INTRODUCTION

Asthma is an increasingly common disease in the developed world (1–3). In the United States, the second National Health and Nutrition Examination Survey (NHANES II) (1976–1980) estimates of asthma prevalence (4) were 6.9 percent for whites and 9.2 percent for blacks. Most current definitions of asthma (5) characterize it as a (rapidly or slowly) reversible narrowing of the conducting airways of the lungs, usually associated with evidence of airway wall inflammation and eosinophilia (6, 7). Acute and delayed bronchoconstriction can be precipitated by inhalation by the asthmatic individual of a number of agents, such as ozone, cold dry air, proteins (mainly enzymes), or low molecular weight chemicals, and presents clinically as development (and resolution) of dyspnea, wheezing, and cough.

Asthma is clinically heterogenous, but the bulk of cases tend to be characterized by childhood onset, markers of allergic hypersensitiveness such as wheezing and bronchoconstriction following inhalation of antigen (allergen), and elevated levels of total serum immunoglobulin E. There may be remission of symptoms for up to 20 years after childhood, so that earlier mild episodes may be forgotten by the individual, though not by the parent (8, 9). Most genetic studies have concentrated on this type of asthma (i.e., allergic or extrinsic asthma). However, a few studies have attempted to determine if different genes might be acting in the 20 percent of asthmatics who do not exhibit any signs of allergy (i.e., nonallergic or intrinsic asthma).

Because of the intermittent nature of asthma symptoms, some difficulties in standardizing the diagnosis of asthma for epidemiologic purposes have been encountered. Currently, there is increasing emphasis on biologic markers of disease, such as nonspecific bronchial responsiveness or sputum eosinophilia, to confirm the diagnosis.

There has been long-standing interest in the genetics of other phenotypes that tend to be associated with asthma. These include the other two diseases of the "atopic triad," allergic rhinitis and atopic dermatitis, and the immunologic markers of atopy such as serum immunoglobulin E level (both total and allergen-specific), skin prick test response to allergen, and, more recently, T-cell receptor repertoires. Indeed, far more genetic analyses of total serum immunoglobulin E concentration have been performed than of asthma. Several family studies of nonspecific bronchial responsiveness have also been carried out.

General considerations

There are several questions a genetic epidemiologic model of asthma and atopy must address:

1. The nature of the interaction between environmental and genetic risk factors. Studies in Africa (10) and Oceania (11) suggest that asthma and other atopic diseases increase markedly with Westernization, possibly in concert with a fall in mean total serum immunoglobulin E concentration (12, 13). The critical exposure has been variously hypothesized as being to high levels of potent aeroallergens, such as the house dust mite (14, 15), to increased dietary sodium (though an effect on allergic sensitization is less plausible) (16), to exposure (17) or lack of exposure to pathogens (18), or to air pollution (19). Nevertheless, the family studies reviewed below suggest that an individual must be genetically predisposed to respond to the exposure.

2. The selection pressures that kept genes predisposing to disease common in the preindustrial environment. One hypothesis, that the atopic phenotype may protect against parasitic disease, has been previously reviewed (20). The low prevalence of allergic disease in less industrially developed societies sug-
gests that the costs of carrying such genes in the
population may not have been high.

3. The clinical heterogeneity of asthma. It is attrac-
tive to hypothesize that genetic heterogeneity may
underlie this condition. As reviewed below, genetic
studies to date have supported both "lumping" and
"splitting." A related concept is one of genetic het-
erogeneity of atopic disease, such that specific genes
(rather than specific environmental exposures) might
determine why individuals might develop asthma as
opposed to hay fever or atopic dermatitis.

FAMILY STUDIES

Earlier family studies

Familial aggregation of asthma was recognized his-
torically (21, 22). Salter, in his classic text (1860),
states "Is Asthma Hereditary?—I think that there can
be no doubt that it is . . . the number of cases in which
there is a family history of asthma is greater than will
be found . . . on the mere doctrine of chance . . . Out of
thirty-five cases . . . I find distinct traces of inheritance
in fourteen . . . two cases out of every five" (23, p. 109).

Following the rise of Mendelian genetics, Robert
Cooke performed two large studies of the inheritance
of atopy, one reported in 1916 (24) and the other in
1924 (25). The first study examined asthma, hay fever,
urticaria, angioneurotic edema, and acute gastroenter-
itis in 504 subjects. In the second study, only asthma
and hay fever were used to define atopy in a further
462 individuals. All of these subjects exhibited posi-
tive intradermal tests. A control series of 115 non-
atopic probands was also recruited. Family history of
atopy was determined by interviewing the proband
"and in many cases, other members of the family" (25,
p. 522). This is an early example of a "Weinberg
proband-control" study, a case-control study compar-
ing risk of disease to relatives of a case to that of a
control. A family history of atopy was present in 48.4
percent of cases in the 1916 study and in 58.4 percent
of cases in the 1924 study. Only 7 percent of the 115
normals reported a family history of atopy (crude odds
ratio (OR) = 19; 95 percent confidence interval (CI)
9–39).

Cooke used these findings to buttress his classic
definition of atopy as "[a] sub-group of hypersensitiv-
essence restricted to the hay-fever and asthma
group [of diseases]. . . . inherited, subject to a dominant
gen[e] . . . " (26, pp. 166, 168).

The numerous family studies of atopy performed in
the 1920s and 1930s generally replicated the finding of
familial aggregation, but often found a simple domi-
nant hypothesis untenable. Wiener et al. (21), for
example, proposed a plausible codominant (or additive)
model, with a decreasing age at onset with increasing
number of disease alleles.

The large Weinberg study of Schwartz (27), per-
formed in the 1940s, examined both idiopathic asthma
(191 subjects) and a particular occupational asthma
(baker's asthma). These subjects were compared with
200 controls (polio patients and medical students).
Schwartz interviewed 2,352 relatives and obtained
questionnaire data from a further 1,463. The asthma-
tics underwent examination of peripheral blood, in-
cluding eosinophil count, and allergen skin testing.
These, along with the history, were used to dichoto-
mize the asthma cases into atopic and nonatopic.
Atopic relatives and a small number of willing healthy
relatives also underwent skin atopy testing and eosin-
ophil count.

