

The Genetics of Asthma: Towards a Personalised Approach to Diagnosis and Treatment

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Key messages panel:

- 1) In addition to environmental exposures, susceptibility genes exert a powerful influence on the inception, severity and treatment of asthma.
- 2) A large number of novel asthma susceptibility genes have been identified by genome wide association studies (GWAS), the functions of which are incompletely known. Polymorphism of different genes influence the origins of asthma, its severity and treatment responses.
- 3) Epigenetic processes such as CpG methylation and histone modification, and genome-wide interaction studies (GWIS) are providing novel insights of how the environment interacts with susceptibility genes.
- 4) Genetic profiles or scores are informing individual asthma susceptibility, disease natural history and therapeutic responses relevant to the emergence of personalized or stratified medicine.

Abstract

Nonbiased approaches, especially genome wide association studies (GWAS) have identified novel molecular targets in the pathogenesis of asthma, but so far only account for a small proportion of the heritability of asthma. Recognition of the importance of disease heterogeneity, the need for improved disease phenotyping and that genes involved in the inception of asthma are likely to be different from those involved in severity widens the impact of asthma genetics. Genes implicated in multiple causal pathways identifies the use of genetic scores to capture the impact of genetic variations on individuals. Gene-environmental interaction adds another layer of complexity which is being successfully explored by epigenetic approaches. Pharmacogenetics is one example of gene-environment interaction which is already having application in determining drug responders from non-responders and those most susceptible to adverse effects. Such applications represent one aspect of personalised medicine designed to help place the individual at the centre of healthcare.

Search strategy and selection criteria

References for this review were identified through searches of PubMed for articles published from January, 1980, to June, 2010, by use of the terms "asthma", "genetics", "epigenetics", and "phenotype". Only articles published in English, French, German and Russian were included.

Introduction

Genetic studies on asthma susceptibility, severity and response to treatment (pharmacogenetics), which are all key components in the development of personalised medicine approaches, will be discussed. However, since it is not possible to include all genetic studies, emphasis has been placed on those that have been helpful in delineating important concepts in asthma pathogenesis and approaches to diagnosis and treatment using a critical evaluation of current literature. Moreover, genomics and genetics will have a central role in stratified medical approaches (personalised, sometimes referred to as precision medicine). Developing genetic profiles (genetic scores) for disease susceptibility using a multigenetic approach (based on an additive genetic model or a more complex model incorporating both genetics and genomics) integrated with clinical subphenotypes will lead to early disease prediction facilitating targeted interventions (1, 2). Molecular profiling will be used to identify “at risk” individuals in order to develop strategies that have the potential to alter the development and natural history across the lifecourse of complex disorders such as asthma. Different gene profiles (genes from different pathways) help explain disease heterogeneity, progression and severity in contrast to those that confer initial disease susceptibility. Defining gene variants that influence disease severity will delineate genetic profiles that better define individuals at greatest risk from their disease as well as for disease progression and severity. Genetic severity profiles represent an important step forward in the development of new therapeutic targets based on identifying and understanding fundamental pathobiologic mechanisms. A pathway-directed approach to asthma will facilitate targeted drug discovery, especially for new biologic therapies aimed at modifying disease progression and preventing the development of more severe disease.

The basis for understanding genetic interactions in the development and progression of asthma is outlined in Figure 1. Asthma susceptibility and severity result from the interaction of genetics/genomics profiles and environmental exposures at different times across the lifecourse. In asthma, susceptibility genes interact with environmental risk factors causing early mild or intermittent asthma. Different genes then interact with additional environmental or epigenetic exposures facilitating disease progression. The varied clinical patterns found in severe asthma reflect individual genetic profiles combined with environmental exposures that initiate persistent bronchial inflammation and tissue injury which then lead to pathophysiological abnormalities and airway wall remodeling (3). One of the characteristics of severe asthma is resistance or reduced

responsiveness to therapy (4, 5). Pharmacogenetic interactions may alter therapeutic responses reducing sensitivity to specific therapies facilitating more severe disease phenotypes. Thus, characterising asthma severity phenotypes, including predictive genetic and genomic biomarkers, will lead to a better understanding of disease heterogeneity and progression and in doing so will facilitate development of new targeted therapies.

