

Review

Genetics of atopy

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J. M. Hopkin

Osler Chest Unit, Churchill Hospital, Oxford, UK

J. M. Hopkin, Osler Chest Unit, Churchill Hospital,
Oxford OX3 7LJ, UK

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Atopy, the state of allergic response to common environmental antigens, is a very common disorder which results from interaction between genetic, developmental, and environmental factors. It is both polygenic and heterogeneous in its origin. Most atopics are allergic to more than one common environmental antigen, and this introduces the concept that the causation of atopy occurs at a variety of levels; a) generalized hyper-IgE responsiveness; b) IgE response to specific allergens or epitopes; c) clinical disease expression. The predominant influences acting at each stage are likely to differ; therefore, the clinical or immunological phenotype utilized in any study of cause will itself determine what factors may be discovered. There is therefore no single definition for atopy, and the principal requirements for studies are that the criteria utilized are plainly recorded and stated.

There are clear indicators of strong environmental factors. It is evident there would be no atopy in an environment with minimal antigen exposure. Studies on populations of similar ethnicity but varying culture/lifestyle show great variations in the prevalence of atopy (1). "Westernization" is associated with an increased risk of atopic disorder of some 2–3-fold (2–4). Migrant studies support the cultural/lifestyle effect since immigrants rapidly acquire the risk of atopy of their new home, e.g., Tokelauans in New Zealand (5) and Asians and West Indians in Britain (6). Within single communities, increasing prevalence and severity of atopic clinical disorders have been noted in the past 20–30 years within single communities (7, 8). Critical analyses of these trends indicate that increased awareness or changes in diagnostic habits cannot account for the changes. All of these studies therefore point to environmental

change(s) associated with Westernization which have a profound impact on the risk of disease. These urgently require discovery.

Twins and familial aggregation

The plainest evidence of an important genetic effect on the development of atopy is derived from twin studies. All reports point to an important genetic effect (9–12); but a recent North American study, on twins reared together and apart, provides the most informative data (13). Whether reared together or apart, monozygous twins showed significantly greater correlation coefficients for total serum IgE levels which indicate that approximately 50% of the variation in total IgE levels can be attributed to genetic factors. The monozygous twins showed a high concordance (71%) for IgE response to *any* one of more common allergens; but the discordance of 29% is a reminder of significant environmental interaction. The data indicate that there are important genetic influences on the phenotype of generalized IgE responsiveness. But the genetic effects on allergen-specific sensitization and clinical disorder were significantly weaker; e.g., concordance for sensitization to grass pollen (*Phleum pratense*) was approximately 15% in dizygotic twins and less than 40% for monozygotic twins (13).

There have been many studies on familial aggregation of atopy which support these conclusions. The risk for developing atopic disorder is clearly enhanced when other first-degree relatives are affected (14, 15), and some studies emphasize the enhanced risk to children associated with maternal atopic status (16).

These various studies indicate clearly that atopic

disorder is due to the interaction of genetic and environmental factors but do not indicate how many factors there are for each phenotypic category of atopy and how interactive these may be. The outbred nature of man and the range of his culture and environment indicate that heterogeneity is most likely, in which the factors underlying the phenotype in different individuals will differ significantly. There will also be many cases where a significant predisposing genetic variable is present but insufficient environmental interaction to cause the phenotype (variable genetic penetrance), and others where substantial environmental factors may cause the atopy phenotype even when genetic factors present are not important (phenocopies).

Approaches to molecular genetic analysis

This multifactorial and heterogeneous nature of atopy, as well as variable penetrance and phenocopies, makes precise genetic analyses difficult.

The potential benefits include the possibility of predictive genetic assays. More importantly, proteins that are genetically variant in their quality or quantity and which entail risk of disease, will be recognized. For those that have a major population effect there is the prospect of pharmacological intervention targeted on the "variant" molecular behaviour and tailored to return this to "normal".

Segregation analysis (or identification of the pattern of inheritance) is an important part of any genetic analysis, but in a very common, multifactorial, and heterogeneous disorder, this is a hazardous undertaking, and so it has proved in atopy. Many studies have reported on the inheritance of IgE levels and clinical phenotypes, and the results are incoherent and confusing – with suggestion of dominant, recessive, and polygenic models (15–18).

Candidate genes

Application of the interweaving techniques and concepts of modern genetics, molecular and cell biology, has made possible radical and relatively efficient investigation of the genetics of common disorders (19). In atopy a range of "proallergic/inflammatory" protein products have been recognized from various cells including mast cells, eosinophils, and lymphocyte subtypes; for many, their genes have been cloned and sequenced (20–22). Each – for example, the interleukin IL-4 or its receptor, which promotes switching from IgM to IgE in the B lymphocyte – might be a "candidate gene" for atopy, and have variants/mutants within the gene or its controlling elements to cause quantitative or qualitative changes in its protein, and thereby differentially inherited risk of atopy. When the genetic

sequence is known, variants can be readily sought by sequence analysis and their importance tested either by epidemiological surveys of association between variants and disease or by functional assays. But the list of potential "candidate" genes is very long, and promoting the case of one rather than another as a likely source of significant genetic variants may be specious.