Schwartz concluded that asthma and atopic disease
aggregated within families, and that some pedigrees
were consistent with a dominant hypothesis. A critical
finding was that there was no difference in risk of
atopic disease between the relatives of allergic and
nonallergic asthmatics. Similarly, no differences were
found for the prevalence of skin atopy or eosinophilia
in these two groups in either unaffected relatives or
those manifesting atopic disease. For asthmatic rela-
tives of allergic and nonallergic asthmatic probands,
for example, the prevalences of a positive allergen
skin test were 20/30 and 29/39, respectively (p = 0.5).
Finally, the probands with baker's asthma and their
families were not found to differ significantly from the
other asthmatic series, thus confirming that a genetic
predisposition was necessary to develop this occupa-
tional disease (gene by environment interaction).

The studies discussed thus far demonstrate familial
correlations between asthma, hay fever, and atopic
dermatitis. Although such coaggregation was con-
firmed in the 361 families examined by Schnyder (28),
an important additional finding was that particular
atopic diseases tended to "breed true," with childhood
astmatic dermatitis being found more frequently in fam-
ilies of dermatitis probands than respiratory allergy
probands. Similar patterns have been seen in more
recent family (13, 29-32) and twin (33) studies. The
inheritance of atopy in families "strongly support[ed]
the hypothesis of a single, autosomal dominant gene
with reduced penetrance (40–50%)" (28, p. 90).

Sibbald et al. (34) described familial risks for 77
asthmatic children (404 relatives) and 87 controls (302
relatives) recruited via a single general practice. All
probands and approximately 25 percent of their rela-
tives underwent skin prick testing. Diagnosis in pro-
bands was reached via clinical examination and in
relatives by interview. This allowed asthma in all the
proband and a subset of relatives to be divided into allergic and nonallergic types.

The prevalence of asthma in the relatives of atopic asthmatics was slightly higher than that among relatives of nonatopic asthmatics. The authors also noted that “in relatives of asthmatics, the prevalence of atopic asthma exceeded the prevalence of nonatopic asthma, irrespective of the atopic status of the proband” (34, p. 672), but this difference is of marginal significance ($\chi^2 = 4.88$, $p = 0.09$, compared with distribution in control families). Positive skin tests were more common in relatives of atopic asthmatics compared with all controls. Closer examination reveals that this is due largely to the relatives of the nonatopic controls, where the prevalence is significantly lower (42 percent) than that for the relatives of the atopic asthmatics (60 percent). The difference between risk to relatives of atopic and nonatopic asthmatics (36 percent) is almost significant ($p = 0.07$), but the small number of nonatopic asthmatics in the study prevents more being made of this. The authors concluded that asthma and atopy are inherited independently, but atopy increases the risk of expressing the asthmatic trait.

Recent studies

A large number of recent epidemiologic studies have collected information on family history of asthma as a risk factor for disease. Most, however, are not as sophisticated as the studies reviewed above, in terms of the depth of information collected on relatives, and merely confirm the magnitude of the parent-offspring or, less often, sib-sib recurrence risk as being approximately twofold larger than the population baseline risk. However, a few complex segregation analyses have been published.

Complex segregation analysis uses maximum-likelihood methods, implemented in computer programs such as POINTER (Population Genetics Laboratory, University of Hawaii, Honolulu, HI), PAP (Pedigree Analysis Package) (Department of Human Genetics, University of Utah, Salt Lake City, UT), and SAGE (Statistical Analysis for Genetic Epidemiology) (Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, OH), to test the hypothesis that aggregation of a trait in a family could be due to the action of a single major locus. The alternative model that the single major locus is often compared with is a polygenic model, where multiple genes, each of small effect, underlie familial resemblances. For a dichotomous trait, the usual polygenic model is the multifactorial threshold model, which assumes multiple genes of small effect act multiplicatively on risk (act additively on the probit of risk). A “mixed model” posits a single major locus acting in concert with a polygenic background. The heritability is an index often referred to when discussing these models and represents the proportion of population trait variance estimated as due to genetic effects (often on the probit scale). In conventional family studies, but less in the classical twin or adoption study, it is difficult to differentiate the effects of polygenes from those of the unmeasured shared family environment.

Several studies of nonspecific bronchial responsiveness, that is to inhaled methacholine or histamine in relatives of asthmatic probands, were performed in the mid 1980s. The interest in these is that increased nonspecific bronchial responsiveness in the absence of clinical asthma or allergic disease might indicate that the relative is carrying an asthma predisposing genotype.

The largest of these studies, by Townley et al. (35), described 51 families (467 individuals) ascertained through an asthmatic, 32 (291 individuals) families ascertained through a nonatopic control, and in 26 cases for a negative family history of allergic disease. Methacholine responsiveness was found to be bimodally distributed in the asthma families, a finding that might be consistent with the action of a major gene (or an all-or-nothing trait or disease state). However, segregation analysis strongly rejected a single major locus model, although familial aggregation was supported. A mixed model was not fitted however. Smaller studies (36–40) also replicated the bimodal distribution of nonspecific bronchial responsiveness, and demonstrated asymptomatic nonspecific bronchial responsiveness to be increased in relatives of asthmatics. Most recently, in the British families described below (41), the heritability of nonspecific bronchial responsiveness (log $PD_{20}$ (provocative dose of agent that caused a 20 percent fall in lung volume) to histamine) was estimated at 27 percent (95 percent CI 13–40), very similar to that seen in the Busselton, Western Australia, study (log $PD_{20}$ to methacholine) at 28 percent (95 percent CI 17–39) (42).

