Understanding clinical variability in response to asthma treatment

'...significant gaps in knowledge still remain and we need several replicative studies in different populations to derive firm conclusions, which may help to bring pharmacotyping into clinical practice.'

Asthma is a complex clinical syndrome with multiple genetic and environmental factors contributing to its phenotypic expression [1]. Multiple epidemiologic and experimental studies indicate that asthma risk may be modified by epigenetic changes, such as DNA methylation, covalent histone modifications, microRNA changes and chromatin alterations, after early or later environmental exposures [2]. This etiological heterogeneity adds to the complexity when addressing variation in the response to anti-asthma treatment. The relevant clinical variability in response to asthma medications may be due to genetic determinants and refers to the polymorphisms in the genes associated with asthma susceptibility, genes encoding either the drug targets or molecular components of the downstream signal transduction pathways responsible for drug action [3].

Clinically the spectrum of asthma severity has three distinct levels: mild, moderate and severe. At each level, the clinical characteristics and the mode of treatment of an individual differs (FIGURE 1). It is critical to determine the level of severity to better understand how to treat and control the asthma. Therapies typically used for the treatment of asthma include: β_2 -adrenergic agonists, for bronchodilation; glucocorticosteroids, for their potent anti-inflammatory action; theophylline and its derivatives, for bronchospasm and inflammation; and leukotriene inhibitors and antagonists as bronchodilators and anti-inflammatory drugs. Anticholinergics may also be used as bronchodilators, although they are less potent than β_2 -agonists. Short-acting β_2 -agonists (e.g., salbutamol, terbutaline, isoprenaline, fenoterol and so on) are the most effective medications used for the treatment of mild asthma, whereas long-acting β_2 -agonists (e.g., salmeterol, formoterol and so on), inhaled corticosteroids (ICs) and leukotriene inhibitors may be used independently or in combination for the treatment of mild-to-moderate asthma. Severe or 'refractory' asthma can be treated

either by oral corticosteroids, by very high dose of inhaled corticosteroids or in combination with theophylline. The degree of responsiveness to these medications varies from person to person. Variability in an individual's response to the prescribed asthma treatment may be due to several other factors, including treatment compliance, severity, intercurrent illness, environmental exposure, age and drug interactions with other medication being taken at the same time [4]. Although heterogeneity in treatment responses are likely to arise in part by environmental factors, it is thought that up to 60–80% of this variability may be due to genetic factors [5]. This indicates the need for finding genes responsible for clinically relevant variability in response to the main classes of asthma drugs. Many genetic variants often consist of just a single base pair substitution resulting in alterations of protein function or expression [6]. These SNPs, as well as their variable linear combinations (haplotypes), may be major determinants of the variability in therapeutic response.

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The pharmacodynamics and molecular basis of the action of β_2 -agonists have been extensively reviewed [7]. A series of SNPs in the β_2 -AR gene have been identified [8,9]. A total of four of these were found to cause changes in the encoded amino acids at residue 16, 27, 34 and 164, and few were found to have particular relevance to pharmacogenetics [10–13]. In a recent placebo-controlled, double-blind study (β -Agonist Response by Genotype; BARGE) [14] suggested that the 16th residue of the β_2 -adrenergic receptor (β_2 AR) has a pharmacogenetic relevance

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despite being neither in the drug-binding domain nor in the intracellular coupling domain of the trimeric G_s protein. Further Drysdale *et al.* indicated that the unique interaction of multiple SNPs within a haplotype may affect biologic and therapeutic phenotypes and may also have a good predictive power as a pharmacogenetic marker [11]. ICs are the preferred first-line choice for the management of mild-to-moderate persistent asthma [15]. They are considered to be the most effective and potent anti-inflammatory medication currently available for asthma treatment. Despite the proven efficacy of ICs in asthma, their precise mechanism of action is still incompletely characterized. They exert their pharmacological action through activation of the cytosolic glucocorticoid receptors. Recently, it has been hypothesized that sequence variants in the genes in the glucocorticosteroid pathway contribute to the variability in inhaled steroid treatment response [16]. Polymorphisms in corticotropin releasing hormone receptor 1 (*CRHR1*) were found to be associated with significantly improved lung function (a difference of 8–10% forced expiratory volume in 1 second [FEV_1]) after 8 weeks of IC therapy. Interestingly, Tantisira *et al.* also recently reported a functional variant in another gene that may be able to predict responsiveness to ICs [17]. They demonstrated that the nonsynonymous variation coding for replacement of histidine 33 with glutamine in the T-box 21 (*TBX21*) gene, which codes for the transcription factor T-bet (T-box expressed in T cells), is associated with significant improvement in the PC_{20}

