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Genetics of asthma and allergy: What have we learned?

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Activity Objectives

1. To understand the purpose of genome-wide associates studies (GWASs).
2. To understand the effects of racial differences on results from GWASs.
3. To understand the difference between disease susceptibility and disease severity.
4. To gain knowledge of the newer applications of genetic studies, such as pharmacogenetics.

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The overall purpose of this review is to present an update on genetic approaches to understanding the susceptibility and expression (severity) of common diseases, such as asthma and allergy. Five key questions are addressed in this review: (1) What phenotypes are being studied? Multiple disease phenotypes in carefully characterized patients are required. (2) Are the same genes that are important in disease susceptibility important in disease severity? (3) Are there racial differences in disease expression and genetic susceptibility? (4) Are the genes important in normal variation in lung function important in asthma severity? (5) Are the genes important in other common diseases, such as chronic inflammatory diseases or chronic obstructive pulmonary disease, important in asthma or allergy? In addition, a discussion of some of current areas of research is presented, including the issue that current genome-wide association study results do not account for a significant portion of trait variability, the potential role of rare variants and large genome-sequencing studies, and pharmacogenetics: is there a role for basing treatment decisions on the results of genetic testing? Finally, the potential usefulness of DNA, personalized medicine, is discussed. (J Allergy Clin Immunol 2010;126:439-46.)

Key words: *Asthma, genetics, asthma genetics, genomics, genome-wide association study, IgE*

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The overall purpose of this review is to present an update on genetic approaches to understanding the susceptibility and expression (severity) of common diseases, such as asthma and allergy. Although current scientific findings will be discussed, one must realize that this is a rapidly evolving field of investigation and realize that new developments are likely (ie, one should always check sources, such as PubMed, for the latest results). It is extremely important to understand the basic principles of genetic approaches because the results of these studies will affect everyone both professionally and personally. Although most of us in the field believe it is still premature, there are multiple companies already offering genetic susceptibility testing for a wide range of common diseases, including asthma.

Emphasis will be placed on the results from genome-wide association studies (GWASs) using case-control or case-only approaches. GWAS approaches are based on the ability to rapidly analyze genetic variants (mainly single nucleotide polymorphisms [SNPs], usually with a high degree of heterozygosity) across the whole genome to determine which genetic variants are associated with disease susceptibility (case-control studies) or which are associated with measures of disease severity or response to treatment (ie, pharmacogenetics; case-only studies).

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Abbreviations used
COPD: Chronic obstructive pulmonary disease
GWAS: Genome-wide association study
NHLBI: National Heart, Lung, and Blood Institute
SNP: Single nucleotide polymorphism

GWASs are also performed in families, especially trios, which are defined as an affected child with genotyping from both parents (eg, the National Heart, Lung, and Blood Institute [NHLBI]'s Childhood Asthma Management Program study identified *PDE4* as an asthma susceptibility gene[1]), but it is generally easier to ascertain and characterize a large number of unrelated cases and control subjects than to study multiple family members.

The basic principle of a GWAS is straightforward: the frequency of each genetic variant is compared between cases (ie, subjects with the disease under investigation) and control subjects without the disease. A statistically significant increased frequency in cases compared with control subjects provides evidence that the genetic variant is related to disease susceptibility. Because many genetic variants (SNPs) are tested (usually 300,000 to 1 million), adjustment for multiple testing is required; for example, in the National Institutes of Health catalog of GWAS results, only those with P values of 5×10^{-8} or less are included in their chromosomal map of association results from many common diseases (www.genome.gov/GWAS).

The results from GWASs are the first step. Replication studies are necessary, and meta-analyses are useful to determine the importance of these variants in multiple populations. Functional biologic studies to understand the role of the identified genes and genetic variants are crucial to further our understanding of disease pathogenesis.[2]

KEY QUESTIONS TO BE ADDRESSED

There are 5 key questions that will be addressed in this review (Table I), followed by a discussion of some of the newest areas of research in this field.

Question 1: What phenotypes are being studied?

