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Genetics of Asthma and Allergy: What have we learned?

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Abstract

The overall purpose of this review is to present an update on genetic approaches to understanding susceptibility and expression (severity) of common diseases such as asthma and allergy. There are five key questions that will be 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 COPD important in asthma or allergy? In addition, a discussion of some of current areas of research is presented, including the issue that current GWAS results did 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.

Keywords

asthma; genetics; asthma genetics; genomics; GWAS; IgE

Introduction

The overall purpose of this review is to present an update on genetic approaches to understanding 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 (so 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 feel it is still premature, there are multiple companies already offering genetic susceptibility testing for a wide range of common diseases including asthma.

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Emphasis will be placed on the results from genome wide association studies (GWAS) using case control or case only approaches. GWAS approaches are based on the ability to rapidly analyze genetic variants (mainly SNPs, single nucleotide polymorphisms, 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, pharmacogenetics (case only studies). GWAS studies are also performed using families, especially trios, defined as an affected child with genotyping from both parents (for example: NHLBI CAMP 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 controls than to study multiple family members.

The basic principle of GWAS is straightforward; the frequency of each genetic variant is compared between cases, subjects with the disease under investigation, and controls without the disease. A statistically significant increased frequency in cases compared to controls provides evidence that the genetic variant is related to disease susceptibility. Since many genetic variants (SNPs) are tested (usually 300,000 to 1 million), adjustment for multiple testing is required; for example in the NIH catalog of GWAS results, only those with p values $\leq 5 \times 10^{-8}$ are included in their chromosomal map of association results from many common diseases (www.genome.gov/GWAS).

The results from GWAS 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 five key questions that will be addressed in this review (Table 1) 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 which is classified phenotypically as mild, moderate, or severe based on guidelines (3,4) but more recently, five asthma severity phenotypes were identified using an unsupervised hierarchical cluster analysis (5). In the NHLBI Severe Asthma Research Program (SARP), 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 controller medications (82%) and minimal health care utilization. Cluster 2 (n=321) consists of subjects with early onset atopic asthma and preserved lung function, but increased medication requirements (29% on ≥ 3 controllers) and increased health care utilization. Cluster 3 (n=59) is a unique group of mostly older more obese women with late onset nonatopic asthma, moderate reductions in FEV1 and require 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 regards 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 while cluster 5 is less atopic, somewhat later disease onset and fixed airways obstruction, clinical characteristics observed in COPD, although these are non-smokers. All clusters contain subjects who meet the ATS 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 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 measure of lung function including percent predicted FEV₁ are key variables for analysis of disease severity and essential for categorizing asthma severity for both current guidelines classification or 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 doctor'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 GWAS of common diseases (www.genome.gov/GWAS). However, now that susceptibility genes have been identified, in order to further understand the roles of these genes, in-depth phenotypic analyses are necessary. For example, genetic association analyses of genes detected by GWAS and their role in subphenotypes, for example, 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 levels, 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 (*FCERIA*) (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 utilizing 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 as 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 (for example: history of asthma exacerbations and levels of lung function) or very importantly, from longitudinal studies (for example: loss of lung function over time). These areas are currently being addressed in several studies using a GWAS approach and have been addressed to a limited extent in candidate gene studies. For example, variation in *ADAM33*, a susceptibility gene identified in family studies (8), has been associated with excess decline in lung function over time in subjects with asthma (9).

A GWAS was performed in a cohort of severe or difficult-to-treat non-Hispanic whites with allergic asthma, a subset of the well phenotyped longitudinally studied TENOR population (10) (Figure 1). Multiple SNPs in the *RAD50-IL13* region on chromosome 5q31.1 were associated with asthma (see Figure 1). Although a 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 GWAS studies are resulting in evidence for different sets of genes which may reflect disease misclassification in large population studies which often depend 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 expression of asthma and genetics are important areas of research for several reasons. First, there may be different phenotypic expression of the disease in a given racial group (that may or may 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 individuals of European descent with asthma compared to appropriate controls, the same allele may or may not be detected in studies of African-Americans due to different allele frequencies. For example, if the allele frequency is 30% in whites and only 5% in individuals 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 due to statistical power and sample size required to identify 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 individuals of African ancestry and showed evidence for SNPs in three 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. Figure 2 shows the range of admixture in African American subjects with asthma and controls. Individuals towards the bottom left have a higher percentage of genetic variants that are observed in West Africa than those more towards the bottom right.

