



Personalized Medicine for Severe Asthma: How Far Have We Achieved?

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Abstract

There is increasing pharmacogenetic literature on the heterogeneity in the treatment responses to different anti-asthma drugs including inhaled corticosteroid (ICS), which are indicated for patients with moderate-to-severe asthma. A number of genetic targets including STIP1, CRHR1, CYP3A4, GLCC11, T gene and FBXL7 are potential pharmacogenetic biomarkers for predicting patients' response to ICS. Knowledge on predictive variants in these genes allows for the genotyping and selection of patients with severe asthma for personalized treatment with high-dose ICS treatment. There is an emerging trend to unravel genetic variants that predict treatment responses among patients with different asthma endotypes. Some patients with severe asthma are refractory to maintenance corticosteroids, and several biological agents targeting type 2 helper T lymphocyte pathway offer hope of optimizing their disease control. The efficacy of subcutaneous pitrakinra is dependent on patients' IL4R status. Nonetheless, such pharmacogenetic effect has not been investigated for other biological agents such as mepolizumab. The adoption of a personalized pharmacogenetic approach to health care delivery facilitates the optimal use of novel, expensive and potentially toxic therapies in patients with severe asthma.

Asthma is characterized by airway inflammation, and is caused by complex interactions between many genetic and environmental factors. Anti-inflammatory therapies such as inhaled corticosteroid (ICS) are therefore an integral component of asthma pharmacotherapy under different international guidelines. There is substantial inter-individual variability in patients' response to anti-asthma treatments. According to Global Initiative for Asthma guideline, patients with severe controlled asthma require maintenance oral corticosteroid or anti-immunoglobulin E treatments. A number of biologic agents have recently been shown to be treatment alternatives for these patients. Pharmacogenetic approach facilitates personalized medicine by differentiating treatment responders from non-responders, whereby substantially reducing the economic burden of asthma. Candidate gene and pathway-based pharmacogenetic methods have identified a number of candidate genes and their functional variants, but larger-scale pharmacogenomics has drawn more and more attention over the past decade. Our group has previously discussed the genetic targets for bronchodilator responses to β_2 -agonists and leukotriene modifiers. This editorial focused on recent advances in the pharmacogenetics of ICS and the novel biological agents as treatment modalities for patients with severe asthma.

Inhaled Corticosteroids

Corticosteroids [1-10] are the first-line anti-inflammatory therapy for patients with persistent asthma [11-15]. A subset of patients with severe uncontrolled asthma requires maintenance oral and high-dose inhaled corticosteroid (ICS) treatment [16-19]. Some of these patients are classified as steroid resistant or refractory (once poor treatment adherence has been excluded) [20,21], and emerging evidence supported the importance of genetic variations in determining corticosteroid responsiveness. For instance, polymorphic markers of *STIP1* encoding the heat shock organizing protein that plays a critical role in the assembly and activation of glucocorticoid receptor hetero-complex has been associated with differences in FEV₁ in response to ICS treatment [22]. Similar pharmacogenetic findings have been reported with other candidate genes along the corticosteroid pathway (e.g. corticotropin releasing hormone receptor 1 [*CRHR1*]) [23] and genes involved in its metabolism (e.g. 3A4 isoform of cytochrome P450 enzyme [*CYP3A4*]) [24].

Adopting the whole-genome approach, Tantisira *et al.* found a functional single-nucleotide polymorphism (SNP; rs37973) of glucocorticoid-induced transcript 1 gene (*GLCC11*) to be associated with substantial decrements in response to ICS treatment in asthma patients under the Childhood Asthma Management Program (CAMP) [25]. Such finding was replicated in which the combination of rs37973 of *GLCC11* and rs1876828 of *CRHR1* predicted 66% of FEV₁ change following ICS treatment [26]. Another pharmacogenomics study of 418 white asthmatics identified T gene, a transcription factor, as a novel locus for ICS response [27]. Two variants rs3127412 and rs6456042

were strongly associated with patients' ICS response. A two-fold to three-fold difference in FEV₁ response was noted between subjects homozygous for the wild-type and minor alleles.

A more recent genome-wide association study (GWAS) targeted symptomatic response to ICS instead of lung function and disease exacerbations as the study outcome [28]. Three SNPs, namely rs1558726, rs2388639 and rs10044254 were found in paediatric but not adult cohorts. Rs10044254 situated in the intronic region of F-box and leucine-rich repeat protein 7 (*FBXL7*) was associated with decreased expression in immortalized B cells and improved symptomatic response to ICS. Besides, pharmacogenetic studies of ICS response in adults must not be extrapolated to children whose phenotypes may be different by being either naive to ICS or on it for a shorter time period. Children with a shorter duration of asthma may have different extent of irreversible airway remodeling.