Asthma Genome Wide Association Studies (GWAS)

In recent years genome-wide association studies (GWAS) have been extensively utilised to investigate the genetic basis of common complex diseases including asthma (6, 7). Before GWAS, there were many candidate gene studies for asthma susceptibility (8, 9); however, the majority of the positive associations were not replicated in GWAS either due to differences in phenotype definition, populations (either in terms of ancestry or environmental exposures), or being due to false positives and small sample sizes (10). GWAS utilise genotyping arrays with up to millions of single nucleotide polymorphism (SNP) markers located throughout the genome. This provides an unbiased or hypothesis-independent means to identify the underlying genetic variants that contribute to disease, its severity and partial phenotypes such as lung function and bronchial hyper-responsiveness (BHR).

The first comprehensive GWAS in asthma was reported by Moffatt and colleagues in 2007, and identified a novel locus on 17q21 locus containing a number of genes including *ORMDL3* and *GSDML* (11). This revealed the potential for GWAS for uncovering novel susceptibility genes to identify previously unknown biological processes involved in asthma susceptibility.

Subsequently, the 17q21 locus for asthma has been the most highly replicated (12-17).

Subsequent GWAS utilizing genotyping arrays that provide information on greater numbers of variants and larger case-control populations have identified further loci consistently associated with asthma including *IL33* on chromosome 9p24 (15, 17, 18), *HLA-DR/DQ* on 6p21 (17, 19-24), *IL1RL1/IL18R1* on 2q12 (12, 15, 17, 18, 24, 25), *WDR36/TSLP* on 5q22 (15, 18, 23), and *IL13* on 5q31 (17, 22) (Table 1). In populations with different racial backgrounds, GWAS have uncovered evidence for loci that may be ethnic specific such as *PHYNN1* observed in African-American asthmatics (15). However, as with other common diseases, on an individual gene basis, genes observed in GWAS do not explain a large degree of the heritability of asthma; for this a multigenetic approach is needed. In an Australian GWAS (16), the utility of genetic loci identified to predict disease status in the European consortium GABRIEL (17) was assessed.

While a multi-SNP score computed based on the 10 most associated loci reported in the GABRIEL study was significantly associated ($p=8.2 \times 10^{-15}$) with asthma in the Australian population, low sensitivity and specificity were observed, emphasising the need for even more complex genetic models and improved phenotyping for disease prediction.

The low risk conferred by disease-associated variants reflects the complex interactions between different genetic and environmental factors underlying disease. In large GWAS, genetic variation is measured across a range of often unknown environmental exposures and ignores the effects of gene-gene interactions (epistasis). This has led some to question the usefulness of genetic approaches for disease prediction (26). However, this interpretation ignores the important insights into disease mechanisms through the identification of previously unrecognised biological pathways associated with asthma pathogenesis.

It has also become apparent that by using a simple phenotype of asthma diagnosis (often “doctor diagnosed asthma” driven by the need to increase sample size by combining samples across cohorts), the effect of genetic variants is further diluted as many different asthma phenotypes (an observable characteristic or trait of a disease) or endotypes (a distinct functional or pathobiological mechanism) are analysed together (27). The assumption is often made that genetic variants will contribute to disease susceptibility equally. However, at the simplest level, while some loci are associated with both childhood- and adult-onset asthma (23), there are some genomic regions unique to each (17, 28). Recent studies have also demonstrated the utility of “unbiased” clustering approach in multidimensional data to identify different asthma phenotypes (29, 30). Definition of asthma endotypes with more precision will allow more accurate identification of genetic and environmental disease risk factors, preventing these signals from being diluted by phenotypic heterogeneity. For example, a recent GWAS analysis for wheeze phenotypes identified through latent class analysis in a large longitudinal birth cohort provided evidence of etiologic differences among wheezing syndromes (31).

