures at different time points (12, 13), the definition of allergic disease is often unsatisfactory and heterogeneous definitions, such as 'drug allergy', 'food allergy', 'asthma', 'rhinitis', 'dermatitis' and 'urticaria' are listed. These studies reinforce the definition of epidemiologists, made by Krause, as individuals who, "in the most simple terms ... count", but do not give information of the role of genetic and environmental factors in the changing incidence of allergic diseases. On the contrary, Gregg made the sensible statement that "epidemiological studies [of allergic diseases] should not be undertaken out of mere curiosity concerning their prevalence ... but they should be designed ... to better understand their pathogenesis ... and to elucidate their natural history" (14).

Are allergic diseases inherited or acquired?

Several studies and extensive reviews have considered the relative roles of genetic and environmental

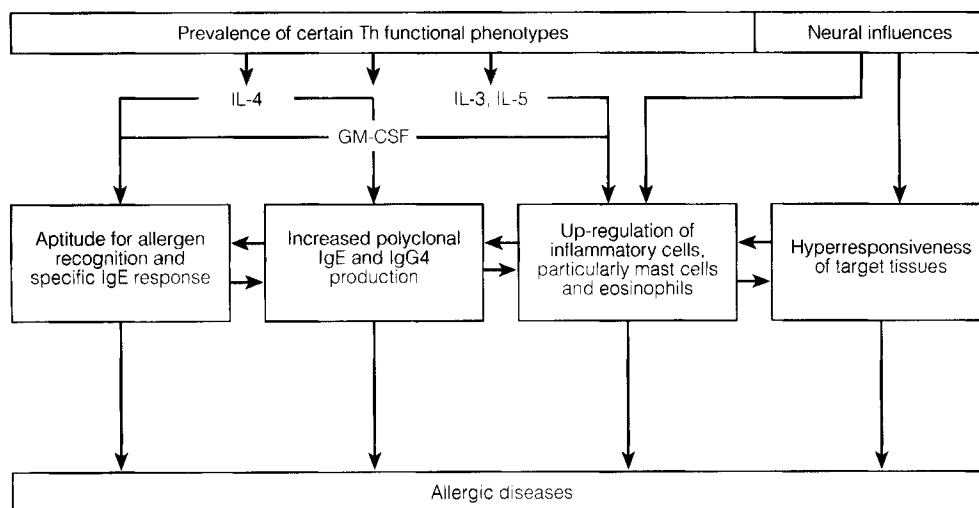


Fig. 1. Hallmarks of allergic diseases and the main factors influencing them.

factors in allergic diseases (10, 15–17). Twin studies can provide a useful approach to the investigation of inheritance in allergy. Although they cannot elucidate the mechanisms of heritability or environmental factors causing the phenotypic expression of allergy, investigations of monozygotic and dizygotic twins can offer an insight into the relative prevalence of genetic vs environmental influences in disease.

We have compared clinical data from 32 monozygotic and 71 dizygotic twin pairs, including information derived from personal and family histories, physical examinations and allergy and pulmonary function tests (18). Concordance for allergic diseases was seen in 50.0% (16/32) of monozygotic and in 35.2% (25/71) of dizygotic twin pairs. This difference is not statistically significant. In only five monozygotic (29.4%) and three dizygotic twin pairs (12.0%) the same atopic disease (asthma) was present in both twins. This was also not significant. Positive skin tests and/or radio-allergosorbent test (RAST) to common allergens were shown in 51.7% (15/29) of monozygotic twin pairs and in 36.8% (21/57) of dizygotic twin pairs (not significant), while only 24.1% (7/29) of monozygotic twin pairs and 14.0% (8/57) of dizygotic twin pairs were concordant for positive skin tests and/or RAST to the same allergens. No significant difference was observed between the concordance rate of monozygotic (20%, 1/5) and dizygotic (25%, 3/12) twin pairs for a positive exercise test. The test was usually only positive in subjects with asthma.