Asthma is a heterogeneous disease that is classified phenotypically as mild, moderate, or severe based on guidelines,[3,4] but more recently, 5 asthma severity phenotypes were identified by using a unsupervised hierarchic cluster analysis.[5] In the NHLBI Severe Asthma Research Program, cluster analysis was performed on 726 subjects with 34 variables. Five groups were identified. Subjects with asthma in cluster 1 (n = 110) have early-onset atopic asthma with normal lung function usually treated with 2 or fewer controller medications (82%) and minimal health care use. Cluster 2 (n = 321) consists of subjects with early-onset atopic asthma and preserved lung function but increased medication requirements (29% taking ≥3 controller medications) and increased health care use. Cluster 3 (n = 59) is a unique group of mostly older, more obese women with late-onset nonatopic asthma, moderate reductions in FEV_1, and a requirement for frequent oral corticosteroid use to manage exacerbations. Subjects in clusters 4 (n = 120) and 5 (n = 116) have severe airflow obstruction with bronchodilator responsiveness but differ with regard to their ability to attain normal lung function, age of asthma onset, atopic status, and use of oral corticosteroids. Interestingly, the asthmatic subjects in cluster 4 appear to represent the more severe spectrum of early-onset atopic asthma seen in clusters 1 and 2, whereas those in cluster 5 are less atopic, have a somewhat later disease onset, and have fixed airways obstruction, clinical characteristics observed in patients with chronic obstructive pulmonary disease (COPD), although these are nonsmokers. All clusters contain subjects who meet the American Thoracic Society definition of severe asthma, which reflects the clinical heterogeneity observed in asthma and the need for new approaches for the classification of disease severity in patients with asthma. Therefore in genetic studies of disease severity, it will be important to analyze different asthma subphenotypes rather than ignore heterogeneity in asthma.

Quantitative phenotypes, such as measures of lung function, including percent predicted FEV_1, are key variables for analysis of disease severity and are essential for categorizing asthma severity for both current guidelines classification and for the cluster approach described previously. Additional related phenotypes, such as measures of allergy, including total serum IgE levels and skin test responsiveness to common allergens, should be included in relevant genetic analyses.

The first GWAS of asthma used a physician's diagnosis of asthma as the phenotype and found strong evidence for a gene not previously identified for asthma susceptibility: *ORMDL3*.[6] This approach has been used successfully in many GWASs of common diseases (www.genome.gov/GWAS). However, now that susceptibility genes have been identified, in-depth phenotypic analyses are necessary to further understand the roles of these genes. For example, genetic association analyses of genes detected by using GWASs and their role in subphenotypes (eg, cluster phenotypes), indices of bronchial inflammation, or lung imaging phenotypes would provide additional insight into the role of genetic variation and further our understanding of disease severity.

A GWAS has been performed for total IgE level, a quantitative trait related to both asthma and allergy, resulting in evidence for association with functional variants in the gene encoding the α chain of the high-affinity receptor for IgE *(FCER1A)*.[7] Additional evidence for association with allergen sensitization was also observed. An association was also observed with *RAD50* on chromosome 5q and IgE levels and, in additional analyses, with atopic eczema and asthma. This is an example of using a quantitative phenotype that is relatively easy to obtain and related to asthma and allergy.

Question 2: Are the same genes that are important in disease susceptibility important in disease severity?

Although there are several ongoing studies evaluating genetic susceptibility to asthma using genome-wide approaches, a key question is whether the same genes identified for asthma susceptibility are important in determining the genetics of asthma severity. To address this question, appropriate phenotypes need to be available either from cross-sectional (eg, history of asthma exacerbations and levels of lung function) or, very importantly, from longitudinal (eg, loss of lung function over time) studies. These areas are currently being addressed in several studies by using a GWAS approach and have been addressed, to a limited extent, in candidate gene studies. For example, variation in A*DAM33*, a susceptibility gene identified in family studies,[8] has

TABLE I. Key questions to be addressed

- What phenotypes are being studied? Multiple disease phenotypes in carefully characterized patients are required.
- Are the same genes that are important in disease susceptibility important in disease severity?
- Are there racial differences in disease expression and genetic susceptibility?
- Are the genes important in normal variation in lung function important in asthma severity?
- Are the genes important in other common diseases, such as chronic inflammatory diseases or COPD, important in asthma or allergy?