Although GWAS has been useful for many common diseases, there are limitations that need to be considered. First, most GWAS panels contain common and not rare variants and have been developed for populations of European white descent. Therefore, these panels may not be appropriate for other races. Second, although most genes are well represented on genotyping panels, when investigating a specific gene, it is important to determine if the appropriate SNPs are on the panel. A negative result may be due to lack of sufficient SNPs to completely cover the gene. Third, GWAS results are usually based on a single gene model, not considering the

effect of multiple genes or the environment. Fourth, although replication is important to avoid false positives due to multiple testing, lack of replication does not always imply a false positive result. The demographics and clinical features of the original and replicate populations need to be comparable. Fifth, GWAS are often performed on populations with a physician's diagnosis with little other clinical data in order to have a large sample size. Then, it is not possible to further investigate the clinical profile of individuals with the at-risk genotypes

Gene/Environmental Interactions

GWAS approaches are being extended in other ways to gain further insights into the genetics basis of asthma (32). For example, utilisation of genome-wide gene/environment interaction studies (GWISs) may provide further important insights into the biological mechanisms underlying the response to specific environmental exposures. Ege and colleagues undertook a genome-wide interaction study of early life exposure to a farming environment on the risk of childhood asthma. Counter intuitively perhaps, they uncovered rare (but notably not common variants) which interacted with farming status to influence asthma development such as the glutamate receptor, metabotropic 1 gene (33). In a study of two birth cohorts utilising previously reported GWAS results, evidence emerged for a significant association with variants in the ORMDL3-GSDMB loci and development of asthma in children who had rhinovirus-induced wheezing in early life, but not in those whom wheezing had been triggered by respiratory syncytial virus (34). Despite the challenges of statistical power and data collection, environmental interactions remain an important area of investigation (35).

Chemical modification of DNA and chromatin histone proteins which can be passed down to the offspring (epigenome) is considered to play a critical role in translating environmental interactions with the genome. Epigenome-wide association studies (EWAS) are a promising approach through which this interaction can be systematically explored (36). Caution must be exercised where the direction of causality is unknown, as epigenetic marks could be either a cause or consequence of disease (37). However, epigenetic studies for asthma are now underway and the utility of combining epigenetic data with genetic data has been demonstrated (38, 39). For example, it has been demonstrated that DNA methylation modulates the risk of asthma related to genetic variants in the IL4R gene suggesting that combining genetic and epigenetic assessment may lead to significantly improved disease prediction in the future (40). Increasing knowledge about the functionality of the genome will also improve interpretation of GWAS results. Integration of GWAS data with data sets such as those provided by the

ENCyclopedia Of DNA Elements (ENCODE) project (41), are providing insights into mechanism of action of disease-associated gene variants to elucidate new biological pathways linked to asthma. The ENCODE Consortium is an international collaboration funded by the National Human Genome Research Institute (NHGRI) to build a comprehensive list of functional elements in the human genome, including elements that act at the protein and RNA levels, and regulatory elements that control cells and circumstances in which a gene is active. ENCODE will provide additional insight into pathogenic mechanisms by utilising the large number of moderately associated SNPs identified in GWAS which are often disregarded to reduce the level of Type I errors (42). Comparison of genetic analyses across species has recently also shown utility; Himes and colleagues identifying a new asthma candidate gene in humans encoding the Kv channel-interacting protein (*4KCNIP4*), by integrating a mouse BHR GWAS with human asthma and BHR GWAS data (43).