There have been many recent studies of total serum immunoglobulin E concentration (42–58). Most of these conclude that immunoglobulin E level is highly heritable (60–70 percent), more so than nonspecific bronchial responsiveness, and single major locus models with high allele frequencies often fit the pattern of familial transmission. Borecki et al. (59) described a bivariate segregation analysis of atopic disease (asthma or eczema) and total serum immunoglobulin E. The 173 Saskatchewan families originally described by Gerrard et al. (45) were used, in which the prevalence of so-defined atopy was 21 percent. This sample was unselected for a history of atopic disease. A single
major locus model was found to best fit the data, with an estimated allele frequency of 42 percent, the gene acting in either an additive (intermediate) or a recessive fashion for liability to clinical disease, and as a recessive for serum immunoglobulin E. No unshared environmental factor unique to atopy (as opposed to one common to total serum immunoglobulin E concentration) was detected.

Mrazek et al. (60) performed segregation analysis using POINTER on 145 families ascertained via a female asthmatic proband. Significant familial aggregation was detected, and under the polygenic model the heritability was 0.96 (asymptotic standard error (ASE)) = 0.05). The best single major locus model was a common recessive model, with a homozygote penetrance of 62 percent, and 1 percent for the other genotypes, a gene frequency of 0.22, and a proportion of phenocopies estimated at 17 percent. This model gives a population prevalence for asthma of 3.5 percent.

Lawrence et al. (41) reported a study of 131 families (631 completely phenotyped individuals) from Southampton (United Kingdom). Asthma was represented as a combination (first principal component) of a respiratory questionnaire score (including results from a video questionnaire) and level of bronchial responsiveness to histamine inhalation. The phenotypic correlation between asthma score and total serum immunoglobulin E concentration was 0.4. Heritability of the resulting asthma score was approximately 28 percent, while that for total serum immunoglobulin E concentration was 61 percent.

Segregation analysis using POINTER was supportive of a dominant gene for asthma, with no residual heritability (increasing allele frequency 0.24). Similar results were obtained when fitting a two-locus model (with one locus acting as a pseudopolygene) via the program COMDS (61). The models fitted to bronchial hyperresponsiveness alone and wheezing (questionnaire) alone differed in having gene frequencies closer to 0.5, and acting in a recessive fashion.

A segregation analysis of physician-diagnosed asthma in the Tucson (Arizona) Children's Respiratory Study was presented by Holberg et al. (62). Diagnosis was available via questionnaire for a total of 3,369 individuals in 906 nuclear families. Class D regressive logistic segregation analyses were performed, with age at onset included in the penetrance function. Strong familial aggregation was confirmed. A single major locus model did not fit the data well, with the closest fitting Mendelian model being of a common recessive gene explaining only part of the aggregation. Ethnicity and personal and passive smoking did not contribute detectably to the residual correlation between family members.

These segregation analyses suggest that a major gene could be involved in the etiology of asthma. However, different “best” genetic models were obtained in the studies. A similar finding for total serum immunoglobulin E concentration has been interpreted as evidence for genetic heterogeneity, that is multiple, individually uncommon, genes of large effect. The multivariate analyses are most consistent with the action of genes specific to particular forms of atopic disease. Nonallergic asthma aggregates within families, but it is still unclear whether it is genetically distinct from allergic asthma.

TWIN STUDIES

The twin design has two main advantages over the conventional family studies described above: One is the estimation of the effects of family environment, which in other designs are confounded with genetic effects, and the second is the detection of nonadditive genetic effects (63), either dominance or epistasis, which otherwise may require the collection of reliable data on third-degree relatives (64). I will concentrate on the several large community-based twin studies of asthma reported in the literature.

Edfors-Lubs (65) and Lubs (66) reported results from a questionnaire study of 7,000 pairs of twins born between 1886 and 1925 from the Swedish Twin Registry. The monozygotic recurrence risk for asthma was 33.7 percent; that for the dizygotic twins was 8.6 percent. The large monozygotic:dizygotic risk ratio is consistent with strong dominance or epistasis. Under the multifactorial threshold model, the heritability of asthma in this study was 63 percent for asthma (95 percent CI 54–73 percent).

A similar study was carried out in the Finnish Twin Cohort, which contains 13,888 pairs of same-sex twins born between 1905 and 1957 and was assembled using centralized birth and death information (67). In the baseline questionnaire survey, monozygotic twin recurrence risks for doctor-diagnosed asthma ranged in the different sex and age groups from 32 percent to 87 percent, and the dizygotic risks ranged from 0 percent to 24 percent. Refinement of the asthma diagnosis was reported by Nieminen et al. (68) via linkage of the twin register with databases on hospital admission and asthma medication usage. Using this definition, the monozygotic male and female recurrence risks were 8.2 percent and 16.5 percent, respectively; for the dizygotic twins, 8.6 percent and 4.9 percent, respectively. The estimated heritability (multifactorial threshold model) combining the sexes was 36 percent (with broad confidence limits) (69).
In unpublished preliminary data from the Virginia Twin Registry (Eaves LJ, and coworkers, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia, 1990) for 4,310 twin-pairs (and 14,380 relatives), doctor-diagnosed asthma was reported by 5.5 percent of questionnaire respondents. Under the multifactorial threshold model the heritability of asthma was 54 percent.

Duffy et al. (33) describe a questionnaire survey of the Australian Twin Registry carried out in 1981. Responses were received from 3,808 twin-pairs. For wheezing, the monozygotic recurrence risks were 54.9 percent for monozygotic males, 42 percent for monozygotic females, and 21.8–24.0 percent for the three dizygotic groups, with no significant birth cohort effects. The monozygotic:dizygotic ratios are consistent with dominance in males but not in females; the heritability under the multifactorial threshold model was 60 percent for women and 75 percent for men. Multivariate genetic analyses of asthma, hay fever, and eczema replicated the finding of trait-specific genetic influences in addition to common genetic determinants (such as might underlie atopy).