Genetic influences on allergy probably do exist, as suggested by the well-recognized clustering of allergic disease in families (19). These twin studies, however, indicate that genetic influences are not evident when considering allergic disease and sensitization in general, whether relating to a specific sensitization or a particular disease. In these cases, it can be assumed that several concomitant genetic and/or environmental factors are operating. Thus, if allergic diseases are polyfactorial, as it appears from this study (18) and from other data in the literature, a more accurate understanding of their genetic and environmental influences can only come from studying each factor involved in the pathogenesis of these disorders.

What is inherited in allergic diseases?

Genetic and environmental influences on the four abnormalities of allergic diseases can be discussed separately. These abnormalities are also expected to be polyfactorial, and so further separation of more specific factors is desirable.

Allergen recognition and specific IgE response

Several studies have indicated that allergen recognition and antibody response are genetically influenced by Ir HLA-linked genes (10, 14, 20). The basis for these studies is the role of HLA class II antigens in the interaction between specific allergen epitopes and T cell receptors during antigen presentation. They have mainly been performed using allergens from *Ambrosia artemisiifolia* and *Lolium perenne*. Marsh found that increased responsiveness to Amb a V (Ra5) was associated with HLA-DR2/DW2, while a response to Lol pI and Lol pII was associated with HLA-DR23 and DR5 (21). It should be noted that the increased responsiveness to purified allergens is not isotype specific, involving both IgE and IgG.

It is relevant that, in these studies, purified simple allergens were used, and that the masking effect of other genetic influences, such as those acting on total IgE levels, were avoided (20). On the contrary, results from population studies of the association between HLA antigens and allergic diseases or sensitization to crude allergens are contradictory and of limited value. For example, we failed to show any association in population studies of allergic patients (22).

Genetic influences appeared to have a minimal influence on IgE and IgG responses even to purified allergen in our studies of twins (18). Serum levels of IgE antibodies to *Lolium perenne* (RAST) and IgG antibodies to grass and house dust mites (SpA test) were measured in 48 (18 monozygotic and 30 dizygotic) and 54 (20 monozygotic and 34 dizygotic) twin pairs, respectively (18, 23, 24). Serum IgG1 and IgG4 level determination was performed to *Dactylis glomerata* and house dust mite using RAST in 38 (15 monozygotic and 23 dizygotic twin pairs) and 22 (10 monozygotic and 12 dizygotic) pairs of twins, respectively. Serum levels of IgE and IgG antibodies to major antigens of grass (Lol pI and Rye 1) and *Dermatophagoides pteronyssinus* (Der pI and P1) were also measured in 22 (6 monozygotic and 16 dizygotic) and in eight (3 monozygotic and 5 dizygotic) pairs of twins, respectively, using an antigen binding assay. No significant difference was observed between the mean intrapair variances of IgE and IgG antibodies to grass in monozygotic vs dizygotic twin pairs. Although the number of observations was low and did not permit definite conclusions to be made, the intrapair correlation coefficients of IgE and IgG antibodies, even to low molecular weight allergens such as Lol pI and Der pI, was usually low in monozygotic twin pairs, and not different from those of dizygotic twin pairs. Furthermore, no correlation was found between these antibody

responses and specific HLA antigens. Different classes and subclasses of antibody responses usually showed a good correlation in the twin pairs, with subjects having a high IgE response to an allergen also showing high IgG, IgG1 and IgG4 responses.

These data indicate that, despite evidence indicating that the IgE and IgG response to purified antigens is controlled by HLA associated genes, genetic influences on serum levels of specific antibodies to allergens are usually less pronounced than environmental influences. Thus, the atopic condition should be regarded as uncommitted susceptibility to allergic diseases in general, and environmental factors such as the quality, intensity, route and duration of allergen exposure might be more relevant than genetic factors in causing an effective response to allergens.