Third, the correlation between genetic variants (linkage disequilibrium) in a given gene may differ based on historical geographical ancestry. This is an important tool that can be utilized in genetic studies. A common issue is that the SNP identified from a GWAS study may be strongly associated with one or more additional SNPs in the same gene or even across neighboring genes (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 “Guilty 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 may 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* (encodes a protein that interacts with the tumor necrosis factor a receptor) on chromosome 1 was observed for asthma susceptibility (14). In the white population of European descent, 20 SNPs showed evidence for 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 four correlated SNPs of the 20 SNPs showing the strongest evidence for association. In addition, in the African-American subjects, the associated allele was the alternate allele, 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 may differ due to 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 identified candidate genes for asthma were evaluated using GWAS data. Significant evidence was observed for several

genes including *DPP10* (which was observed in the African-American GWAS, 12), *TGF- β 1*, *IL1RL1* and *CYFIP2*) (15).

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

Two large meta-analyses of genome-wide association studies of lung function in general populations of European descent identified 11 candidate genes/regions. Although a small percent of these populations had a history of asthma or COPD, the results were similar whether or not these individuals 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 FEV₁ and eight genes (*HHIP*, *GPR126*, *ADAM19*, *AGER-PPT2*, *FAM13A*, *PTCH1*, *PID1*, and *HTR4*) were associated with FEV₁/FVC (16). A second GWAS meta-analysis for lung function in general populations (20,288 participants of European whites ancestry: SpiroMeta consortium), identified four genes (*HHIP*, *GSTCD*, *TNSI*, and *HTR4*) associated with FEV₁ and three loci (*HHIP*, *NOTCH4-AGER-PPT2*, *THSD4*) associated with FEV₁/FVC (17).

While these genes may 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 asthma is important since it will lead to improved understanding of biologic factors that regulate lung function in asthma which is a fundamental determinant of asthma severity (5).

Since the genes that have been associated with lung function in the general population have not reported for asthma susceptibility in the 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 due to the strong correlation (linkage disequilibrium, LD) between SNPs in *HHIP* in the white population. Therefore, studies in other ethnic groups such as African-Americans are needed since 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 chronic obstructive pulmonary disease (COPD), *HHIP* was associated with the risk of developing COPD (18). Another GWAS of COPD susceptibility identified variants in *FAM13A* (19). Both *HHIP* and *FAM13A* were associated with level of lung function in the general population as discussed in question 3 so it is possible that the association with COPD may partially reflect the association with lung function since the definition of COPD is based on abnormal levels of lung function. These genes have not identified in previous GWAS of asthma susceptibility (1,6,10,14), suggesting possible genetic differences between the development of asthma or COPD. However, it is important to remember that subjects with asthma may have normal levels of baseline lung function, especially subjects with mild asthma.

On the other hand, asthma and COPD, and other lung diseases may share some common genetic pathways. Certainly multiple genes have been associated with both susceptibility to asthma and COPD using a candidate gene approach. For example, 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 decline in lung function in 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 the GWAS previously described (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, for example: *IL6*, *IL10*, *MMP12*, and *TGFB1* have been observed in genetic studies of COPD (23–27). As more GWAS 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 eosinophils 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 over 9,000 subjects from Iceland, replicated in another Icelandic data set and then, the SNPs with the smallest p values were analyzed in a large asthma population resulting in significant evidence for a SNP in *IL1RL1* being associated with both blood eosinophil levels and asthma.