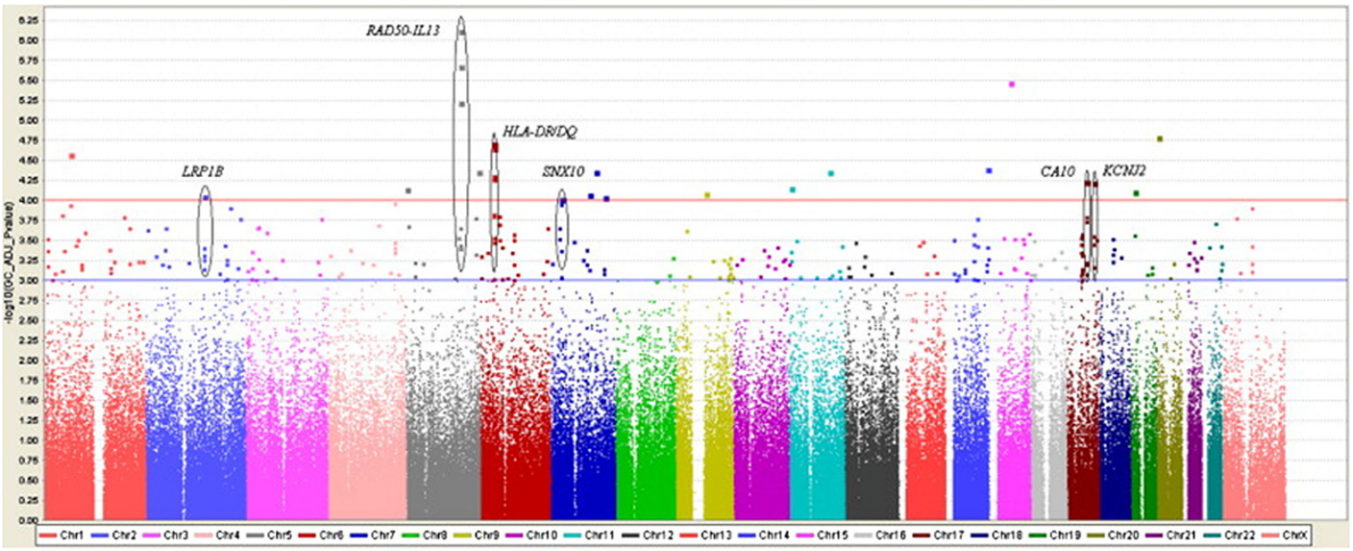

FIG 1. Genome-wide association showing evidence for association of *RAD50-IL13* and *HLA-DR/DQ* with asthma susceptibility. The *x-axis* shows the chromosomes in color, with the results from all the SNPs analyzed. Negative log-transformed *P* values are on the *y-axis*.[10]

been associated with excess decrease in lung function over time in subjects with asthma.[9]

A GWAS was performed in a cohort of non-Hispanic white subjects with severe or difficult-to-treat allergic asthma, a subset of the well-phenotyped longitudinally studied TENOR population (Fig 1).[10] Multiple SNPs in the *RAD50-IL13* region on chromosome 5q31.1 were associated with asthma (Fig 1). Although an SNP in *RAD50* showed the strongest evidence for association with asthma susceptibility, there is correlation between SNPs in *RAD50* and *IL13*, making it difficult to separate their specific effects. The *HLA-DR/DQ* region on chromosome 6p21.3 was also associated with asthma susceptibility. This is an important example of observing a relevant biologic candidate gene in a GWAS analysis. It raises the issue of why different GWASs result in evidence for different sets of genes, which might reflect disease misclassification in large population studies, which are often dependent on a physician's diagnosis, as well the severity and heterogeneity of asthma in the subjects being studied.

Question 3: Are there racial differences in disease expression and genetic susceptibility?