In all these twin studies, the effects of family or household environment are estimated to be small or absent compared with the genetic contribution to familial resemblance. The estimates of heritability are consistent with those from other types of studies.

**LINKAGE AND ASSOCIATION ANALYSES**

The complexity of the immunologic network involved in the allergic response, and the great variety of pathogenetic mechanisms hypothesized for asthma, mean that there are numerous plausible candidate genes for this disease. Many of these genes overlap with other immunologic diseases. A number of such candidates have been examined, and more recently results of whole genome scans have been reported. Two types of genometric studies have been used. Allelic association studies test for correlation between a specific allele at a locus with the phenotype, such as asthma or nonspecific bronchial responsiveness. This can be performed using unrelated cases and controls (a procedure open to the possibility of confounding due to ethnic difference), or family material. Genetic linkage analysis by contrast requires pedigree data, and is performed either via maximum likelihood (decimal log likelihood ratio (lod score)) methods, or regression-based relative pair methods.

**Early studies**

The paper of Zieve et al. "On the linkage relations of the genes for allergic disease and the genes determining the blood groups, MN types and eye colour in man" (70), is the first of its kind. A sample of 66 nuclear families (383 individuals) was ascertained. Diagnosis of asthma, hay fever, urticaria, eczema, angioneurotic edema, and gastroenteritis was made by the investigators based on personal interview. Linkage analysis carried out using the methods of the time did not detect linkage to blood group or eye color. Reanalysis of the pedigrees using MLINK (71) and SIBPAL (Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, OH) actually finds weak hints of linkage to the ABO blood group (mean identity by descent sharing among affected sib-pairs is 0.61, \( p = 0.02 \)).

No further linkage studies were reported in the literature until 1985, when an abstract by Eiberg et al. (72) reported a maximum lod score of 2.07 between total serum immunoglobulin E concentration and esterase D (recombination fraction = 0.00, chromosome 13q14). Linkage to this chromosomal region was not replicated by Cookson et al. (73) but was by Daniels et al. (74).

**Linkage and association to the human lymphocyte antigen region**

The human lymphocyte antigen literature on asthma is quite extensive and inconclusive. Strong evidence of association between human lymphocyte antigen haplotypes and allergic sensitization to particular allergens exists, most notably ragweed pollen (75, 76) and house dust mite feces (77, 78). However, the bulk of studies find no evidence for linkage of asthma to the region with one exception (see table 1). Caraballo and Hernandez (79) examined human lymphocyte antigen segregation in 20 Columbian nuclear families (\( n = 107 \)) ascertained to contain two atopic asthmatic probands. All probands were allergic to *Dermatophagoides farinae* on allergen skin prick test. No associations between human lymphocyte antigen haplotypes and asthma were detected. In sib-pair analyses, there was evidence of linkage to asthma (\( \chi^2 = 21.9, p = 1.8 \times 10^{-5} \)). In several family studies published subsequently, no linkage has been found (80–82).

Allelic association between human lymphocyte antigen class I and II genes and asthma have often been reported (81–88). Because the alleles at the various human lymphocyte antigen loci are so numerous, these results are often vitiated by the large number of statistical tests required to detect the effect, and have been difficult to replicate (82, 88). A very recent paper by Moffatt and Cookson (89) has reported an association between the tumor necrosis factor-α gene (TNF,
6p21.3) and asthma (see discussion of Animal models below).

**Association with other chromosome 6 loci**

Platelet activating factor is a potent bronchoconstricting mediator. Miwa et al. (90) reported the results of biochemical analyses and a small family study of the enzyme platelet activating factor acetylhydrolase (recently mapped to chromosome 6p12–21 (91)), one of the two enzymes responsible for the degradation and resulting brief half-life of platelet activating factor in serum. Enzyme activity was assayed in 816 adults and 211 children. The frequency distribution of activity in the children was definitely bimodal, while the adult results were unimodal. There were 40 healthy subjects found to exhibit no acetylhydrolase activity at all. These results were shown to be consistent with a single major locus model.

Enzyme levels were next examined in 175 asthmatic children. Lower amounts of activity were associated with increasingly severe asthma. Complete absence of activity was found significantly more often in the most severe classes of asthma (asthmatics experiencing 10 or more skin prick wheals with a mean diameter 1 mm greater than the negative control, or a total serum immunoglobulin E more than two standard deviations above the population mean, or one or more positive allergen-specific immunoglobulin E assay (radioallergosorbent test) results. Four families contributed a maximum lod score of 5.24 at a recombination fraction of 6 percent. All the families gave a lod score of 6.39 at a recombination fraction of 10 percent—the other families, where cigarette use was high, were less informative.

The same group (92) described an analysis of 64 newly recruited nuclear families. These families were ascertained through children (under the age of 15 years) reporting eczema, hay fever, or asthma. The same diagnostic criteria for atopy described above were used. Under an assumption of equal recombination distance in both sexes, the maximum lod score was 3.8, but there was strong evidence for a male-female difference. Relaxing the equality constraint led to a maximum lod score of 5.2, with $\Theta_m = 0.18$ and $\Theta_F = 0.001$ (where $\Theta$ stands for recombination fraction between two genetic loci).

In an effort to explain this sex difference, Cookson et al. (93) described sib-pair reanalyses that examined sharing of maternal and paternal marker alleles ($n = 723$). Affected sib-pairs were significantly more likely to share a maternal chromosome 11 than a paternal chromosome 11, using any of several different definitions of affection. In families where the father was atopic and the mother nonatopic, the sharing of maternal alleles was 19/32 (0.59 percent, exact binomial 95 percent CI 0.41–0.76), which trends in the same direction as the previous results. The authors note that explanations for this include genetic imprinting, or

**Linkage to chromosome 11q**

The report of strong evidence for linkage of asthma and atopy to the marker D11S97 (formerly λ-MS51) on the long arm of chromosome 11 by Cookson et al. (73) was the first of a number of studies examining this chromosomal region. In this initial report, seven extended pedigrees were ascertained either through an atopic asthmatic attending a clinic or via media appeals and advertising seeking multiplex (i.e., multiply affected) families. The trait chosen for analysis was a broadly defined "atopy," characterized as either one or more skin prick wheals with a mean diameter 1 mm greater than the negative control, or a total serum immunoglobulin E more than two standard deviations above the population mean, or one or more positive allergen-specific immunoglobulin E assay (radioallergosorbent test) results. Four families contributed a maximum lod score of 5.24 at a recombination fraction of 6 percent. All the families gave a lod score of 6.39 at a recombination fraction of 10 percent—the other families, where cigarette use was high, were less informative.