Increased polyclonal IgE and IgG4 production and up-regulation of inflammatory cells

Several studies of populations, families and twins have indicated that total serum IgE is subject to strong isotypic genetic control, even in the face of environmental influences, such as smoking (25), which may also be relevant for modulating serum IgE levels (15). The mechanism of inheritance, however, is still controversial, and different models have been proposed, such as autosomal dominant, autosomal recessive and polygenic models (26). Cookson et al. recently assigned a gene for the IgE response with maternal inheritance to chromosome 11q (27). However, their data – which have been confirmed by some groups but disproved by others – are based on a definition of atopy which includes both a higher than normal concentration

of total serum IgE and positive skin prick tests and/or RAST.

The most interesting finding in this area is the identification of genes for IL-3, IL-4, IL-5 and GM-CSF on chromosome 5 (28). This cluster of cytokine genes may have a fundamental role in the genetics of allergy, in view of the regulatory effects of the expressed cytokines on IgE and IgG4 isotype switching and production (effected by IL-4), as well as on the growth, activation, priming, mediator release and survival of mast cells and eosinophils (effected by IL-3, IL-5 and GM-CSF) (29). As the polyclonal activation of total IgE and IgG4 and the up-regulation of inflammatory cells, particularly mast cells and eosinophils, are common features of all allergic diseases, it might be speculated that a genetically or environmentally-induced overexpression of the cytokine gene cluster represents the basic abnormality of allergic diseases, as well as the basis for an uncommitted predisposition to both IgE-mediated and non IgE-mediated allergy. It may also be speculated that polyclonal IgE up-regulation is capable of influencing the appearance of a specific IgE response to various allergens. Subjects with the 'right' HLA linked Ir genes, however, can develop a monospecific sensitization, even in the absence of an up-regulation of the total IgE response.

Our studies in twins indicate that strong genetic influences regulate total serum IgE and IgG4 level, in addition to variables of secondary inflammatory effector mechanisms, such as basophil releasability, independent of factors regulating the specific allergen response.

We measured total serum IgE in 89 sets of twins (30 monozygotic and 59 dizygotic twin pairs). The intrapair correlation coefficient of total serum IgE

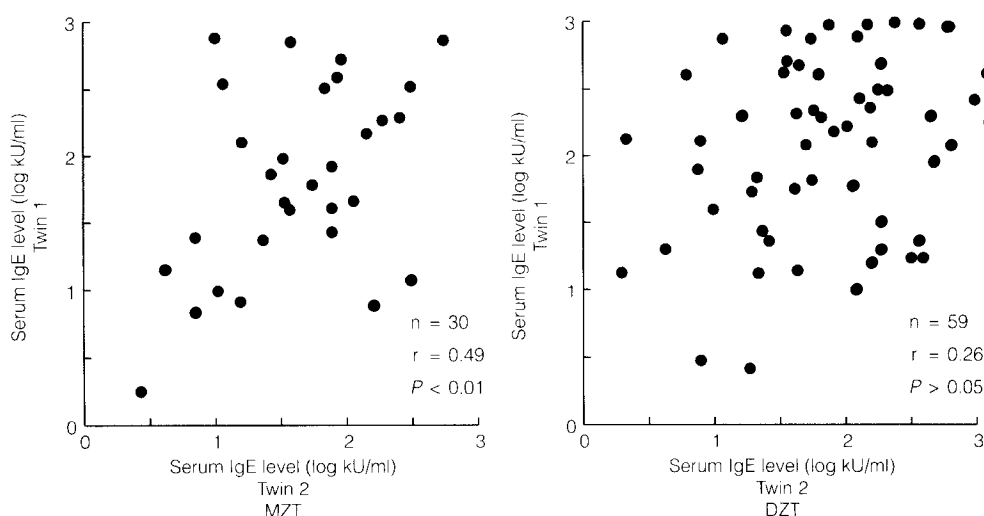


Fig. 2. Correlation between serum IgE levels in 30 monozygotic twin (MZT) and 59 dizygotic twin (DZT) pairs.