Genetics of lung function and asthma severity

The major emphasis for genetic studies in common diseases including asthma have focused on disease susceptibility. However, there is accumulating evidence that a proportion of genes and genetic variants important in asthma susceptibility differ from those that determine disease progression and severity (44). This is an important concept since severity genes may expose causal pathways that are more relevant targets for new therapies than those conferring asthma susceptibility. Traditional definitions of severe asthma include patients with asthma who are uncontrolled despite maximum standard treatments (4, 5). However, within this broad descriptor, there exist subpopulations each with different phenotypic characteristics (29, 30, 45).

Several early GWAS studies have compared subjects with severe asthma to those without asthma (12, 19). As might be expected, these all reported previously described asthma susceptibility genes. These patients were more likely to have a firm asthma diagnosis due to the severity of their disease, as compared to GWAS that tended to rely on a physician's diagnosis of asthma where misclassification is possible. Thus, when investigating genetics of disease severity and progression, subjects with more severe phenotypes need to be evaluated and compared to 'controls' with mild disease.

An objective measure closely related to asthma severity is the level of baseline lung function specifically percent predicted forced expiratory volume in 1 second (FEV_1) which reflects excess decline in lung function over time (30, 45). Genetic studies of lung function in the general

population should provide insight into genes that are important in determining lung function in asthma patients and may reflect genetic effects on lung growth and rate of lung function decline in adulthood (46). Large meta-analyses of GWAS for lung function in the general population (cross-sectional data) have been performed in subjects of European white descent and revealed evidence for multiple genes influencing lung function such as *HHIP* (encoding hedgehog interacting protein) which is associated either with differences in FEV₁ or the FEV₁/forced vital capacity (FEV₁/FVC) ratio (47, 48). To determine if genetic variants in genes associated with lung function in the general population also modulate lung function in asthma, Li et al. tested 14 SNPs in the 11 genes previously identified in general populations for their possible association with pulmonary function in asthmatic subjects (49). Significance was observed for multiple genes, including *HHIP*, for which each copy of the risk allele was associated with 252 ml lower FEV₁ in African-Americans and 85 ml lower FEV₁ in whites of European descent. This has led to the development of a genetic score (cumulative effects of multiple genetic variants in different genes on disease or trait) for asthma severity (Figure 2) where an increased frequency of more severe disease, based on either American Thoracic Society severe asthma classification (45) or clinical asthma severity clusters (30), was associated with an increased number of risk alleles in this five gene model.

A GWAS of lung function in asthma reported that genes in the T helper lymphocyte 1 (Th1) pathway influence disease severity in contrast to genes in the pro-allergic Th2 pathway which are important in disease susceptibility (44). Since asthma susceptibility genes differ from those implicated in disease severity, it is important to define these severity gene pathways in order to utilise genetic approaches to understand the pathophysiology of asthma progression and to answer the question of why only a subset of patients go on to develop more severe disease (Figure 3).

A multigene model is necessary to develop a genetic score for predicting progressive disease such as a decline in lung function over time. Additional studies are needed in asthma cohorts with longitudinal follow-up incorporating measures of asthma heterogeneity. For example, in the NIH Severe Asthma Research Program (SARP) cluster analysis, allergic asthmatics of increasing severity were observed (mild, moderate and severe clusters reporting a high degree of family history of asthma) whom appeared to differ genetically from the late age of onset asthmatics and asthmatics with fixed airflow obstruction (lower frequency of a positive family history) (50).

Variation in Drug Responsiveness - Pharmacogenetics

Another area of asthma genetics of major interest is the role of genetic variation in response (or lack of response) to a pharmacological therapy. Pharmacogenetics represents a further example of gene/environment interaction in which this time, the environment is exposure to a pharmacological agent/biologic and the outcome is a therapeutic drug response (including adverse events). Several examples from different classes of drugs used for asthma management will be discussed in order to emphasize different key concepts in pharmacogenetic studies, and how these approaches have an integral role in personalised medicine (Panel 1). Unlike the discussion on asthma susceptibility, this review focuses on candidate gene pharmacogenetic studies since only a few GWAS have been performed to date for response to therapy. However, GWAS are appropriate for pharmacogenetics and should be performed in new clinical trials.

