Genetic Factors in the Predisposition to Drug-induced Hypersensitivity Reactions

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ABSTRACT

Drug hypersensitivity reactions can occur with most drugs, although the frequency, severity, and clinical manifestations vary. Case reports have suggested that there may be familial clustering of drug hypersensitivity suggesting a genetic predisposition. As with most other forms of drug response, predisposition to drug hypersensitivity reactions is likely to be multifactorial and multigenic. Given the immune pathogenesis of these reactions, it is perhaps not surprising that the most significant genetic associations have been identified in the major histocompatibility complex for drugs such as abacavir, carbamazepine, and allopurinol. For abacavir, it has been suggested that preprescription genotyping for HLA-B*5701 in whites may reduce the incidence of hypersensitivity. It is likely that as our knowledge of variation in the human genome improves, coupled with improvements in technology, many more significant genetic predisposing factors for drug hypersensitivity are likely to be identified in the next decade. However, as we search for these genetic factors, it is important that we do not forget environmental predisposition, and to bear in mind that a genetic marker for drug hypersensitivity in one population may not necessarily be relevant for another population. Notwithstanding the advances in genetic technologies, the ultimate determinant of success in this area of research will be the identification and careful phenotyping of patients with drug hypersensitivity reactions. As we progress to whole genome scanning, in order to satisfy the requirements for adequate statistical power, the identification of large numbers of carefully phenotyped patients will be feasible only through international collaborations.

KEYWORDS: hypersensitivity, pharmacogenetics, drugs, HLA, polymorphisms

INTRODUCTION

Drug hypersensitivity can be defined as an inappropriate immune response leading to tissue damage from an otherwise

nontoxic agent. Drug hypersensitivity reactions therefore fall into the category of type B (or bizarre) adverse drug reactions, according to the classification proposed by Rawlins and Thompson.¹ By definition, therefore, these reactions cannot be predicted from the known pharmacology of the drug, do not show a simple dose-response relationship and, of importance, affect a minority of patients taking the drug. The factors predisposing individuals to hypersensitivity reactions with individual drugs are in most cases unknown. Genetic factors have long been postulated to be important, but it was not until recently, that we began to uncover the genetic basis of drug-induced hypersensitivity.

The incidence of hypersensitivity varies according to the drug, the disease being treated, and the ethnicity of the patient.² There are reports of hypersensitivity reactions (in their general sense) with most drugs on the market, but in most instances, the reactions are usually mild. More severe reactions are relatively uncommon, even when there is a high frequency of mild reactions. For instance, with phenytoin, skin rashes occur in up to 16% of patients at initiation of therapy,³ while hypersensitivity syndrome is much less common occurring in 1 in 5000 to 10 000 patients.⁴ The clinical manifestations of hypersensitivity reactions are also widely variable, and the reasons for why some patients develop extracutaneous manifestations such as injury to the liver and bone marrow (Figure 1),⁵ while most do not, are unknown. Whether genetic factors are important in determining the severity and pattern of clinical manifestations is unknown and will require investigation through large well-executed studies.

FAMILIAL OCCURRENCE OF DRUG HYPERSENSITIVITY

Twin studies, where the incidence of a disease is compared between monozygotic and dizygotic twins, have long been used to ascertain the heritability estimates of many diseases.⁶ However, this would be extremely difficult to accomplish with drug hypersensitivity, as it would require an enormously large study (which would probably be economically unfeasible) comprising twins with the same disease that had the same drug treatment, and were then compared with respect to the incidence of hypersensitivity. In the absence of such studies, evidence of genetic

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Figure 1. Manifestations of drug-hypersensitivity reactions can vary in terms of severity of the reaction and the organ systems affected. The data were derived from a case-note survey in a large epilepsy clinic and represent the frequencies of different clinical manifestations in hypersensitivity reactions associated with CBZ and lamotrigine.

predisposition to drug hypersensitivity can be gleaned from case reports that describe the occurrence of similar hypersensitivity reactions in different family members treated with the same drug (Table 1).⁷⁻¹¹ For example, hypersensitivity syndrome has been reported in identical twins, both of whom were being treated with carbamazepine (CBZ) for primary generalized epilepsy.⁷ The mechanistic basis of genetic predisposition was investigated by Gennis et al¹¹ in 3 siblings who developed hypersensitivity with phenytoin. Using the *in vitro* lymphocyte cytotoxicity assay first devised by Spielberg et al,¹² they were able to show that cells from affected patients and 4 other siblings (who had never been exposed to anticonvulsants) showed a higher death rate *in vitro* compared with controls, suggesting an inherited predisposition.