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phenotypic maternal effects, so a pair of sibs carrying this atopy gene are more likely to express it after transplacental or breast milk exposure to maternal immunoglobulin E or other factors. Since the presence of atopy in offspring of atopic fathers is increased, they also concluded that atopy must be genetically heterogenous.

Of six linkage studies performed by other groups published up to 1992, only one supported linkage to chromosome 11q, but more recently, another two confirmations have been published (see table 2). More critically, Sandford et al. (107) localized a strong candidate gene to chromosome 11q, that for the high-affinity immunoglobulin E receptor β-subunit. Polymorphisms of the gene were associated with atopy and asthma (107a).

Association to chromosome 11q

Shirakawa et al. (107a) first sequenced the FcεRI β-subunit gene in six atopic and six nonatopic subjects. Three (6th exon) mutations were found in one atopic individual leading to substitutions of leucine for isoleucine at position 181, and leucine for valine at position 183. A polymerase chain reaction-based assay for these two mutations was developed.

In a “random sample” of 163 patients unselected for allergic disease (undergoing venesection for other purposes), 25 were found to carry the Ile181Leu mutation, but none, the Val183Leu. A total serum immunoglobulin E greater than 100 IU/ml was present in 41 (25 percent), of whom 11 carried the Leu181 mutation (OR = 3.1, 95 percent CI 1.2–7.5). A similar association was found for the presence of grass pollen specific immunoglobulin E (OR = 2.6, 95 percent CI 1.1–6.4).

The Leu181 mutation was also found to segregate in 10 of 60 of the atopic nuclear families. In each family, the mutation was transmitted from the mother (and was present in the proband). Among 14 nonproband offspring, four were atopic and two carried Leu181; none of the 10 nonatopic offspring carried the mutation. Furthermore, the two sporadics arose in bilineal atopy—that is the father was atopic and did not carry Leu181.

In the Busselton family study (108), 232 unselected nuclear families (1,020 individuals, 556 children) were typed for the Leu181 mutation in the FcεRI β-subunit gene. This gene was found in 28 subjects. There were eight children carrying the gene where the parent of origin was the mother—three with asthma, the remaining five with hay fever. Specific immunoglobulin E and skin prick test wheals to house dust mite (as well as a sum of radio-allergosorbent test scores) were significantly higher than in controls on Wilcoxon test. Further analysis (109) found similar levels of association to another polymorphism (7th exon) in the same gene.

### TABLE 2. Studies of linkage of atopic disease to chromosome region 11q

<table>
<thead>
<tr>
<th>Study and year (reference no.)</th>
<th>No. of subjects (no. of families)</th>
<th>Decimal log likelihood ratio (lod score)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cookson et al., 1992 (93)</td>
<td>7</td>
<td>6.4 to D11S97 (10 cM)</td>
<td></td>
</tr>
<tr>
<td>Young et al., 1992 (92)</td>
<td>281 (64)</td>
<td>5.2 to D11S97 (M 18 cM, F 0.1 cM)</td>
<td></td>
</tr>
<tr>
<td>Inacio et al., 1991 (94)</td>
<td>83 (17)</td>
<td>No linkage to D11S97</td>
<td></td>
</tr>
<tr>
<td>Shirakawa et al., 1991, 1994 (95, 96)</td>
<td>4</td>
<td>4.88 to D11S97</td>
<td></td>
</tr>
<tr>
<td>Amelung et al., 1992 (80)</td>
<td>117 (20)</td>
<td>&lt; -2.0 within 12 cM of FGF3</td>
<td>Families linked to chromosome 5</td>
</tr>
<tr>
<td>Hizawa et al., 1992 (97)</td>
<td>60 (4)</td>
<td>&lt; -2.0 within 4 cM of D11S97</td>
<td></td>
</tr>
<tr>
<td>Lympnany et al., 1992 (98)</td>
<td>89 (9)</td>
<td>&lt; -2.0 within 4 cM of FGF3</td>
<td></td>
</tr>
<tr>
<td>Rich et al., 1992 (81)</td>
<td>67 (3)</td>
<td>&lt; -2.0 within 5 cM of D11S97</td>
<td></td>
</tr>
<tr>
<td>Coleman et al., 1992 (99)</td>
<td>407 (95)</td>
<td>-7.88 multipoint D11S97, PGYM, CD20</td>
<td>12 families with affected mothers and unaffected fathers gave lod score of 0.8</td>
</tr>
<tr>
<td>Collie et al., 1993 (100)</td>
<td>52 (26)</td>
<td>Increased affected sib pair sharing D11S97</td>
<td></td>
</tr>
<tr>
<td>Branton et al., 1994 (101)</td>
<td>12 (12)</td>
<td>Negative lod score</td>
<td></td>
</tr>
<tr>
<td>van Herwerden et al., 1995 (102)</td>
<td>248 (123)</td>
<td>Increased affected sib pair sharing FoxRI-pca</td>
<td></td>
</tr>
<tr>
<td>Duffy et al., 1994 (103)</td>
<td>424 (212)</td>
<td>No increased affected sib pair sharing FoxRI-pca</td>
<td></td>
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<tr>
<td>Watson et al., 1995 (104)</td>
<td>560 (131)</td>
<td>Negative lod scores for three markers</td>
<td>Combined segregation-linkage</td>
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<tr>
<td>Martinaś et al., 1996 (105)</td>
<td>213 (45)</td>
<td>No increased affected sib pair sharing FoxRI-pca</td>
<td>Unable to detect Leu181 mutation</td>
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<td>Neely et al., 1996 (106)</td>
<td>218 (12)</td>
<td>Increased affected sib pair sharing (and positive TDT) INT2, D11S1369</td>
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of a maternal effect. In a subsequent case-control study (110, 111), 500 atopic patients (allergic (early and late onset) and nonallergic asthma, hay fever, or eczema) ascertained via Osaka hospital clinics were compared with 100 controls attending a health examination company. Restriction fragment length polymorphisms in FceRIβ (Rsa1), CD20, and GIF (the latter are two neighboring loci that might be alternative candidates) were examined. Significant differences in genotype frequencies were detected for the FceRIβ polymorphism (alone) between the controls and several different subgroups of the patients, most strongly for childhood onset allergic asthma and not at all for the nonallergic asthma group. The Leu181 mutation was not detected at all in the sample (111), but Gly237Glu was found in 6 percent of controls, 8 percent of nonallergic asthmatics, and 18 percent of atopic asthmatics (OR = 3.43, 95 percent CI 1.50–9.35).