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Wang et al. conducted a GWAS for drug response-associated genes in 120 randomized participants who inhaled multiple doses of corticosteroids [29]. By implementing a Pharmacodynamic model, they detected associations of genome-wide significance between FEV₁ response to ICS and five loci. Many of these loci contained metabolic genes related to lung function and asthma risk. In particular, pooling of results from several replicating trials pinpointed rs6924808 on chromosome 6 and rs1353649 on chromosome 11 as the most important candidate loci. Nonetheless, the significance of these novel pharmacogenetic loci remains unknown at present.

Interethnic differences in genetic epidemiology must be taken into consideration in designing and interpreting asthma pharmacogenetic studies. Our case-control association studies revealed substantial discrepancies in the frequencies of SNPs and haplotype blocks for asthma genes between Chinese and other populations. We performed pyrosequencing on 100-kilobases spanning each of 10 asthma loci identified by the large consortium-based genome-wide association study in 24 healthy Hong Kong Chinese children [30]. For 17q21 locus, we found substantial variation in the haplotype structures that were constructed from 224 common SNPs among our subjects and six ethnic groups reported under 1000 Genomes Project. These sequence variations must be considered during the selection of tagging SNPs for replicating genetic associations between populations.

Replication works should be performed to confirm the importance of the above candidate genes for ICS response. Rs37972 of *GLCCI1* was genotyped in three cohort studies of north European asthmatic children with a reported use of ICS [31]. This SNP was not significantly associated with an increased risk of oral corticosteroid use, asthma-related hospital visits, uncontrolled symptoms or higher ICS dosages. As reported in the initial study, variation in *GLCCI1* only accounted for 6.6% of the overall variability in clinical response to ICS [25]. Responses to corticosteroid treatment in asthma are probably affected by several genetic variants. The development of a genetic score formed from the presence of risk alleles or genotypes in multiple SNPs will be the ultimate goal to guide the selection of type and dose of ICS treatment in patients with severe or difficult-to-treat asthma (i.e. personalized medicine).

The disease status of asthma can be assessed by patients' clinical scores, spirometric parameters, induced sputum analyses and exhaled biomarkers [32]. In 2006, Wenzel proposed that the diagnostic label of "asthma" in different patients be defined by different phenotypes that are partly dependent on different disease processes in each individual [33]. These disease phenotypes, such as airway hyperresponsiveness (AHR) to methacholine and increased exhaled nitric oxide level, describe clinically relevant "observable characteristics" that represent many different asthma variants with different etiologies and pathophysiologies. The classification based on asthma phenotypes does not necessarily relate to or give any insight into the underlying disease processes. Understandably, studies of unselected cohorts failed to identify reproducible genetic and environmental risk factors for asthma.

The concept of classifying asthma into distinct "endotypes" has gained increasing popularity in recent years [34]. An endotype is "a subtype of a condition which is defined by a distinct functional or pathophysiological mechanism" [35]. In contrast to phenotypes, endotypes describe distinct disease entities with a defining etiology and/or a consistent pathophysiological mechanism. Different SNPs and genetic pathways are implicated in different asthma endotypes. Clemmer and coworkers hypothesized the presence of a single

quantitative corticosteroid responsiveness endophenotype that captured the clinical phenotypes of lung function, bronchodilator response, airway responsiveness, symptoms, need for oral steroids and frequency of emergency department visits and hospitalizations [36]. They found the composite endophenotype to be superior to the six individual clinical phenotypes in the study population as well as four replication populations. Patients with this endophenotype of corticosteroid responsiveness may in turn be grouped under one of the endotypes of allergic asthma (adults), asthma predictive index-positive preschool wheezer and severe, late-onset hypereosinophilic asthma [35]. It makes biological sense to search for genetic predictors for asthma therapies such as β_2 -agonists and leukotriene modifiers among patients with different endotypes for corticosteroid responsiveness. The selection of study outcomes in relation to different asthma endotypes is an emerging concept that facilitates more accurate and reproducible evaluation for asthma pharmacogenetic biomarkers.

