Pharmacogenetics of asthma

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Clinicians are always struck by the marked disparity in treatment response between individuals with a given disease of a particular severity. There are many explanations for variability in treatment response and these can be split up into defined categories (table 1). This perspective deals with the genetic factors which may potentially play a role in determining treatment response in patients with asthma.

The study of pharmacogenetics is in its infancy. However, the idea that genetic factors may be important in determining treatment response to a given drug is not new. The best examples of pharmacogenetic factors influencing drug treatment response relate to drug metabolizing enzymes. For example, individuals carrying particular cytochrome P4502D6 alleles show altered metabolism of several clinically important drugs including nortryptiline and the clinical effectiveness (and incidence of side effects) on treatment is largely determined by genotype. Other examples include the role of P4502C9 alleles in warfarin metabolism and cytochrome P4502A6 alleles in nicotine dependence [1–4]. The magnitude of effect of these genetic variants is considerable. Indeed a case could probably be made on pharmacoeconomic grounds for routine screening of individuals before commencing isoniazid therapy (especially in racial groups with a high prevalence of the slow metabolizer status). Interestingly, a deoxyribonucleic acid (DNA) chip is already marketed in the USA and Scandinavia for genotyping of cytochrome P450 allelic forms.

Few agents used in the treatment of asthma have critical metabolic pathways for which genetic variants control drug levels. However, attention has recently focused on the possibility that the response to a given agent at the cell level may be determined by genetic variants of the target protein. Polymorphism within genes within the human genome is common. In general ~1 in 1,000 base pairs within coding regions are polymorphic, although because of redundancy in the amino acid coding system not all single nucleotide polymorphisms (SNPs) result in an amino acid change in the relevant protein. The rate of polymorphic variation also varies at different loci, with some genes having much higher levels of polymorphism. A recent screen of candidate genes for hypertension suggested the majority contained at least one SNP [5]. A comprehensive screen of genes likely to be important in determining asthma treatment response has not been performed, although the author’s group and others have been systematically looking at the genes coding for primary targets, searching for polymorphic variation. However, it is important to realize that most polymorphisms are likely to have no major functional effects, and so before searching for clinical associations between a given polymorphism and a treatment end-point, it is essential to assess the potential functional effects of the polymorphism in question. A summary of the main variants in asthma treatment response genes which have been identified, to date is shown in table 2.

For a polymorphic variant to be important in determining treatment response at the population level it must be reasonably common. A good example of a rare polymorphism which may be important, but only in occasional individuals, is the threonine-isoleucine (Thr-Ile)164 β2-adrenoceptor polymorphism. *In vitro* functional studies in recombinant cell systems have demonstrated that the isoleucine 164 β2-adrenoceptor variant shows markedly reduced coupling to catechol ligands and it could be predicted that individuals homozygous for this variant (all individuals carry two copies of the β2-adrenoceptor gene which is situated on chromosome 5q) would show a markedly reduced response to many β2-agonists [15]. However, the allelic frequency of this polymorphism in the Caucasian population is only ~3% and to date the author’s group have not identified a homozygous individual. In contrast the arginine-glycine (Arg-Gly)16 polymorphism in the β2-adrenoceptor is common in the general population [9]. The glycine 16 form of the receptor *in vitro* demonstrated increased down regulation following agonist exposure [16] and two clinical studies have suggested that individuals homozygous for the glycine 16 variant of the β2-adrenoceptor show reduced treatment response following either acute or chronic exposure to β2-agonists [7, 17]. The magnitude of effect in these studies was relatively small and other studies have shown no association of this polymorphism with fatal asthma or long term deterioration on β2-agonists [18]. The key question as to whether individuals homozygous for the glycine-16 variant of the β2-adrenoceptor show reduced responsiveness to long acting β2-agonist remains to be fully assessed. If indeed reduced responses

<table>
<thead>
<tr>
<th>Disease specific</th>
<th>Disease severity</th>
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<tr>
<td>Disease subtype (e.g. aspirin-sensitive asthma)</td>
<td>Compliance</td>
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<tr>
<td>Individual factors</td>
<td>Genetic</td>
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<tr>
<td>Intercurrent illness</td>
<td>Other medication</td>
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<td>Environmental exposures</td>
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Table 1. – Some factors affecting treatment response

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that steroid responsiveness varies markedly between asthmatic individuals [13]. Finally, the author has recently been examining polymorphic variation in the phosphodiesterase type 4 isomorf family [22]. Database searches suggest that polymorphic variants do exist in this gene family although the potential functional relevance of these polymorphisms remains to be determined. Because there are several different phosphodiesterase type 4 family members, and also splice variants of the different genes, evaluating the significance of polymorphisms in this gene family will be difficult.

In summary therefore it is clear that genes whose products are important targets for asthma treatment contain functionally relevant polymorphisms. In general the magnitude of any functional effect of these polymorphisms is smaller than for established polymorphisms in, for example, hepatic drug metabolizing pathways. Advances in chip technology have made large scale genetic screening of individuals for given polymorphisms easy to perform but no adequate studies on the cost effectiveness of this approach have been carried out to date. For such studies to proceed, an adequate assessment of the contribution of a given polymorphism to variability in response to a given drug needs to be made, and this is the challenge for asthma pharmacogenetic studies in the next few years. The possibility that pharmacogenetic factors may influence treatment response is particularly important in small phase II studies because if a small group contains by chance an excess of individuals with one particular genotype which affects treatment response it would be easy to either overestimate or underestimate the efficacy of the compound being studied. In addition the possibility that genetic variation may be important in determining the magnitude of treatment response has implications for the drug licencing process in that it is likely that regulatory bodies will need to be reassured that novel compounds coming to the market have been assessed in an appropriate population in terms of genetic variability.

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References


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