was significantly higher and the mean intrapair variance significantly lower in monozygotic than in dizygotic twin pairs (0.49 vs 0.26 and 0.15 vs 0.51, respectively). Heritability index was calculated using the formula $H=2(r_{\text{MZT}}-r_{\text{DZT}})$, where r is the correlation coefficient between values of a given variable. This index was 0.46 in the entire twin population, while it was 0.71 in the 48 (18 monozygotic and 30 dizygotic) grass sensitive twin pairs (18, 23, 24; Fig. 2). In the same study and in a subsequent unpublished study by Bonini and Aalberse, total IgG and IgG4 serum levels were also measured. As seen in IgE serum levels, a marked genetic influence was seen on IgG4 serum

levels (Fig. 3), with the intrapair correlation coefficient being significantly higher in monozygotic than dizygotic twin pairs ($P<0.01$). It is interesting to note that both IgE and IgG4 are present in small quantities and show bimodal distributions and restricted heterogeneity. Genetic influences on total IgG serum levels were less pronounced; the mean intrapair variance was 17.33 in monozygotic and 28.44 in dizygotic twin pairs ($H=0.39$). From these reported data it can be concluded that serum levels of total IgE and total IgG4 are under a marked genetic control.

The release of mediators from mast cells and basophils is a crucial pathogenetic event in allergic

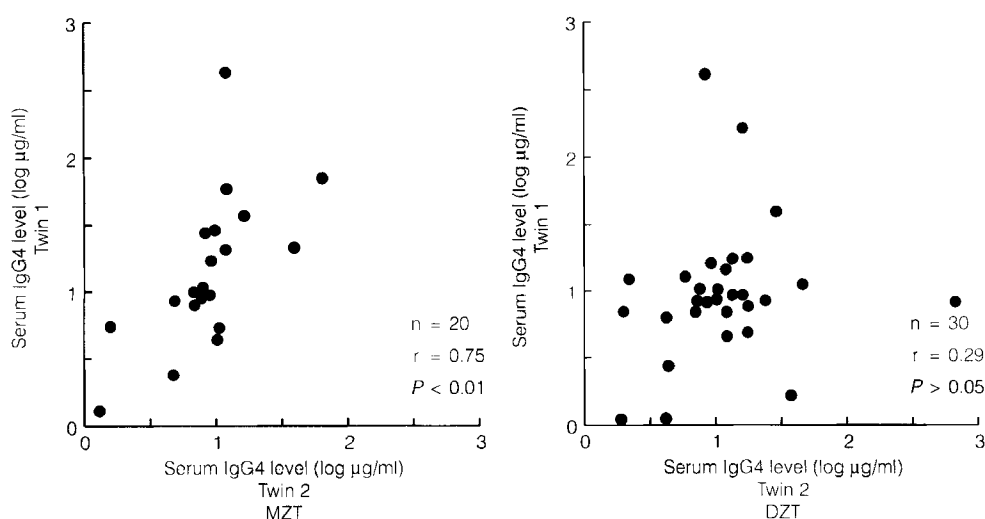


Fig. 3. Correlation between serum IgG4 levels in 20 monozygotic twin (MZT) and 30 dizygotic twin (DZT) pairs.