Given the large amount of GWAS data available for many diseases, the results can be interrogated across studies to determine if the same genes are being observed in different diseases even if there is not there is 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 2). An important issue is the concept of “missing variability” which refers to what some investigators feel are disappointing results from GWAS studies. 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 where there have only been a limited number of GWAS; additional studies may identify more genes. Since 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 may 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 where multiple variants each have an additive effect on disease susceptibility (31). These finding 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, since GWAS studies are designed to investigate common variants, it is possible that rare variants either in the genes already identified or in additional genes may 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; “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 than can be genotyped in larger populations to determine their phenotypic effects. Currently, 200 African-Americans with asthma from the NHLBI Severe Asthma Research Program (SARP) are being sequenced

(due to the efforts of Dr Kathleen Barnes and ARRA NHLBI funding). The results will be available to other investigators through the dbGap mechanism. Rare variants can also be identified through family studies especially by utilizing 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 as useful for asthma or allergy where “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 IL4R α antagonist, preliminary evidence for an association was observed with treatment response and two functional SNPs in *IL4R α* . 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), 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 where patients are genotyped before enrollment so that a sufficient number of individuals with the important genotype are studied. There have been two genotype stratified trials performed for response to long acting beta-agonists where 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 (35,36). 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 ACRN trial, the two homozygote genotypes were enrolled while in the other trial, an equal number of subjects with each of the three 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 in order to facilitate preventive strategies and individualize therapeutic regimens (Table 3)? First, since these diseases are not single disorders or disorders due to a limited number of genes with large effects (“disease causing” mutations; for example, as in Cystic Fibrosis), diagnostic testing is not applicable. Susceptibility testing may become appropriate but it is crucial to understand that this is not a diagnostic test but a test that will determine whether a given individual is at increased risk for developing a specific disease. It is already possible to obtain your genetic risk profile for a number of common diseases (for example: www.decodediagnostics.com). The question remains as the usefulness of such testing given the depth of our current knowledge, since 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 3, 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 develop the disease. However, a specific infant may have inherited the genetic variants associated with increased risk while an infant with the same family history may 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 due to small family size.

Thus, the usefulness of genetic testing remains a question (37,38). 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 “life style” 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 may become useful in order 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 figure 3, an overall approach to genomic studies is presented. This is the current approach that is being utilized in our ARRA funding Grand Opportunity NHLBI grant (GO) (Principal investigators: Deborah Meyers PhD, Eugene Bleeker 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 (39). In this approach, significant evidence for the same gene observed by 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.

Key Messages

- * Accurate phenotyping is needed to characterize disease heterogeneity
- * Understanding the role of genetics and genetic testing for disease susceptibility, severity and response to treatment is very important as the field is rapidly progressing
- * Thorough technological advances, it is now possible to scan an individual's genome for genetic variation - both common and rare
- * In the future, DNA testing for susceptibility to developing common disease such as asthma may be available but is unlikely to a diagnostic test
- * In the future, DNA testing for response to specific therapeutic approaches such as new biologic therapies may be available

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Figure 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 logarithm transformed p values are on the Y axis) (10).

Figure 2.

The triangle shows the admixture in the African-American cases (insert color dot) and controls (insert yellow dot) used for GWAS analysis compared to 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 whites (12).

Genetic Approaches in Asthma and Allergy

Figure 3.

This flowchart shows an overall genetic and genomic approach for studying common diseases. Genome wide association studies (GWAS) continue to be performed for diseases such as asthma and allergy. The importance of well characterized cohorts with in depth phenotyping, for example 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 (39). System 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 SE Wenzel MD).

Table 1

Key questions to be addressed

<ul style="list-style-type: none">• 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?

Table 2

Key areas being addressed in current studies

<ul style="list-style-type: none">• Current GWAS results did 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
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Table 3

Role of genetic testing in common diseases

<ul style="list-style-type: none">• Genetic information is already be utilized since family history of common diseases is routinely asked.• However, a positive family history means a higher risk in general. A specific individual may 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 since the common variants identified so far do not account for a large proportion of the variation observed for a given diseases.• Technology for genetic testing is available, reproducible and reasonable in expense (is used for single disorders such as CF routinely).