Biological Agents

In 1989, Mosmann et al. first proposed that helper T (Th) lymphocytes could be sub-classified based on their repertoire of cytokines into Th1 and Th2 lymphocytes [37]. In humans, Th1 cells secrete interferon (IFN)- γ and tumour necrosis factor (TNF)- β whereas Th2 cells produce IL-4, IL-5, IL-9 and IL-25. Both classes produce TNF- α , IL-2, IL-3, IL-10 and IL-13. Simplistically, there remains an inverse relation between the tendency of helper T lymphocytes to produce IFN- γ as opposed to IL-4 or IL-5. Th2 cells produce IL-4, IL-5, and IL-13 and function in the relative absence of IFN- γ to induce allergic immune responses. Asthma has been reported to be characterized by infiltration of activated T lymphocytes and eosinophils into the bronchial mucosa [38]. These cells, along with resident mast cells, secrete IL-4, IL-13 and other inflammatory mediators to result in non-specific AHR. A number of randomized clinical trials tested drugs, such as anti-IL-5 [6-8], anti-IL-4Ra [9], anti-IL-13 [10,11] and more recently anti-TSLP [12], that target this Th2 process. The lack of therapeutic efficacy in some of these studies has lessened enthusiasm for this pathway's singular importance. Because asthma is a heterogeneous syndrome with different "endotypes" [35], it was perhaps not surprising to find negative trial findings in some of these clinical trials. The challenge would be to identify a responder subset that is embedded in a larger population that is unresponsive overall [39].

An illustrious example was found from antagonist of interleukin-4 receptor- α (IL-4Ra). The selective targeting of either IL-4 or IL-13 might have been too selective [40,41]. In view of the ability of IL-4Ra to bind both of these Th2 cytokines [42], a recombinant human interleukin-4 variant called pitrakinra that competitively inhibits IL-4Ra receptor complex was developed. In humans, pitrakinra reduced disease severity, lowered circulating IgE concentrations and normalized T-cell subsets in patients with severe atopic eczema [13]. Wenzel et al. showed treatment benefits in patients with atopic asthma who received subcutaneous administration of pitrakinra [14]. In a subsequent dose-ranging study, a significant dose-response effect of pitrakinra on the primary outcome of asthma exacerbation was observed only in individuals with a specific *IL4R* genotype that was found roughly in a third of the population [15]. On the other hand, authors reporting dupilumab, a fully humanized monoclonal antibody to IL-4Ra, did not address the issue whether its efficacy might be predicted by patients' *IL4R* status [16]. The finding with pitrakinra illustrated the promise of advancing personalized medicine approaches through responder analyses based on pharmacogenetic parameters. Since the above targeted biological drugs are expensive, biomarkers derived from

pharmacogenetic analyses can help to identify which patients are likely to be responsive to which specific anti-asthma treatments.

Mepolizumab has been developed to antagonize IL-5 that is a potent cytokine driving circulating eosinophilia and eosinophilic asthma. Published clinical studies of mepolizumab yielded conflicting findings. Some studies showed that mepolizumab reduced asthma exacerbations [6,7] whereas another clinical trial failed to detect any benefit of this drug in lowering asthma symptoms [8]. Unfortunately, none of these clinical trials on anti-IL-5 drugs attempted to stratify patients' responses based on their *IL5* genotypes as with the successful story of *IL4R* for pitrakinra. The identification of main variants in *IL5* and other genes regulating the Th2 pathway that modulate mepolizumab response allows for the personalized treatment among asthmatic patients for recommending this expensive targeted biological agent.

Conclusions

During the past decade, there has been explosion in pharmacogenetic literature that saw substantial progress on understanding the heterogeneity in the treatment responses to different anti-asthma drugs. Corticosteroids given either orally or in high-dose via inhalation are the first-line controller treatment for patients with moderate-to-severe asthma. A number of genetic targets including *STIP1*, *CRHR1*, *CYP3A4*, *GLCC11*, *T* gene and *FBXL7* are potential pharmacogenetic biomarkers for predicting patients' response to ICS. Some patients with severe asthma are refractory to maintenance corticosteroids, and several biological agents targeting the Th2 pathway offer hope of optimizing their disease control. The efficacy of subcutaneous pitrakinra is dependent on patients' *IL4R* status, with its dose-response effect being found only in carriers with a particular *IL4R* genotype. On the other hand, such pharmacogenetic effect has not been investigated for other biological agents such as anti-IL-5, anti-IL-13 and anti-TSLP. The benefit of a personalized, tailored approach to health care delivery is needed in the development of expensive biological agents directed at a specific biologic pathway. These findings will ultimately allow us to choose a treatment regime with maximal therapeutic benefit for an individual asthmatic while minimizing the risk for adverse events.

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