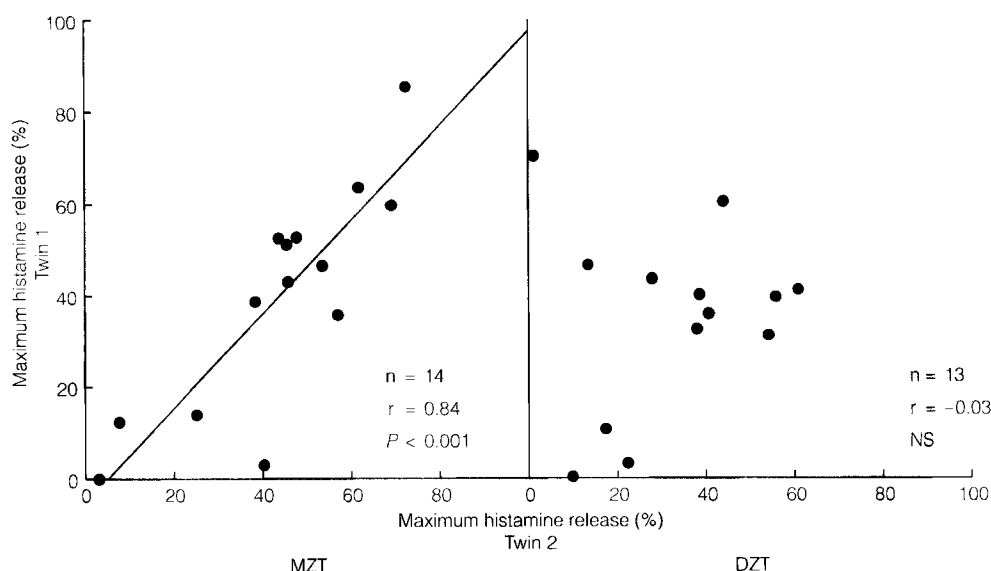


Fig. 4. Correlation between maximal percentage values of anti-IgE induced histamine release from basophils *in vitro* in 14 monozygotic twins (MZT) and 13 dizygotic twins (DZT) pairs. Adapted with permission from Marone et al. (36).

diseases, representing the final event responsible for pathophysiological changes and symptoms of allergy. It has been shown by Conroy et al. (30) and, more recently, by McGlashan (31) that histamine release from human basophils in response to anti-IgE is not related to serum IgE levels, but to the absolute quantity of IgE antibody present on these cells when stimulated with anti-IgE or specific allergen. Thus, subjects with an identical IgE response may possibly show different basophil mediator release depending on this intrinsic cellular property, defined as 'releasability' by the pioneer work of Lichtenstein and Conroy in this field (32). It is conceivable that the concept of releasability can also apply to other inflammatory cells, such as eosinophils (33, 34).

Despite the central regulatory role of inflammatory cell releasability in the pathogenesis of atopic diseases, very few data are available on the environmental factors affecting this mechanism and no extensive studies have been carried out to investigate whether eosinophilic inflammation is under genetic control.

We have investigated IgE-mediated (anti-IgE) and non-IgE-mediated (f-methyl-leucyl-phenyl-alanine; calcium ionophore, A23187) basophil releasability in 14 monozygotic twin pairs aged 25.7 ± 2.5 years and 12 dizygotic twin pairs aged 17.8 ± 0.7 years (35, 36; Fig. 4). A significant intra-pair correlation coefficient in anti-IgE-induced

histamine release was found in monozygotic twin pairs ($r=0.84$) but not in dizygotic twin pairs, the difference between intrapair variance in monozygotic and dizygotic twin pairs being statistically significant ($P<0.01$). No correlation was found between serum IgE levels and basophil anti-IgE histamine release.

Our data indicate that basophil releasability is under genetic control and is a relevant feature of an atopic constitution. Genetic and environmental influences on basophil releasability are probably different from those affecting IgE antibody response.

Hyperresponsiveness of target tissues

The response of target tissues to mediators released following IgE-mediated allergic phenomena is a fundamental event in determining the final clinical outcome in sensitized subjects exposed to specific allergens. Data on this subject are limited, and mainly deal with genetic and environmental influences on bronchial responsiveness (37), while factors governing the response of other tissues, such as skin, nasal tissues, conjunctiva and gut, are as yet largely unexplored.