GENETIC BASIS OF DRUG HYPERSENSITIVITY: EARLY INVESTIGATIONS

Given the pivotal role of the major histocompatibility complex (MHC) in the immune response, many of the early studies on drug-hypersensitivity reactions focused on human leukocyte antigen (HLA) phenotyping. Several positive

associations were identified (Table 2); however, there were also contradictory data between different groups, which arose because the numbers of patients studied were small, there was poor case definition, and the serological typing used was relatively insensitive and unable to distinguish between different alleles.

MULTIGENIC ETIOLOGY OF DRUG HYPERSENSITIVITY

In the early days of pharmacogenetic investigations, the prevailing hypothesis was that predisposition to drug response, be it efficacy or toxicity, was determined by a single gene. However, it is now clear that in most cases, drug response (including drug hypersensitivity) is a multifactorial and multigenic process, dependent on a complex interaction between multiple genes and the environment (Figure 2). Each gene contributes to the risk of developing the hypersensitivity reaction, but each individual gene is neither necessary nor sufficient by itself to cause the reaction.¹⁴ Perhaps the first demonstration that more than one gene was needed to predispose to an immune-mediated adverse drug reaction was with hydralazine-induced systemic lupus erythematosus (SLE). Patients deficient in N-acetyl transferase type 2 (NAT2), so-called slow acetylators, were found to be susceptible to developing SLE.¹⁵ Later on, further work showed that predisposition to hydralazine-induced SLE was also dependent on the presence of HLA-DR4.¹⁶

With the completion of the human genome project, many novel genes are likely to be identified as predisposing factors for drug hypersensitivity over the next few years. With our current state of knowledge, it is possible to divide predisposing genes into several categories (Figure 2)¹⁷:

- **Drug bioactivation:** the process of converting stable drugs into unstable chemically reactive metabolites through the process of drug metabolism. The most important enzymes in this group are the P450 superfamily of enzymes, many of which are polymorphically expressed (<http://www.imm.ki.se/CYPalleles/>).

Table 1. Case Reports of the Familial Occurrence of Drug Hypersensitivity Reactions

Drug	Family Members Affected	Nature of the Reaction	Reference
CBZ	Monozygotic twins	Hypersensitivity syndrome	7
Thiabendazole	3 siblings	Erythema multiform and Stevens-Johnson syndrome	8
Abacavir	2 siblings	Hypersensitivity reaction	9
Pyrazolone derivatives	Grandmother, 2 great aunts and granddaughter	Fixed-drug eruption	10
Phenytoin	3 siblings	Hypersensitivity syndrome	11

Table 2. HLA and Drug Hypersensitivity Reactions*

Drug	Adverse Reaction	HLA Association
Dipyrrone	Agranulocytosis	A24, B7, DQ1
Gold	Proteinuria, dermatological reactions, thrombocytopenia	DR3
Hydralazine	SLE	DR4
Levamisole	Agranulocytosis	B27
Oxicam	Toxic epidermal necrolysis	A2, B12
Penicillamine	Penicillamine toxicity	DR3
Sulphonamides	Toxic epidermal necrolysis	A29, B12, DR7

*HLA indicates human leukocyte antigen. The list of HLA associations is not meant to be exhaustive. It is also important to remember that most of these findings are based on single studies and were identified through serological testing. Adapted from Park et al.¹³

- **Drug bioinactivation:** the process by which stable compounds and unstable metabolites can be detoxified to prevent toxicity through accumulation or binding to cellular and humoral proteins, respectively. Many pathways are involved in bioinactivation, including phase I and phase II drug-metabolizing enzymes.
- **Immune responsiveness:** the process by which the bodys immune system recognizes a drug/drug metabolite as being foreign or antigenic, and thereby mounts an immune response, conceived to be protective, but which perversely leads to clinical manifestations typical of hypersensitivity. The genes encoding for immune responsiveness include MHC, T-cell receptors, and costimulatory molecules.
- **Tissue injury and repair:** the process by which an immune response is translated into tissue injury, the nature and extent of which can be counteracted by repair mechanisms that limit any tissue damage. Typical candidates include cytokines, chemokines, and prostaglandins.