Further evidence for association in the region was described by Doull et al. (112). As part of the Southampton study described above, allelic effects of two markers were detected on different phenotypes: allele 168 of D11S527 with nonspecific bronchial responsiveness (p = 0.0003, Bonferroni corrected for 13 alleles p = 0.004), and allele 235 of D11S534 with total immunoglobulin E (p = 0.007, Bonferroni corrected for 14 alleles p = 0.09).

In contrast, an Australian twin study (103) of 215 dizygotic twin-pairs ascertained for wheezing did not detect linkage of atopy (skin test or serum immunoglobulin E), nonspecific bronchial responsiveness, or serum immunoglobulin E to FceRIβca. No evidence of the Leu181 mutation was found in the twins, their parents, or a set of controls (n = 939), a finding confirmed by sequencing in 19 most atopic individuals (113). Similar findings were reported in three other studies (105, 114, 115).

We can conclude that the Leu181 and Glu237 are two mutations in the FceRI β-subunit associated with atopy. They were present in 3 and 5 percent, respectively, of the general population sample from Bussleton. The maternal effect seems to hold up for Leu181.

Linkage to chromosome 5

In 1994, Marsh et al. (55) reported a linkage between total serum immunoglobulin E and markers in the strong candidate region on chromosome 5q31 containing the interleukin gene cluster, β-adrenoceptor, and granulocyte-macrophage colony stimulating factor genes. This study was carried out in a sample of 11 old order Amish families (subsequently extended to 12) unselected for clinical atopy (though containing at least one member with detectable allergen specific immunoglobulin E).

This finding was swiftly confirmed by Meyers et al. (116) in 92 Dutch families (538 individuals), all ascertained through a hospital-diagnosed asthmatic parent (in the case of nuclear families) originally studied in 1962 to 1970. Linkage to serum immunoglobulin E and nonspecific bronchial responsiveness (117) was detected both by sib-pair and lod score analyses.

Blumenhal et al. (118) reported an absence of linkage of chromosome 5q markers to serum immunoglobulin E level in their four large atopic families (110 typed individuals). Maximum likelihood linkage analysis (under a common dominant gene model) and Haseman-Elston analysis using SIBPAL were performed. The maximum lod score among 12 markers spanning chromosome 5 was 0.06 (Θ = 0.23), with lod scores of −2.3 at Θ = 0 for IL-9, and −0.4 at Θ = 0 for IL4-R1. Similarly, the best p value from sib-pair analysis was 0.29. Linkage to the region was also not detected in the genome scan of Daniels et al. (74) (see below).

Association to chromosome 5

Weak evidence of allelic association for IL9 and total serum immunoglobulin E concentration has been presented by Doull et al. (112) and Borish et al. (119). A polymorphism in the distal IL4 promoter region was associated with wheezing (p = 0.03) and presence of house dust mite-specific immunoglobulin E (p = 0.01), but not several other related phenotypes, was reported by Walley and Cookson (120). Interest is now more focussed on the proximal promoter region.

Szentivanyi (121) is usually cited as the first worker to propose the unifying hypothesis that asthma represents an underresponsiveness of the lungs to sympathetic neurotransmitters. He argued that the defect in asthma must be “nonimmunologic,” and suggested the β-adrenoceptor gene as the most likely site for this. A number of recent studies have looked at functional mutations in β-adrenoceptor gene (chromosome 5q31–32) in asthmatics (122–127). Although the two most common mutations do not seem to be significantly more common in asthmatics than nonasthmatics, three studies have detected effects in particular asthma subgroups. Reishaus et al. (123) found that severe asthmatics, requiring oral steroids or immunotherapy, were more likely (75 percent) to be Arg16Gly homozygotes than controls (59 percent). Turki et al. (124), compared 23 nocturnal asthmatics (who tended to have a lower mean diurnal forced expiratory volume in one second (FEV1), and to be more likely to be steroid dependent) to 23 “normal” asthmatics. The Arg16Gly frequency was 80.4 percent in the nocturnal
Linkage to chromosome 12

Gamma interferon (chromosome 12q13) plays an important role in T-cell regulation that makes it another good candidate gene for involvement in allergic disease. The first published examination of this region was that of Watson et al. (104). The maximal lod score for IGF1 (tightly linked to D12S318 and PAH and approximately 30 cM distal to gamma interferon) was 0.09 at 25 percent recombination distance.