'Therapy

Short-acting β_2 -adrenoceptor agonists (SABA) and long-acting β_2 -adrenoceptor agonists (LABA) are the most commonly prescribed medications for treating bronchoconstriction and as controllers for long-term symptom relief in asthma. Pharmacogenetic studies have concentrated on coding variants in the β_2 -adrenergic receptor gene (*ADRB2*) to test for association with short term bronchodilator response (i.e. bronchodilator responsiveness performed in a clinical setting) and to identify a subgroup of patients with worsening symptoms during this symptomatic treatment (51, 52).

One of the first genotype stratified trials was the Beta-Agonist Response by Genotype (BARGE) study by the NIH-NHLBI sponsored Asthma Clinical Research Network (ACRN) in which asthma patients were stratified by genotype prospectively at the Gly16Arg locus. The rationale for a genotype stratified trial was to insure that there are sufficient numbers of patients with each genotype in order to have adequate statistical power, in this case, only the two homozygote genotypes were included (Arg/Arg and Gly/Gly). Patients were randomized to receive either regular dosing or intermittent dosing of a SABA, then crossed over to receive the alternative treatment (53). The results showed that Arg16 homozygous patients improved when receiving placebo with as needed intermittent SABA therapy compared to showing no improvement on regular SABA treatment. The opposite result was observed for Gly16 homozygotes that had improved response to regular SABA therapy, with similar genotype-specific effects for several

other clinical outcomes. The authors concluded that the *ADRB2* Gly16Arg locus may affect long-term responses to regular therapy with SABA therapy (53).

There have been several small studies that suggested chronic use of LABA with or without the use of inhaled corticosteroids (ICS) in Arg/Arg homozygotes was related to adverse outcomes specifically worsening of lung function during therapy (54, 55). However, analysis of a large clinical trial with a second replicate study population of asthma patients treated with LABAs in combination with ICS showed no effects of *ADRB2* genotype on therapeutic responses including pulmonary function and asthma exacerbations, strongly suggesting there was no adverse effects in moderate to severe asthma patients receiving combination LABA/ICS treatment (56). To further confirm these results, two prospective, genotype-stratified trials identified no major effect of Gly16Arg genotype on responses to LABA therapy. One of these studies evaluated both a LABA and the LABA/ICS combination, and failed to observe any effects of Gly16Arg genotype on the LABA response (57, 58). The finding of no *ADRB2* LABA pharmacogenetic effect represents important evidence-based data for asthma treatment. This is an important finding since the majority of patients with more severe asthma are treated with LABA/ICS combinations as is recommended by practice guidelines (59, 60), though it is worth noting that high dose ICS can increase the level of expression of β_2 -adrenoceptors on the cell surface of responsive cells.

Such studies on responsiveness to β_2 -adrenoceptor agonist therapy and coding variants in the receptor gene (*ADRB2*) stress the need for adequately powered pharmacogenetic analyses, either of a sufficient size that prior genotyping is not needed or utilising genotype-stratified trials to ensure sufficient numbers of each genotype. However, a limitation of genotype stratified trials is that only a small number of genotypes can be pre-specified for stratification while, in reality, multiple SNPs and genotypes may be important in determining drug responsiveness. In addition, more extensive genetic studies investigating other genes in the β_2 -adrenoceptor agonist pathway on therapeutic or adverse responses are still needed. In addition, since adverse responses to β_2 -adrenoceptor agonists therapy are rare, studies of rare genetic variants in *ADRB2* and other pathway genes may well help define at risk individuals for rare severe events (61). A GWAS study of acute reversibility to bronchodilators has identified variants in the *SPATS2L* gene as a novel gene which needs to be investigated further in future clinical trials of LABAs (62).