Although several arguments have been brought in favour of a genetic basis for susceptibility to airways hyperreactivity, this matter is still debatable. Further studies are needed to investigate the effects

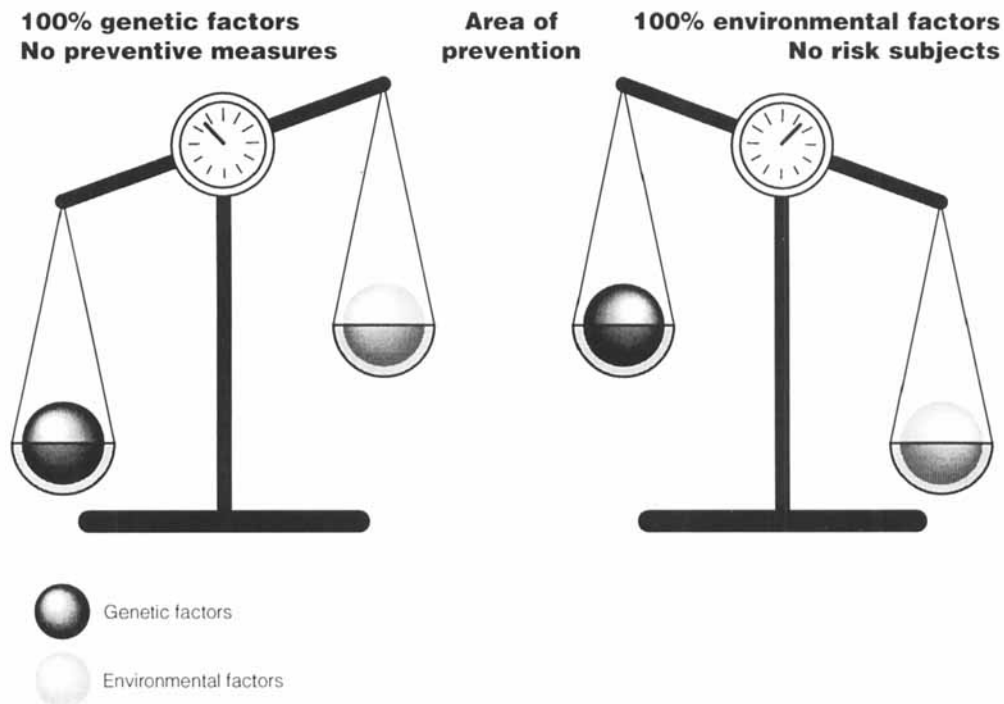


Fig. 5. The relative role of genetic vs environmental factors in the spectrum of human diseases.

of genetic and environmental influences on the complex neural mechanisms regulating tissue organ hyperreactivity (5).

Impact of genetic and environmental factors on preventing allergic diseases

The pathogenesis of human diseases may be viewed as a balance between genetic and environmental factors, with the relative prevalence of each factor determining the disease of the sufferer (Fig. 5). If preventive measures are considered, it will be appreciated that prevention is difficult in diseases at both ends of the spectrum, whether genetic or environmental factors are 100% responsible for pathogenesis. When genetic factors are 100% responsible for disease, no preventive measures are possible, as pathogenetic factors are carried chromosomally. When environmental factors are 100% responsible for disease preventive measures might be applied, but it is impossible to identify those subjects at risk from the disease. Thus, preventive steps are most effective in diseases in which genetic and environmental factors both have a role. In such diseases, adequate control of the relevant environmental factors can be made in subjects known to be genetically at risk from such conditions. This is the case in allergic diseases, and results from studies of these conditions may provide useful information for a practical strategy of prevention of allergy. Data from such studies indicate that the atopic constitution may be considered as an 'uncommitted' susceptibility characterized by the ability to produce high levels of IgE and IgG4, and to up-regulate inflammatory processes. The environment seems mainly responsible for inducing specific sensitization and the involvement of various target tissues.

A tentative strategy of prevention might comprise:

- identification of asymptomatic subjects who show clinical markers of atopy
- application of measures of environmental control in these subjects based on the avoidance of allergens and conditions which may facilitate specific organ involvement.