Barnes et al. (128) have reported evidence of linkage and association between asthma and total serum immunoglobulin E concentration over a region stretching from close to IGF1 up to gamma interferon in two different populations, the Amish families originally used to detect linkage to chromosome 5q and a sample of 29 Barbadian pedigrees (693 individuals) ascertainment through a proband with a history of asthma. Asthmatic sib-pairs exhibited increased ibd sharing at D12S379 (61.8 percent), D12S95 (67.2 percent), PAH (58.5 percent), and D12S360 (58.6 percent). Similarly, Haseman-Elston regression analyses were significant for PAH and D12S360. In the Amish sample, where a diagnosis of asthma was not available on any family members, there were significant Haseman-Elston results for D12S360, IGF1, as well as PLA2. Several replications of this finding have recently been presented (129).

Chromosome 14

Linkage between the T-cell receptor αδ-subunit genes and atopy was reported by Moffatt et al. (130). Families containing at least two atopic siblings were ascertained in Busselton (413 subjects), as well as in the United Kingdom (410 subjects). Mean ibd sharing was increased for T-cell receptor α-subunit alleles in sib-pairs concordant for several different phenotypes including high immunoglobulin E level (p = 0.002), house dust mite (p = 2 × 10^{-5}), cat (p = 6 × 10^{-5}), and timothy grass (p = 0.02) allergen sensitization. No such linkage was seen for a T-cell receptor β-subunit polymorphism.

There has been one interesting case report (131) of a highly atopic individual with multigene deletions in the heavy chain immunoglobulin gene region, but this is not a common association (132). Oxelius et al. (133, 134), have examined Gm type (a electrophoretically detectable polymorphism in the heavy chain constant region) in atopic children and controls. Particular phenotypes were associated with atopy and with elevated immunoglobulin G_{4} subclass levels.

α-1-antitrypsin

Complete and partial deficiencies of α-1-antitrypsin (α-1-AT, chromosome 14q31.2 (135)) are associated with obstructive lung disease (136, 137). The common normal allele is M; those associated with deficiency states are the S and Z alleles. The PiZZ phenotype (phenotype associated with the Z/Z genotype) is the most severely affected (by panacinar emphysema and cirrhosis), while the PiSZ and PiSS phenotypes are at increased risk of lung disease, especially following exposures such as cigarette smoking. The disease association with PiMS and PiMZ is smaller and is not seen in all studies.

Fagerhol and Hauge (138) have reported high proportions of PiMS and PiSS subjects among asthma patients, while Hyde et al. (139) also found that PiMS and MZ asthmatic children required more intense drug treatment than control PiMM asthmatics. Buist et al. (140) found an excess of asthma in heterozygotes in a matched 2:1 case-control study (3 of 21 cases and 2 of 42 controls). Townley et al. (141) have recently described results of α-1-antitrypsin phenotyping of 723 subjects from the Natural History of Asthma study. These included the families of asthmatic probands and families ascertained for a three-generation absence of atopic disease. Asthmatics made up 36 percent of the PiMS group and 21 percent of the PiMM group (p = 0.04). The PiMS group also had significantly lower levels of nonspecific bronchial responsiveness, and removing the current and former asthmatics did not alter this finding. Serum immunoglobulin E level was the same for all three Pi phenotypes.

Gaillard et al. (142) reported similar findings for subgroupings of the MM phenotype. The M_{2}M_{2} phenotype was found to be more frequent in 90 asthmatics than in 240 controls. Asthmatics were also found to have higher plasma levels of α-1-antitrypsin, but lower levels of elastase inhibitory capacity. These findings are suggestive, especially when one notes that elastase inhibitory capacity level and the elastase inhibitory capacity/α-1-antitrypsin level ratio (a measure of molar efficiency of the different Pi types) are lowest for PiM_{2}M_{2} of the MM subtypes, with the exception of the M_{2}M_{3} subtype (143).

In Nigerian asthmatics, Awotedu and Adelaja (144) found 74 of 99 asthmatics to be MM phenotype compared with 98 of 100 controls. The MZ phenotype was
present in 19 asthmatics and one control. A similar study of Puerto Rican asthmatics (145) in New York found 41 of 55 nonsmoking asthmatics to be MM, and 49 of 61 controls—not a significant difference.

Lindmark has performed a number of studies of α-1-antichymotrypsin, deficiencies of which lead to a clinical syndrome similar to that associated with α-1-antitrypsin deficiency (146). In a recent study (147), Lindmark screened 12 women heterozygous for α-1-antichymotrypsin and their relatives for asthma and allergic rhinitis, comparing them with a group of 58 controls. The index cases were three times more likely to report asthma (95 percent CI for OR 1.05–9.80) but not hay fever. Relatives with decreased levels of α-1-antichymotrypsin (n = 15) were also more likely to report asthma (OR = 3.1; 95 percent CI 0.96–9.83). Since this deficiency occurs in only 0.5–1 percent of the Swedish population, it cannot be a major determinant of asthma.

**Linkage to other chromosomal regions**

The first genome scan to be published (74) was of two subsamples from the Busselton (80 families, 364 subjects) and Oxford, England (77 families) study families, with the Oxford families being used to replicate any positive findings in the first panel. The chromosome 11 findings were, of course, replicated. Different regions of the genome gave positive results for differing phenotypes: Nonspecific bronchial responsiveness was linked to chromosomes 4, 7, and 16; total serum immunoglobulin E concentration to chromosomes 6, 7, and 16; eosinophil count to chromosomes 6 and 7; and atopy (combining skin tests and immunoglobulin E) to chromosomes 6 and 13. Replication in the second panel was of atopy to chromosome 13 and of asthma to chromosome 16. Interestingly, maternal linkage was stronger than paternal linkage for, in addition to FceRIβ, markers on chromosomes 4 and 16.

**Other genetic associations**

The relation between several other electrophoretically or serologically typeable polymorphisms have been investigated. Ronchetti et al. (148) described a study of asthma and polymorphisms in the adenosine deaminase gene (ADA, chromosome 20q13). Adenosine is a bronchoconstrictor on inhalation, and the different ADA gene isozyms differ in enzymatic activity. The ADA gene 1–1 phenotype was significantly more common among 347 asthmatic children than among controls (OR = 1.6, 95 percent CI 1.45–1.7). Other unreplicated case-control studies have found associations with the angiotensin converting enzyme I/D polymorphism (149), haptoglobin (150), and complement C3 type (151).