Racial differences in both the expression of asthma and genetics are important areas of research for several reasons. First, there might be different phenotypic expression of the disease in a given racial group (that might or might not be confounded by environmental differences).

Second, the frequency of genetic variation varies between races. For example, if a disease susceptibility allele has a significantly increased frequency in subjects of European descent with asthma compared with appropriate control subjects, the same allele might or might not be detected in studies of African Americans because of different allele frequencies. For example, if the allele frequency is 30% in white subjects and only 5% in subjects of African descent, it does not mean that this allele is not important in individuals of African descent but that this association would not be easily detected because of statistical power and the sample size required to identity a rarer variant. In addition, for some genetic variants, the most common form (allele) is the less frequent form in a different race.

A GWAS for asthma susceptibility was performed in subjects of African ancestry and showed evidence for SNPs in 3 genes (*ADRA1B* on chromosome 5q, *PRNP* on chromosome 20p, and *DPP10* on chromosome 2, a gene previously identified in family studies of asthma[11,12]). In replicate populations of European white descent, none of these associations were replicated, even though *DPP10* was originally identified in families of European white descent. An important aspect of analysis in admixed populations is to adjust for differences in racial backgrounds. Fig 2[12] shows the range of admixture in African American subjects with asthma and control subjects. Subjects toward the bottom left have a higher percentage of genetic variants that are observed in West Africa than those more toward the bottom right.

Third, the correlation between genetic variants (linkage disequilibrium) in a given gene might differ based on historical geographic ancestry. This is an important tool that can be used in genetic studies. A common issue is that the SNP identified from a GWAS might be strongly associated with 1 or more additional SNPs in the same gene or even across neighboring genes (ie,

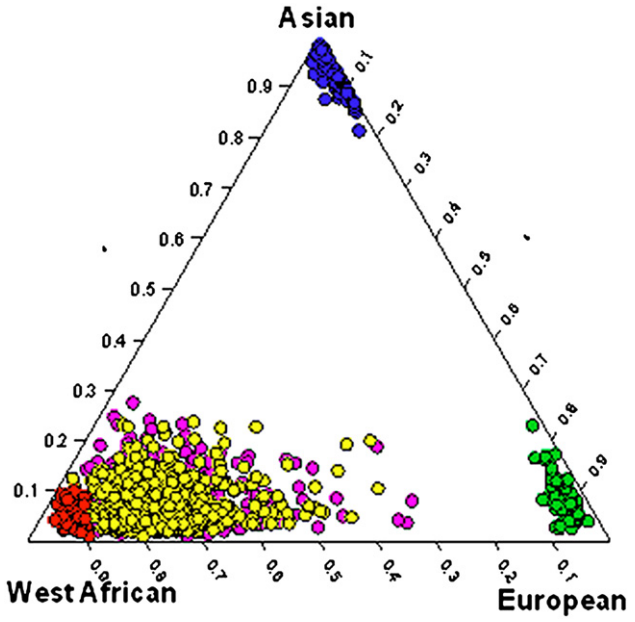

FIG 2. The triangle shows the admixture in the African-American cases *(pink dots)* and control subjects *(yellow dots)* used for GWAS analysis compared with standards from the International Hap Map Project (shown in each corner). African Americans are an admixed population of different levels of descent from Africans and European white subjects.[12]

linkage disequilibrium). For example, SNPs in *ORMDL3* were identified in a GWAS of asthma; however, there was association observed between SNPs in multiple genes in this region on chromosome 17, leading to the article "ORMDL3—guilt by association?," which raised the question as to whether *ORMDL3* is the relevant gene.[13] This correlation between SNPs makes it difficult to determine in a genetic study which specific SNPs should be investigated in biologic or functional studies. However, the degree of correlation between SNPs might differ between races, allowing the identification of the most relevant SNP if subjects from different racial backgrounds are studied.