Detection of subjects at risk

As high levels of IgE production appear to be a major factor in allergy, the presence of a family history of atopy may be the most easily detectable feature for the identification of subjects at risk of allergic disease (26, 38).

The importance of high levels of total IgE in cord serum has recently been stressed by several groups (38–40). Such high levels appear to be strongly indicative of the subsequent development of atopic disease. High levels of IgE have been reported in healthy children, and were detectable for a varying period before clinical sensitization and symptoms (26). In our studies of twins, several healthy twins had high serum IgE and detectable amount of specific IgE antibody. Unpublished results of a six-year follow up study showed that three out of 20 of these subjects developed clinical allergy, while none of 20 control twins matched for sex and age and without high IgE levels, specific IgE antibodies or a family history of atopy, experienced allergic diseases during the same period of time.

Several clinical and immunological abnormalities, such as the Th2 phenotype, recurrent respiratory infections, T cell defects and a transient deficiency of secretory IgA, have also been associated with the subsequent development of a high IgE response and allergy. Possible markers for subjects at risk of allergic disease are shown in Table 1 (39, 40).

With reference to complement deficiencies, in our twin studies (18), twins with clinical allergy had mean C2 serum activity which were lower than apparently healthy twins and healthy controls. A strong genetic effect was also shown for both C2 and C4. Some apparently healthy twins had levels of C2 activity as low as their affected sibling. These observations seem to suggest that reductions in C2 levels are not a consequence of the allergic disease, but may have a primary genetic origin. Prospective studies are underway to evaluate whether reduced C2 levels may be a predisposing factor to allergy.

It has been suggested that the IgE response to purified antigens may be linked to well-defined phenotypes of polymorphic systems, mainly in the

Table 1. Markers for the detection of subjects at-risk for allergic diseases

Direct markers	Indirect markers	Genetic markers
• Family history of atopy • High IgE levels in cord blood or serum during first years of life • Positive skin test or RAST in absence of clinical symptoms	• Th2 phenotype • Recurrent respiratory infections • Immune deficiencies (T cell defects, IgA defects, C2 defects)	• Linkage with particular phenotypes of polymorphic systems, such as HLA • Specific probes for allergy genes, such as the cytokine gene cluster on chromosome 5

Table 2. Measures of environmental control in subjects at-risk for allergy which may aid in the prevention of allergy development

- Prolong breast feeding and introduce solid food into diet late
- Reduce levels of house dust mites and moulds, such as in mattresses, carpets and air-conditioning systems
- Avoid contact with pets
- Avoid active and passive smoking
- Control occupational environment

HLA region. Prospective family studies of subjects with at-risk phenotypes may yield interesting results.

The most promising development in the investigation of genetic involvement in allergy is the recent introduction of molecular biology techniques. These may allow the identification of the genes involved in allergic diseases, such as the cytokine gene cluster on chromosome 5.

Control of the environment

Several studies have suggested that early contact with allergens may be of crucial importance in inducing sensitization and symptoms in subjects at-risk for allergy. It is interesting to note that the month of birth may be relevant for the type of sensitization which subsequently develops in at-risk subjects. Parental smoking and dietary regimen has also been said to play a major role, and prolonged breast-feeding has been considered a useful preventive measure in newborns at-risk for allergy (40). Although the subject is still controversial, with some authors speculating that preventive measures may only postpone, but not reduce, the subsequent development of allergy, practical environmental control measures (Table 2) should stimulate further prospective investigations in this field.

Conclusions

The molecular study of allergic diseases has brought several advances in the understanding of the mechanisms causing hypersensitivity and allergic symptoms. Epidemiological studies should now be made, in addition to genetic and environmental investigations, by separating the heterogeneous group of 'allergic diseases' into well defined conditions studying each one. It is conceivable that the final picture of allergic disease which will come from the assembly of these separate studies of allergic conditions would provide new epidemiological classifications of allergy, improved understanding of the pathogenesis of these conditions, and more accurate diagnosis, treatment and prevention of allergic diseases.

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