(a measure of airway responsiveness) of asthmatic children in a large clinical trial spanning 4 years. Studies of leukotrienes and their role in asthma have prompted great interest in agents that affect leukotriene activity [18–20]. Although antileukotriene agents have an anti-inflammatory function, they are not as potent as corticosteroids and are generally restricted to mild asthma as a substitute for ICs, or in severe asthma as an add-on therapy. Two essential pharmacologic approaches have been taken in an attempt to reduce the effects of leukotrienes: interruption of leukotriene biosynthesis (leukotriene inhibitors) and blockage of the leukotriene receptor (leukotriene antagonists). In the leukotriene biosynthetic pathway, some key enzymes are encoded by polymorphic genes that can affect the therapeutic response of leukotriene therapy.

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Theophylline has been widely used as a bronchodilator for the treatment of bronchial asthma and has been suggested to modulate immune response. The molecular mechanism for the anti-inflammatory action of theophylline is currently unknown, but low-dose theophylline is known to control asthma through increasing activation of histone deacetylase which is subsequently recruited by corticosteroids to suppress inflammatory genes [21]. Other actions such as adenosine receptor antagonism and phosphodiesterase inhibition have also been suggested. Anticholinergic agents are used as bronchodilators in asthma and other airway diseases. In asthma, airways function and response to bronchospastic stimuli (e.g., allergens, irritants and inflammatory mediators) is controlled in part by cholinergic muscarinic receptors, which regulate smooth muscle contraction. Out of the five known muscarinic receptors, airway smooth muscle contains M2 and M3 receptors [22] and the bronchoconstriction of the airway smooth muscles is mainly mediated by M3 receptors [23]. The genetic variations in these receptors could potentially affect treatment responses to anticholinergic agents [24–26], but the few studies conducted so far have failed to support a pharmacogenetic association. Possible reasons for lack of association might be an inadequate sample size and underpowered study design.

However, the possibility of involvement of unknown variations of these genes for drug response still needs to be elucidated.

Owing to the complexity of drug action and its therapeutic response, a broader genomics approach will provide an edge in finding new drug targets from categories such as the protein receptor at which the drug directly binds, signal transduction cascades or downstream proteins, and proteins involved in disease pathogenesis, and optimizing therapy for the individual patient [27,28]. The pharmacogenetic literature explicates that the consideration of only one protein or receptor as an efficient drug target will not be of much clinical relevance to predict the therapeutic response. Specific problems to date include the inability of a single polymorphism to be highly predictive of response, and inconsistencies across studies of the same polymorphism. It seems likely that an important factor in the above limitations is the approach of focusing on a single polymorphism in a single gene. Considering that a drug response may involve a large number of proteins, it seems unlikely that a single polymorphism in a single gene would explain a high degree of drug response variability in a consistent fashion. Thus, it shows that a polygenic or genomic approach will be more appropriate. The attempts in this direction will provide a new dimension in personalized medicine, drug efficacy and drug development in the future.

Pharmacogenetic studies of asthma have not yet been adequately replicated in different populations; hence they cannot be adopted as the standard-of-care as a diagnostic. Furthermore, due to the influence of environmental factors in asthma, it is worth to speculating that the direct association of any sequence variation with the variability of drug response cannot be obtained. So, the

frequency and penetrance of sequence variants (such as SNPs, microsatellites and so on) affecting responsiveness to a particular drug and potential interactions with other genetic and environmental factors should be assessed in multiple population-based samples [29,30]. Therefore, there is a pressing need for numerous large-scale prospective studies in order to further elucidate gene–environment interaction in asthma pharmacogenomics. Such studies have to be carried out in different ethnic groups, as genetic association findings of one population will not necessarily be valid for other populations. Apart from what we have already achieved in asthma pharmacogenetics, there is still a long way to go before the pharmacotyping concept and its knowledge are translated into clinical practice. In conclusion, despite of new developments and recent studies in asthma pharmacogenetics, significant gaps in knowledge still remain and we need several replicative studies in different populations to derive firm conclusions, which may help to bring pharmacotyping into clinical practice.

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