Response to corticosteroids

Glucocorticoid (GCs) steroids are currently the most common anti-inflammatory therapy for the management of persistent asthma. There is a great deal of evidence to suggest that regular use of inhaled corticosteroids improves asthma control and reduces asthma exacerbations (51). However, chronic corticosteroid exposure is associated with systemic side effects that are reduced by inhaled delivery to the lung. In most cases, oral corticosteroids are used only for severe asthma exacerbations, although there is subset of severe asthma patients that require both high-doses of inhaled in addition to oral corticosteroids to achieve optimal asthma control (30, 45). Despite the ubiquitous use of corticosteroids in asthma management, these drugs may not be equally effective in every patient and subjects with severe asthma are classified as steroid resistant or refractory (63, 64).

There have been multiple candidate gene studies targeting different genes in the corticosteroid pathway including one (*STIP1*) that encodes a protein which is part of the heterocomplex that activates the glucocorticoid receptor. Genetic variation of *STIP1* has been associated with differences in FEV₁ in response to inhaled corticosteroid treatment (65). Similar pharmacogenetic effects have been reported with other corticosteroid pathway-related candidate genes such as *CRHR1* (corticotropin releasing hormone 1) (66). In another candidate gene study, response to inhaled corticosteroids in children with asthma was studied in relationship to drug metabolising genes: CYP3A4, CYP3A5 and CYP3A7 (67). In a small subset of children with a specific CYP3A4 genotype, asthma control scores were increased. However, this genotype occurred in only 7% of the children demonstrating the need for additional larger studies, possibly using a genotype stratified trial design.

Most pharmacogenetic studies in asthma have been based on candidate genes identified from relevant biologic pathways. A GWAS for corticosteroid response in 418 asthmatics of European white descent has uncovered evidence for a novel gene, *T* gene, with a 2-3 fold difference in FEV₁ response dependent on genotype (68). Another GWAS has been performed for response to corticosteroid therapy in asthma, first in a childhood cohort and then replicated in additional cohorts (69). Based upon an analysis of half a million SNPs across the genome, significant evidence was observed for genetic variants in the glucocorticoid-induced transcript gene, *GLCCI1*. Several polymorphisms in this gene are strongly correlated with each other (i.e. are in linkage disequilibrium, LD) making it difficult to isolate the specific functional variant. In these populations, variation in this gene accounted for 6.6% of the overall variability in clinical response to ICS. It is likely that responses to corticosteroid therapy in asthma are influenced by

a number of genetic variants. Thus, the development of a genetic score will be important primarily in the more severe or difficult-to-treat asthmatic to help guide selection and doses of corticosteroid therapy. Such an application would represent a genetic approach to personalised medicine in these intransigent asthma patients.

Response to Leukotrienes

Leukotriene modifying drugs are used clinically as add-on therapy in patients with severe asthma and in some countries, as primary therapy for childhood asthma. The two types of drug class available are the cysteinyl leukotriene receptor (cyst LTR) 1 antagonists and inhibitors of the 5-lipoxygenase (5-LO) enzyme, the rate limiting enzyme in the cyst LT biosynthetic pathway and encoded by the *ALOX5* gene (70-72). An early study showed that promoter variation in *ALOX5* gene identified a subset of asthma subjects with reduced enzyme activity and lack of response to treatment with 5-LO pathway inhibitors (73). A recent *ALOX5* study in children with asthma showed that children who were homozygous for the variant (non-5-repeat) alleles had higher urinary LTE levels (the terminal cyst LT metabolite), lower baseline FEV₁ and were less likely to be on cyst LT-directed therapy (74). This study highlights the importance of studying different racial groups, since variant alleles for this tandem repeat polymorphism occur at a much higher frequency in African-Americans than in children of European white descent. Further studies are needed to determine if African-Americans with a higher degree of African ancestry at this locus may be less responsive to this class of drugs.