In the GWAS study of childhood asthma, significant evidence for *DENND1B*, which encodes a protein that interacts with the TNF-α receptor, on chromosome 1 was observed for asthma susceptibility.[14] In the white population of European descent, 20 SNPs showed evidence of association with asthma susceptibility; however, these 20 SNPS were correlated with each other. In the African Americans studied, there was less correlation between SNPs, with 4 correlated SNPs of the 20 showing the strongest evidence for association. In addition, in the African American subjects the associated allele was the alternate allele and not the initial allele associated in the white population. This finding has interesting biologic implications and raises the question of whether genetic variants important in susceptibility might differ because of interaction with environmental factors at different stages of asthma, resulting in different alleles being important in different cohorts.

Once a GWAS is performed in a population, it is easy to mine the data for many genes. For example, in a study of Mexican children, 200 previously indentified candidate genes for asthma were evaluated by using GWAS data. Significant evidence was observed for several genes, including *DPP10* (which was observed in the African American GWAS[12]), *TGFB1, IL1RL1*, and *CYFIP2*.[15]

Question 4: Are the genes important in normal variation in lung function important in asthma?

Two large meta-analyses of GWASs of lung function in general populations of European descent identified 11 candidate genes/regions. Although a small percentage of these populations had a history of asthma or COPD, the results were similar, irrespective of whether these subjects were included in the analyses. A recent GWAS meta-analysis for pulmonary function in 20,890 participants from general populations of European white ancestry (CHARGE consortium) found that genes in the *INTS12-GSTCD-NPNT* region were associated with FEV_1, and 8 genes (*HHIP*, *GPR126*, *ADAM19*, *AGER-PPT2*, *FAM13A*, *PTCH1*, *PID1*, and *HTR4*) were associated with FEV_1/forced vital capacity ratios.[16] A second GWAS meta-analysis for lung function in general populations (20,288 white participants of European ancestry: SpiroMeta consortium) identified 4 genes (*HHIP*, *GSTCD*, *TNS1*, and *HTR4*) associated with FEV_1 and 3 loci (*HHIP*, *NOTCH4-AGER-PPT2*, and *THSD4*) associated with FEV_1/forced vital capacity ratios.[17]

Although these genes might only influence lung function in subjects without respiratory diseases, a key question is whether some or all of these genes are important in determining lung function in subjects with asthma. Identifying the genetic variants that influence pulmonary function in patients with asthma is important because it will lead to improved understanding of biologic factors that regulate lung function in patients with asthma, which is a fundamental determinant of asthma severity.[5]

Because the genes that have been associated with lung function in the general population have not been reported for asthma susceptibility in a GWAS to date, analyses of genetic variants in these genes in subjects with different levels of asthma severity are needed. An important point is that these large meta-analyses were performed in white subjects of European descent. For several of the genes identified, such as *HHIP*, it was not possible to identify the most important SNP because of the strong correlation (linkage disequilibrium) between SNPs in *HHIP* in the white population. Therefore studies in other ethnic groups, such as African Americans, are needed because linkage disequilibrium often differs between races, as discussed in question 3.

Question 5: Are the genes important in other common diseases, such as chronic inflammatory diseases or COPD, important in asthma or allergy?

In a GWAS of COPD, *HHIP* was associated with the risk of COPD.[18] Another GWAS of COPD susceptibility identified variants in *FAM13A*.[19] Both *HHIP* and *FAM13A* were associated with the level of lung function in the general population, as discussed in question 3, and therefore it is possible that the association with COPD might partially reflect the association with lung function because the definition of COPD is based on abnormal levels of lung function. These genes have not been identified in previous GWASs of asthma susceptibility,[1,6,10,14] suggesting possible genetic differences between the development of asthma and COPD. However, it is important to remember that subjects with asthma might have normal levels of baseline lung function, especially subjects with mild asthma.

