Pharmacogenetics is the study of genetic factors that contribute to variation in the therapeutic responses of different individuals to drugs. Characterisation of such genetic mechanisms for individual drugs may allow screening to provide better targeting of therapy towards those most likely to benefit, and avoidance in those who may experience serious adverse effects. The main groups of drugs used in asthma management are beta-2 adrenoceptor agonists, glucocorticosteroids, theophylline, anti-muscarinic drugs, and anti-leukotriene drugs. Pharmacogenetic studies in asthma have concentrated heavily on beta-2 agonists, with less evidence available on the others.

**Beta-2 receptor polymorphism**

Beta-2 agonists relax airway smooth muscle principally by activating the beta-2 adrenoceptor, a G-protein-linked 7-transmembrane receptor of 413 amino acids that signals via adenylate cyclase and raised cAMP. Beta-2 receptors can become desensitised by uncoupling from the Gs protein, followed by internalisation and phosphorylation of the receptor. The beta-2 receptor is encoded by an intronless gene (ADRB2) on chromosome 5q32-34. The 5' region upstream of ADRB2 is a putative promoter region containing several transcriptional regulatory motifs, and which also encodes a 19 amino-acid protein, the Beta Upstream Protein (BUP), which exerts negative control on translation of ADRB2 mRNA into protein.

Single nucleotide polymorphisms (SNPs) are common throughout the genome, and most have no functional effect. SNPs within a coding region may affect the amino acid sequence and hence modulate the protein's activity as a receptor or enzyme, while those in regulatory regions may affect gene transcription and hence alter the amounts of the protein expressed in cells. Eight SNPs have been identified within the regulatory region of the ADRB2 gene and a further nine within the coding region. Of the former, one that causes an Arg19Cys substitution in the BUP regulatory protein increases expression of beta-2 receptors in human airway smooth muscle cells, but there is little evidence that the remaining regulatory region SNPs have functional effects. Of the nine SNPs in the coding region, four alter receptor structure. A common SNP at nucleotide position 46 (C to G) results in an arginine at amino acid position 16 being changed to glycine (Arg16Gly), and three other SNPs cause the Glu27Gln, Val34Met, and Thr164Ile variant receptors. The latter two are rare (<1%), and most functional studies have focussed on Arg16Gly and Glu27Gln.

Polymorphic forms of the beta-2 receptor may be differentially active in relaxing airway smooth muscle, or differently downregulated by endogenous catecholamines. Some studies described associations between Gln27 and asthma susceptibility, and Gly16 has been linked to measures of asthma severity including FEV1, nocturnal symptoms, and use of other medications, but evidence from other studies is contradictory. The most consistent evidence is that Gly16 and Gln27, both individually and in combination as a haplotype, are associated with increased bronchial responsiveness in asthmatics, but analysis of further haplotypes is
required. Polymorphic forms of the beta-2 receptor may also alter responsiveness to beta-2 agonist therapy, most likely by an increased tendency of the Gly16 allele to undergo desensitisation as reported in vitro. In asthmatics, several studies indeed report a reduced bronchodilator response to inhaled salbutamol (albuterol) in Gly16 homozygotes than in Arg16 homozygotes. In 22 asthmatics treated with formoterol for 4 weeks, Gly16 homozygotes showed greater desensitisation than Arg16 homozygotes. However, other studies show no loss of bronchodilator response induced by therapy with short-acting and long-acting beta-2 agonists, and paradoxically an increased number of asthma exacerbations has been reported in asthmatic Arg16 homozygotes treated with salbutamol (albuterol) compared to salmeterol or placebo. The confusion in the literature may arise from a profusion of relatively small studies of only one or two polymorphisms in a limited number of subjects. Marked divergences in haplotype frequencies have been noted between ethnic groups, and more studies of multiple SNPs within the context of validated haplotypes in larger numbers of subjects from diverse ethnic groups are required to clarify the picture.

Responses to Glucocorticosteroids, Antimuscarinic Drugs, and Theophylline.
Glucocorticoids interact with a cytosolic glucocorticoid receptor to exert their diverse anti-inflammatory activities. Familial glucocorticoid resistance is associated with a rare missense mutation in the glucocorticoid receptor gene (GCCR), and common polymorphisms in the gene may also modulate in vitro and in vivo responses to exogenous glucocorticoids. However, no mutations were found in a small group of asthmatics clinically characterised as steroid-resistant. Ipratropium and other anticholinergic drugs bronchodilate airways and reduce mucus secretion by blocking muscarinic receptors in the lung, of which the most important are M3 receptors. No amino acid-changing SNPs nor any polymorphisms within putative promoter regions have been described in the M2 and M3 receptor genes. Theophylline is a bronchodilator that inhibites isozymes of phosphodiesterase (PDE), but its use is limited by adverse effects and by highly variable pharmacokinetics, including variable hepatic elimination rates. Twin studies provide evidence for a single bi-allelic autosomal gene responsible for most of the variable hepatic elimination of theophylline, but the gene has not been identified.

Leukotriene pathway polymorphisms
The cysteinyl-leukotrienes (cys-LTs) are bronchoconstrictor and pro-inflammatory lipids derived from the 5-lipoxygenase (5-LO) pathway. Polymorphism in the putative promoter region of the 5-LO gene (ALOX5) has been identified, consisting of a variable number of tandem repeats (VNTR) of short motifs that modulate transcriptional activity in reporter assays. In 681 asthmatics treated with an oral 5-LO inhibitor for 12 weeks, patients homozygous or heterozygous for the wild-type allele showed a significant mean improvement in FEV1 compared to placebo, while patients homozygous for variant alleles showed no change in FEV1 [8]. Thus, the variant ALOX5 alleles are recessive, and homozygotes for the variant alleles, who account for about 6% of the asthmatic population, fail to respond to leukotriene modifier therapy.

Preliminary evidence that a common polymorphism in leukotriene C4 synthase affects responses to anti-leukotriene therapy in 40-50% of asthmatics will be discussed separately.

Review articles.