Leukotriene signaling occurs through G-protein-coupled receptors encoded by two and possibly 3 genes *CYSLTR1*, *CYSLTR2* and *GPR99* (encoding the oxoglutarate receptor, OXGR1 or the purinergic receptor, P2Y15) (75, 76). There have been previous candidate gene pharmacogenetic studies of the two former genes with conflicting results highlighting the importance of well-designed and adequately powered genetic studies. Pharmacogenetic studies are often difficult to perform since they tend to utilise pre-existing data generated in clinical trials that were not designed to investigate these genetic outcomes. Both genetic and environmental differences in the populations that are intrinsic to clinical trials complicate interpretation of pharmacogenetic results and may lead to inconsistent results.

Future directions: Pharmacogenetics and Severe Asthma

Personalising therapies based on genotypic profiling are now becoming a reality for some diseases, especially cancers although not yet applicable to asthma. However, multiple studies

of new targeted therapies are currently underway in asthma and hold the promise of advancing personalised medicine approaches, including responder analyses based on pharmacogenetic parameters. For example, in a dose ranging study of a biologic (pitakinra, a recombinant human IL-4 variant) inhibiting the IL4/13 pathway, there was a significant dose response effect on the primary endpoint of asthma exacerbation observed only in individuals with a specific IL4R genotype (Figure 4) (77). This analysis showed that approximately 1/3 of the population was responsive to this intervention while those expressing other genotypes were non-responsive. Not surprisingly, the overall trial was negative illustrating the difficulties in identifying a responder subset which is embedded in a larger overall unresponsive population.⁷⁰ Given that the targeted biologic therapies that are being developed will be expensive, biomarkers such as those derived from pharmacogenetic approaches are needed to determine which patients are more likely to be responsive to these specific therapeutic interventions. Issues such as sample size, generalisability and replication that are critical for genetic studies in general, are especially important in pharmacogenetic studies.

Stratified, Personalised or Precision Medicine

In view of the ongoing changes in health care and led by cancer, it is becoming increasingly important to “personalise” medical care beginning with strategies to prevent disease development and extending to appropriate individualized therapy for treatment and reduce further disease progression (78). Personalised medicine is based on individual characteristics such as age, BMI, race and local environment with incorporation of predictive biomarkers including genetic profiles or “scores” (combination of multiple risk genetic variants). It is important to note that this approach will be cost effective since it will be possible to tailor level of preventive screening to an individual subject instead of screening based on general health guidelines (79). Health care professionals should understand that many of the biomarkers including genetics will not be diagnostic but will provide risk estimates which will guide the screening process and preventive strategies while pharmacogenetic profiles will help to determine individualised therapies (80).

Inception of asthma: Genetic scores will provide an estimate of the risk of developing asthma based on combinations of genetic variants in multiple genes as described in the previous sections. The specific approaches will include additive models or more complicated statistical models (for example, weighting genetic variants based on risk ratios for each variant). A legitimate question to ask is how a personalised approach could be used by health care

professionals and their patients to guide disease management? For example, when an asthmatic mother brings in her young child with an upper respiratory infection, the physician is immediately concerned that this child may develop wheezing and subsequently clinical asthma. Although such children are at greater risk of developing asthma in general because of a family history of asthma, this individual child may be at either high risk or at low risk (similar to subjects without a positive family history) based on their individual genetic score. If the child is at high risk for developing asthma, appropriate preventive measures including treatment for upper respiratory infections, early use of anti-asthma medications as well as comprehensive environmental modifications may be indicated and discussed with the family (81) As shown in Panel 2, it is important to realise that a negative family history often represents a non-informative family history due to small family size often observed in today's society. In addition, a parent may be genetically at risk for asthma but was fortunate not to have environment triggers and, therefore, did not develop this disease (although if testing was performed, the parent may have some characteristics of asthma such as bronchial hyper-responsiveness). Therefore, genetic profiles may be important even in the presence of a negative family history.