On the other hand, asthma and COPD and other lung diseases might share some common genetic pathways. Certainly multiple genes have been associated with both susceptibility to asthma and COPD by using a candidate gene approach. For example,

TABLE II. Key areas being addressed in current studies

• Current GWAS results do not account for a significant portion of trait variability: What is missing?
• Potential role of rare variants
• Large genome-sequencing studies
• Pharmacogenetics: Is there a role for basing treatment decisions on the results of genetic testing?
• Combining genetic and genomic approaches
• Personalized medicine

variation in *ADAM33* has been associated with susceptibility to COPD,[20] although it was first identified in family studies of asthma[8] and has been related to a decrease in lung function in patients with asthma,[9] as discussed previously. Variation in *IL13*, which has been associated with asthma susceptibility in multiple studies of candidate genes,[21] as well as in a previously described GWAS,[10] has also been shown to have an interactive effect with level of smoking (number of pack-years) and lung function in long-term smokers.[22] Several genes related to asthmatic bronchial inflammation, such as *IL6*, *IL10*, *MMP12*, and *TGFB1*, have been observed in genetic studies of COPD.[23-27] As more GWASs are performed for both asthma and COPD, potential overlapping gene pathways will be identified.

An additional approach is to investigate whether genes seen in other common diseases are important in asthma. Genes in inflammatory pathways are obvious candidates for such studies. One approach is to study a related phenotype, such as blood eosinophil counts, in a large general population and determine whether genes related to eosinophil level are related to asthma susceptibility or severity.[28] In this study a GWAS was performed on blood eosinophils from more than 9,000 subjects from Iceland and replicated in another Icelandic dataset, and then the SNPs with the smallest *P* values were analyzed in a large asthmatic population, resulting in significant evidence for an SNP in *IL1RL1* being associated with both blood eosinophil counts and asthma.

Given the large amount of GWAS data available for many diseases, the results can be interrogated across studies to determine whether the same genes are being observed in different diseases, even if there is not a known relationship between the diseases. GWAS results from across 118 studies were analyzed to determine the SNPs and genes most commonly observed in different diseases.[29] Evidence for the MHC region on chromosome 6 was observed across many studies, and genes involved in cell adhesion, signal transduction, and protein phosphorylation were the most likely to be observed in different disease entities. This bioinformatics approach can be useful for identifying potential similarities between disease processes that can be investigated further.

KEY AREAS THAT ARE CURRENTLY BEING STUDIED

Several key areas of current research are important to address (Table II). An important issue is the concept of "missing variability," which refers to what some investigators believe are disappointing results from GWASs. In many diseases the genes identified do not account for a large percentage of the observed trait variation.[30] In other words, although statistically significant, the predictive value of using single genetic variants is very low. Possibly for some diseases, including asthma and allergy, in which there have only been a limited number of GWASs, additional studies might identify more genes. Because common diseases, such as asthma, are influenced by multiple genes, each having a small but significant effect on disease susceptibility, it is probable that there might be synergistic or additive effects of the different associated genetic variants. This approach has been used by our group to characterize susceptibility to prostate cancer in which multiple variants each have an additive effect on disease susceptibility.[31] These findings emphasize the importance of investigating the effects of multiple genes in the development and potentially the progression of common diseases, such as asthma and allergy. In addition, because GWASs are designed to investigate common variants, it is possible that rare variants either in the genes already identified or in additional genes might be important in determining disease susceptibility and expression.

Rare variants and DNA sequencing

Sequencing of specific candidate genes to detect rare variants is commonly performed in genetic studies. However, now it is possible to perform sequencing across the genome; this is known as "exome sequencing," which refers to sequencing of all the coding regions (exons) in the human genome. These studies, especially in admixed populations, such as African Americans, will identify rare variants with potential functional importance. The variants identified then can be genotyped in larger populations to determine their phenotypic effects. Currently, 200 African-Americans with asthma from the NHLBI Severe Asthma Research Program are being sequenced (because of the efforts of Dr Kathleen Barnes and American Recovery and Reinvestment Act NHLBI funding). The results will be available to other investigators thorough the dbGap mechanism. Rare variants can also be identified through family studies, especially by using families with members who display extreme phenotypes, which leads to the identification of "disease-causing" mutations. For example, there are immune deficiency syndromes that are inherited as single-gene mutations. However, this approach has not been as useful for asthma or allergy, in which "extreme" genetic forms of these diseases have not been identified.