**Disease associations**

A number of studies have observed the co-occurrence of allergic disease with other nonallergic diseases. Such findings, if reproducible, might answer questions about the evolution and persistence of genes predisposing to allergic disease in the population. In addition, if the mechanism is a genetic correlation, it suggests further possible candidate genes.

1. The oldest reported association is a lower than expected number of individuals suffering from both asthma and juvenile-onset diabetes mellitus (152). This was not replicated in one recent smaller study (153).

2. Asthma has been reported to be variously increased or decreased in a number of cancers, both respiratory and nonrespiratory (154–156). The correlation between asthma and increased lung cancer seems to be the most replicable (157) but is unlikely to be genetic—one would suspect an effect of chronic inflammation.

3. The genetic disease familial Mediterranean fever (chromosome 16p13) has been reported to be protective against asthma (158, 159). One study (160) has suggested that heterozygotes also have a decreased incidence (OR = 0.5, 95 percent CI 0.1–2.1).

4. Similar claims have been made recently for the heterozygote carriers of the common ΔF508 mutation of the cystic fibrosis gene (CFTR, chromosome 7q37) (161).

**ANIMAL MODELS**

As in other complex diseases, a number of useful animal models of asthma have been developed. The use of standard crosses and recombinant inbred lines greatly increases the power of linkage methods to detect genes of small effect, especially in the case of quantitative traits associated with asthma. The traits currently most intensely studied in mice have been bronchial responsiveness to methacholine (nonspecific bronchial responsiveness) (162), ovalbumin or sheep erythrocytes (allergic), mediators such as platelet activating factor (163), and chemical irritants such as ozone (164). Such analyses have detected the presence of at least four significant loci, the effects of some overlapping over the different challenges, the locations of which correspond to good human candidate gene regions.

De Sanctis et al. (162) recently described such a linkage analysis in 321 mice from high nonspecific bronchial responsiveness (A/J strain) with low non-
specific bronchial responsiveness (C57BL/6J) strain backcrosses. Three loci were detected, explaining 26 percent of the genetic interstrain variance (backcross heritability was 50 percent). The mouse candidate genes in these regions were tumor necrosis factor alpha (TNF, human chromosome 6p), interleukin (IL2, IL3) receptors (chromosome 22q), and platelet derived growth factor B chain (chromosome 22q). The A/J strain develops increased nonspecific bronchial responsiveness and airway inflammation following ozone exposure (164), which is attenuated by antitumor necrosis factor antibody pretreatment (165). Ewart et al. (165) added a fourth locus, possibly IL5 (chromosome 5q), in another study of nonspecific bronchial responsiveness in the A/J strain. This latter finding may be regarded as further support for the human studies of chromosome 5q (55, 116, 117), as may the report of another mouse locus syntenic to chromosome 5q31.1 modifying the Th1/Th2 responses (166).

CONCLUSIONS

The segregation, linkage, and association studies reviewed above suggest a substantial genetic contribution to the familial aggregation of asthma and allergic disease, almost certainly involving the action of multiple common genes. Several genome scans for asthma close to publication also detect linkage to multiple regions.

One can divide the genes detected to date into “minor” genes (where the disease allele is uncommon or the effect size is small, so that the proportion of cases attributable is small) and major genes, explaining a larger proportion of population variation. Examples of minor genes might include the α-1-AT and β-adrenoceptor polymorphisms.

A finding common to other complex diseases is the often inconsistent results of linkage and association studies of asthma. In the case of chromosome 11q, for instance, the positive studies have come from markedly different ethnic backgrounds. For every positive study however, there have been one or more negative studies in the same ethnic groups. Several hypotheses have been suggested to explain these differences (167, 168). These include the presence of nonstandard genetic mechanisms, such as imprinting, environmental confounding in the presence of gene by environment interaction, and genetic heterogeneity.

The usual use of the term genetic heterogeneity posits uncommon disease alleles present at the different loci, each of which is sufficient to cause disease in its own right in the appropriate environment. The alternative polygenic model assumes that disease alleles are relatively common (either high allele frequency and low number of involved loci, or vice versa), effect sizes associated with any one locus relatively small, and gene effects interact in a simple fashion (e.g., multiplicatively in the multifactorial threshold model). In this case, an affected individual will often carry disease alleles at multiple different loci, and linkage analysis may be difficult. Such polygenic effects seem to underlie nonspecific bronchial responsiveness in the mouse models discussed above.

There are now sufficient positive studies to conclude that a gene on chromosome 11q, probably the FceRI β-subunit, exerts some influence on total serum immunoglobulin E concentration, nonspecific bronchial responsiveness, and asthma. The inconsistency between studies means that an attributable risk due to this single locus could be low or high. There is less (though increasing) evidence for the strong candidate regions on chromosomes 5q and 12q. The allelic associations with the β-adrenoceptor gene suggest it to be more a modifier of asthma severity, and cannot explain linkage to total serum immunoglobulin E concentration level. Similarly, the human lymphocyte antigen allelic associations seem to modify response to specific allergens, but have not consistently been implicated in the presence or absence of asthma, except possibly for that due to particular occupational exposures (87). There is a lack of linkage results applicable to asthma subtypes, especially nonallergic asthma.

Finally, a large number of environmental determinants of asthma are recognized, and must be invoked to explain its increasing incidence in developed countries, and among migrants to these countries. These environmental factors will interact with multiple genes in a complex fashion, as discussed elsewhere in this issue of Epidemiologic Reviews.

ACKNOWLEDGMENTS

The author is an Australian National Health and Medical Research Council Neil Hamilton Fairley Fellow.

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