Asthma progression and severity: Individual genetic scores may be calculated for loss of lung function using a combination of genetic variants (which differ from the variants for asthma susceptibility as discussed previously). This risk estimate of developing more severe disease will allow the health care provider to prescribe therapies and environmental changes (for example, avoidance of both active and passive smoke exposure, weight loss and avoidance of known triggers for asthma exacerbations). Although a healthy life style is recommended for everyone, health issues such as smoking and obesity are widespread. It remains to be seen whether knowledge of individual increased risk for further disease development will be an important stimulus for individual change. However, with the development of specific biologic therapies that for example interfere with allergic mechanisms (anti-IgE, Th2 cytokines and chemokines etc), understanding the importance of biologic pathways in an individual patient will guide personalised therapy (82).

Pharmacogenetics: It is expected that individual response to therapy will be predicted based on genetic testing which will be particularly important for the biologic therapies for those with more severe disease. This may avoid the need for patients to be exposed to costly biologic therapies for long trial periods to help identify pathway-specific therapeutic responsiveness. This concept differs from typical pharmacogenetics based on at-risk gene variants because in this approach,

genetics is used to identify individual asthmatics whose disease is regulated by specific pathways that may be treated with specific therapies.

The future is here. Specific genetic tests and panels of tests have already been developed for both rare and common diseases. Complete genome sequencing is now being offered at multiple health care facilities resulting in a personal risk profile for developing diseases ranging from respiratory diseases to cancers and other both common and rare diseases (e.g. Mayo Clinic - <http://mayoresearch.mayo.edu/center-for-individualized-medicine/>). Although genetic panels for common diseases or complete genome sequencing are now available, it is important to realize that most predictions are based on single genetic variants for diseases such as asthma. Until genetic profiles using multiple associated variants are further developed and tested for validity in new cohorts, the accuracy of such predictions limits their clinical usefulness. However, the field is rapidly progressing and is already clinically useful for other diseases so it is important that clinicians and researchers keep abreast of the latest findings for their disease of interest. It is extremely important to critically examine any proposed tests for accuracy and the need for continued updating as new genetic variants are described.

Preventive measures may then be developed for the individual including lifestyle modifications and increased screening as well as personal recommendations for therapy once a specific disease is diagnosed. It is extremely important that these data be continually updated as more knowledge of the genome is discovered (83). Placing the individual citizen at the centre of healthcare is the basis for personalised medicine with asthma being an excellent example of how companion diagnostics is already able to influence therapeutic decisions (78, 79). However, further rapid advance in this field is critically dependent upon a more collaborative approach to research so that large collections of deeply phenotyped patients and associated biological collections are generated from different countries that should embrace close interactions between patients, biological scientists, clinicians, informaticians and those in industry opening up drug trials for pharmacogenetic analysis and developing a new way of drug target discovery working with academia such as the EU FP7 UBIOPRED project (<http://www.imi.europa.eu/content/u-biopred>) and the US NHLBI Severe Asthma Research Program (SARP, <http://www.severeasthma.org>).

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Legends to figures

Figure 1: Asthma is due to a combination of both genetics and environmental exposures leading to early intermittent asthma. Additional gene variants and further environmental exposures lead to chronic persistent disease with heterogeneous subtypes.

Figure 2: A significantly increasing percent of subjects with severe asthma corresponds to an increasing number of risk alleles using an additive model.

Figure 3: Asthma susceptibility is associated with genetic variants in the Th2 pathway. Once asthma develops, progression of the disease is influenced by both lung function genes that are important in normal lung functions and genetic variants in the Th1 pathway as well as genes in the Th2 pathway leading to decreased lung function and more severe disease.

Figure 4: Subjects with the rs8832 GG genotype demonstrated a significant dose-dependent reduction (placebo/1mg/3mg/10mg) in exacerbations. There was no dose-dependent relationship with exacerbations for subjects with the AG/AA genotypes.

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