Pharmacogenetics

An important area of research is whether individual response to treatment is significantly influenced by genetic variation. Although there have been some studies showing a potential effect for some therapies for asthma,[32,33] this approach is likely to be more useful in evaluating biologic therapies. For example, in a small early-phase mechanistic trial of an IL-4 receptor α antagonist, preliminary evidence for an association was observed with treatment response and 2 functional SNPs in *IL4RA* (unpublished data). Both gene pathway and GWAS analyses are needed in pharmacogenetic studies.

An important issue in pharmacogenetic studies is sufficient sample size to observe an effect if the important variant is of low frequency. For example, with an allele frequency of 20%, only 4% of the population will have 2 copies of the allele (homozygous),

TABLE III. Role of genetic testing in common diseases

- Genetic information is already used because a family history of common diseases is routinely requested.
- However, a positive family history means a higher risk in general. A specific subject might have a higher or lower risk based on the genetic variation inherited.
- Therefore genetic testing could identify those at an increased risk and let others (with the same positive family history) know that their risk is low (general population risk).
- Genetic testing is of limited usefulness at this stage for many common diseases because the common variants identified thus far do not account for a large proportion of the variation observed for a given disease.
- Technology for genetic testing is available, reproducible, and reasonable in expense (and is used for single disorders, such as cystic fibrosis, routinely).

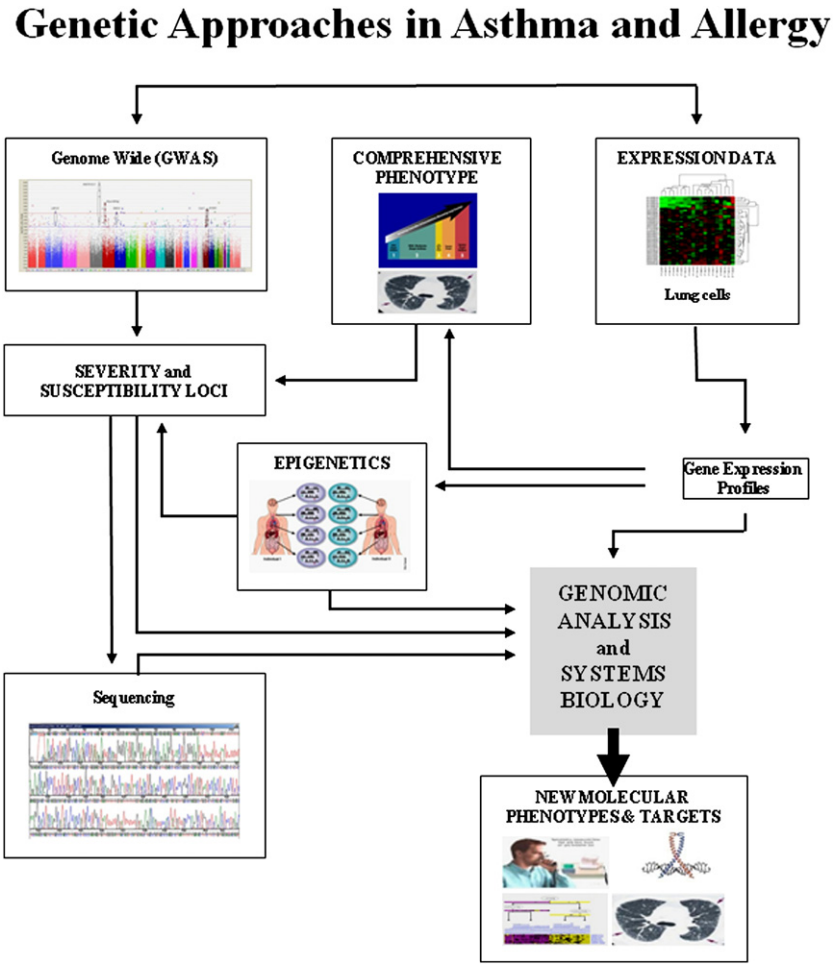

FIG 3. This flow chart shows an overall genetic and genomic approach for studying common diseases. GWASs continue to be performed for diseases such as asthma and allergy. The importance of well-characterized cohorts with in-depth phenotyping, such as lung imaging, is discussed. Sequencing studies to reveal additional genetic variants, especially rare variants, are currently underway. The genomic approach of gene expression in relevant tissues is not discussed in this review but is an important genomic approach. Epigenetics, the study of heritable changes in gene function that occur without a change in the sequence of the DNA, is a relatively new field.[38] Systems biology approaches will provide a powerful tool for integrating results from all these areas to determine the role of genetics and genomics in common diseases. Figure courtesy of N. Kaminski, MD, and S. E. Wenzel, MD.