Genetic linkage

"Reverse genetics" or "positional cloning" offers an unbiased approach, whose application has now been greatly enhanced by the recent identification of very large numbers of polymorphic, highly informative markers spaced at appropriately short intervals along the human chromosomes (23, 24). For example, the exclusive use of variable dinucleotide repeats, examined by automated DNA amplification and electrophoresis, has led to a successful delineation of the major genetic effects underlying type I diabetes (19). The approach is equally valid for atopy; it is based on the simple principle that "atopy loci" will be identified by coinheritance of disease with defined genetic markers, because of their chromosomal proximity (genetic linkage). Establishing a chromosomal location is succeeded by refined genetic linkage mapping (using a larger number of geographically concentrated polymorphic genetic markers) before testing structural genes at the site as candidates. Definition of variants within the coding sequence or controlling elements of a structural gene and the epidemiological demonstration of association with the disease is the immediate goal, before functional studies are conducted. Note that heterogeneity, variable penetrance, and phenocopy effects hamper fine linkage mapping in atopy; but amalgamation of linkage information with molecular biological information on atopy "candidate" genes is a counterbalancing advantage.

What type and scale of family resources and what form of analysis are appropriate for conducting "reverse genetics" for atopy – a common heterogeneous disorder, with undefined modes of inheritance and variable penetrance. The first makes genetic admixture effects likely in large rambling families. All three make standard genetic linkage approaches, by lod scores, difficult and potentially misleading (25). The method of affected sibling-pairs (26, 27) offers substantial advantages under these circumstances because mode(s) of inheritance does not need to be assumed, and because admixture and variable penetrance effects are minimized. Analysis for genetic linkage is reduced to a simple test of whether atopy-affected siblings share parental alleles at particular loci beyond the expected or random proportions of 50% for any single allele for a dominant genetic ef-

fect, or 25% for two alleles for a recessive effect. Because the analysis entails searching for excess allele sharing from some 200 polymorphic loci in a genomic search, chance variations from 50% and 25% can frequently occur. The possibility of making type I (false positive) errors may be countered by using large numbers of sibling-pairs and conducting studies in duplicate. Sibling-pairs can be chosen to share whatever phenotype is of interest; this may have a decisive impact on the likely linkages to be discovered.

Data available from molecular genetic studies

Allergen-specific reactions; cognate immune mechanisms

Twin studies do not suggest that genetic variables are predominant in the determination of allergen-specific responses (13). There are clear indications of environmental effects; e.g., allergen dosage influences the risk of specific sensitization to house dust mite (28).

But there are molecular complexes where genetic variants might significantly contribute to differential risk – the histocompatibility (HLA) complex (in particular, HLA-class 2 molecules) and the T-cell receptor (TCR) complex. Both are highly polymorphic and are crucially involved in cognate interactions between antigen-presenting cells and the helper T cell.

HLA loci (both class 1 and class 2 on chromosome 6p) have been extensively investigated in relation to IgE responses (29). Experiments on the isolation of allergen-specific T-cell clones suggest that HLA-DR B1, B3, and B5 restrict recognition of certain *D. pteronyssinus* antigens (30). Following the original observations of Levine et al. (31), a number of genetic association studies have investigated the relationship between particular HLA class 1 and class 2 types in case-control studies of specific allergen responsiveness (32–34). When low molecular weight, highly purified and characterized subfractions of allergen are investigated, associations have been shown with class 2 types; elevated IgE levels to short ragweed (*Ambrosia artemisiifolia*) pollen allergens Amb a V, Amb t V, and Amb p V have been documented with HLA-DR2/Dw2. Further investigation showed that sensitized individuals had DR B1 and B5 sequences and suggested that DR $\alpha\beta$ 1 heterodimers were the principal HLA-class II molecules mediating the presentation of Amb a V (35). But HLA-class II haplotypes are not clearly related to likelihood of response to whole allergen or clinical disease (36). Formal genetic linkage studies on HLA and atopy in families have also been conducted. An early study excluded linkage between the HLA complex and total serum IgE levels (37). In a recent study HLA-DR and HLA-DP loci were

genotyped in 83 families who had been serotyped for IgE responses to six major aeroallergens; a modest excess of sib-pair sharing was shown for reactions to cat antigen and the mould, *Alternaria* (38).

Overall, there are therefore only weak effects of HLA polymorphism on the risk of IgE sensitization to whole complex allergens and the risk of clinical disease; this may result from the obscuring effects of the vagaries of allergen exposure, the complexity of epitope arrays associated with complex allergens (39), and the possibility that there may be molecular “promiscuity” for both peptide binding and T-cell recognition (40).