32% will be heterozygous (1 copy), and 64% will not have the allele in question. This leads to the concept of a clinical trial stratified by genotype in which patients are genotyped before enrollment so that a sufficient number of subjects with the important genotype are studied. There have been 2 genotype-stratified trials performed for response to long-acting β-agonists in which enrollment was dependent on genotype to determine the role of the Arg 16 variant, which has an allele frequency of 16% in the European white population.[34,35] Blinded to the investigators, patients were first genotyped and then enrolled so that an equal number of subjects with each genotype were studied. In the NHLBI Asthma Clinical Research Network trial the subjects with the 2 homozygote genotypes were enrolled, whereas in the other trial an equal number of subjects with each of the

3 genotypes were enrolled. Neither study showed a significant association for response to therapy and this genetic variant.

Personalized medicine

Finally, how will the results from all these studies be used to diagnose disease when presymptomatic to facilitate preventive strategies and individualize therapeutic regimens (Table III)? First, because these diseases are not single disorders or disorders caused by a limited number of genes with large effects ("disease-causing" mutations, such as in cystic fibrosis), diagnostic testing is not applicable. Susceptibility testing might become appropriate, but it is crucial to understand that this is not a diagnostic test but a test that will determine whether a given subject is at increased risk for a specific disease. It is already possible to obtain a subject's genetic risk profile for a number of common diseases (eg, www.decodediagnostics.com). The question remains as to the usefulness of such testing given the depth of our current knowledge because there is evidence for multiple genes affecting susceptibility to asthma and allergy, each with a relatively small effect. Until the majority of the genes responsible for asthma susceptibility have been identified, there is not strong evidence to support this type of genetic testing at this time. This is not to imply that it will not become useful. As described in Table III, this type of information already influences our thinking. In general, a strong family history of asthma is a risk factor for a wheezing infant to have the disease. However, a specific infant might have inherited the genetic variants associated with increased risk, whereas an infant with the same family history might have inherited low-risk variants and not be at increased asthma risk based on genetics. Also, for many current families, negative family histories are better characterized as uninformative because of small family size.

Thus the usefulness of genetic testing remains a question.[36,37] Clearly it is very helpful in single-gene disorders and other more common diseases, such as some cancers. An important issue is whether these tests will ever be useful in "lifestyle" diseases. Does knowing that one is at increased risk for COPD or lung cancer make it more likely that one would stop smoking in view of current knowledge that smoking is harmful to one's health?

Pharmacogenetics is another form of DNA testing that might become useful to target therapies to the most responsive patients, especially for more expensive therapies or those with increased risk of side effects. Clearly, the technologies are available for genetic testing, and there are many certified laboratories performing these tests for diagnostic purposes in other genetic diseases.

SUMMARY

In Fig 3 an overall approach to genomic studies is presented.[38] This is the current approach that is being used in our American Recovery and Reinvestment Act–funded Grand Opportunity NHLBI grant (principal investigators: Deborah Meyers, PhD; Eugene Bleecker, MD; Naftali Kaminski, MD; and Sally Wenzel, MD). There are additional important genomic approaches not discussed here, such as the use of gene expression profiles from relevant lung tissue to study susceptibility and severity, as well as the important areas of epigenetics.[38] In this approach significant evidence for the same gene observed in different types of studies forms a type of replication important in genetic studies, especially when many genes are being studied simultaneously. Systems biology approaches represent a more sophisticated method that combines data from multiple genomic sources to determine the most important genomic disease profiles.

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