Studies on T-cell receptor (TCR) genetic variants (41) and their relationship to atopy are less well advanced. One genetic linkage study, examining IgE responsiveness to common aero allergens and highly polymorphic microsatellite repeats related to the TCR α/δ complex on chromosome 14 and the TCR- β gene complex on chromosome 7, suggests genetic linkage to the α/δ complex (42). Evidence of increased sib-pair sharing for TCR α/δ -related microsatellite alleles was shown for both specific responses and elevated total serum IgE in families from both the UK and Australia; it is as yet unclear whether the observed linkage to chromosome 14 is necessarily allergen specific.

Nonspecific or noncognate hyper-IgE responsiveness

An Oxford research group has recorded genetic linkage between atopy (defined as elevated total serum IgE levels or specific IgE response to any one of more common allergens) and chromosome 11q (43). The group have made the following observations: linkage of atopy to 11q occurs in only a proportion of their families (derived mainly from Oxfordshire) but perhaps in as many as 60% (44); the linkage is confined to maternal chromosomes (45); and strong genetic association has been observed between coding sequence variants of *FceRI*- β (Leu 181 and 183) at this chromosome 11 location and atopy by maternal descent (46). The maternal genetic linkage of atopy on chromosome 11q is of interest though its origins are obscure. Independent epidemiological surveys emphasize the enhanced risk of atopy in children of affected mothers compared with fathers (16, 47). Phenotypic modification of the foetus or neonate by contact with the atopic mother is one possibility, but another is the phenomenon of genomic imprinting. In the latter, alleles at particular autosomal loci (or non-sex chromosome) are silenced in a parent-specific manner for one generation at either spermatogenesis or oogenesis (48).

Replication of the Oxford findings has been variable and has fuelled controversy (17, 25). At least

four groups, each studying a relatively small number of families, have reported null or negative genetic linkage between atopy and chromosome 11 (49-52).

Two other groups, from Japan and The Netherlands, have found replicated linkage between atopy and chromosome 11 – using lod score methods in a set of extended families (53) and by sib-pair analysis, respectively (54). It remains to be seen whether all the replication difficulties can be attributed to the undoubted heterogeneity that underlies the genetics of generalized atopic IgE responsiveness. The defining of structural variants (involving transmembrane domains) within *FcεRI-β* at the 11q location, and their strong association with atopy by maternal descent support the linkage; similar structural variants in other receptors of 7-helix bundle configuration have been shown to have significant functional effects (55).

Since interleukin (IL-4) plays an important role in determining the switch from IgM to IgE in B lymphocytes, the gene for this protein and contiguous loci for IL-13 and IL-5 on chromosome 5 have been the focus of a candidate gene study (56). In this, sibling-pairs who shared low IgE levels have been studied among 11 Amish families in North America. Using polymorphic microsatellite markers within the interleukin cluster region on chromosome 5, evidence for linkage to the IL-4 locus was presented; segregation analysis suggested a dominant genetic effect. It should be noted that the method of sibling-pair analysis applied to these families, in which multiple overlapping sib-pairs were analysed, is most suitable for non-inbred families; the authors noted that their Amish families did show inbreeding effects with a mean inbreeding coefficient slightly greater than second cousins. Therefore, testing for replication of this linkage, in non-inbred and in non-Amish families, will be of great interest.

End-organ effects

Few modern genetic studies, with appropriate molecular methods, have been applied to organ-specific atopic disease.

One organ-specific locus of interest has been the gene for the human β_2 adrenoreceptor. A search for polymorphisms in its gene led to the identification of a number of variants including a glutamine to glutamic acid substitution at position 27 (57). A series of preliminary observations suggests this variant might influence severity of asthma (58, 59): *in vitro* studies on muscle cell lines show that the β_2 adrenoreceptor, glu 27, downregulates to a lesser extent than gln 27; individuals homozygous for glu 27 show lower airway reactivity in a physiological survey of asthmatic subjects; genetic linkage sug-

gests that two loci on chromosome 5 may contribute to atopic asthma, and one of the microsatellite markers is assigned to a region containing the gene for the β_2 adrenoreceptor. More detailed studies will clarify the potential importance of this locus.

Conclusions

Atopy is a common and heterogeneous condition in which genetic and environmental determinants interact. The environmental factors are of great importance. The possibility that Westernized lifestyles deliver some form of adjuvant(s) for the development of IgE responses needs urgent investigation.

Genetic variants have an important impact on the development of atopy and can be viewed at three levels. For *allergen-specific IgE responses*, there is evidence that variants at both HLA and TCR α/δ complexes may to some degree influence risk of sensitization. For *generalized hyper-IgE responsiveness*, the indications are that genetic factors are strong but also heterogeneous; data support the influences of variants of *FcεRI-β* on chromosome 11 and of IL-4 (or a closely related locus) on chromosome 5. For *end-organ disease*, there are preliminary suggestions that variants of the β_2 adrenoreceptor may enhance bronchial reactivity.

Further painstaking studies are required to clarify the various genetic effects underlying atopy. If most of the genetic risk can be attributed to a reasonably small number of loci, there are real prospects for interesting developments in diagnostics and therapeutics.

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