Figure 2. Scheme illustrating that drug hypersensitivity has a multifactorial and multigenic predisposition.

Although there have been many investigations into the role of drug metabolizing enzyme gene polymorphisms in the pathogenesis of drug hypersensitivity, these to date have not been shown to be of major importance. Indeed, as with the early studies, current investigations have largely focused on the MHC on chromosome 6. Following the completion of the human genome project, and sequencing of the MHC,^{18,19} we now have a much better understanding of the complexity of the MHC. Coupled with our ability to undertake high-resolution genotyping and an increased understanding of the pattern of linkage disequilibrium within the region,^{20,21} this has enabled more detailed studies, which have already produced some striking findings. These concepts are best illustrated with respect to 2 drugs, abacavir²² and CBZ,²³ both of which are associated with well-defined hypersensitivity reactions.

ABACAVIR HYPERSENSITIVITY

The use of abacavir, a potent HIV-1 reverse transcriptase inhibitor, has been hampered by the occurrence of hypersensitivity reaction in ~5% of patients.²⁴ These reactions are characterized by skin rash, and gastrointestinal and respiratory manifestations and can occasionally be fatal, particularly on rechallenge. In an extensive investigation of the MHC, Mallal et al²⁵ found a strong association between abacavir hypersensitivity and the haplotype comprising HLA-B*5701, HLA-DR7, and HLA-DQ3 with an odds ratio of over 100. Subsequent studies have shown that this haplotype resides on the ancestral haplotype 57.1 (Table 3), and that the combination of HLA B*5701 and polymorphism in heat shock protein-Hom (HSP1AL) has greater predictive accuracy than HLA B*5701 by itself.²⁶ This association has now been shown in 2 other cohorts by GlaxoSmithKline Pharmaceuticals, the manufacturer of the drug, and independently in a cohort of patients from the UK.²⁷⁻²⁹ However, the odds ratios in these studies were lower than those obtained by Mallal et al.²⁵ Furthermore, the same association has not been shown in a black population, presumably because of ethnic differences in linkage disequilibrium patterns in the MHC.²⁸ Nevertheless, the association with the MHC in whites is consistent with the identification of drug-specific T cells in patients with abacavir hypersensitivity.^{30,31}

Abacavir does undergo metabolism in the body, with alcohol dehydrogenase being one of the enzymes involved.³² However, genetic analysis has shown that polymorphisms in the genes coding for various drug metabolizing enzymes do not play a major role in the predisposition to abacavir hypersensitivity.²⁷

Mallal et al²⁵ have proposed that in whites genotyping for HLA B*5701 should be performed before prescription of

Table 3. Comparison of the Genetic Association in Whites Across the Major Histocompatibility Complex for Different Drugs Associated With Hypersensitivity Reactions*

Drug	HLA Phenotype [†]	TNF- α Gene Polymorphism	HSPA1L	Ancestral Haplotype
Abacavir	B57	-238	C allele	57.1
CBZ	DR3	-308	T allele	8.1
Sulfamethoxazole [‡]	None	None	None	None

*Data taken from references 25-29, 47, and 48. The sulfamethoxazole data are unpublished (Vilar et al, 2005).

[†]HLA indicates human leukocyte antigen; HSPA1L, heat shock protein-Hom.

[‡]Refers only to HIV-positive patients treated with sulfamethoxazole.

abacavir, and indeed in their clinic, this has resulted in a reduction in the incidence of abacavir hypersensitivity.²⁶ An analysis of the predictive value of prospective HLA B*5701 genotyping prior to abacavir hypersensitivity based on a meta-analysis of 3 cohorts showed that to prevent one case of hypersensitivity, 8 HLA B*5701 positive patients would be denied abacavir, and to identify them, 48 patients would require testing.²⁹ The conclusion from this analysis was that genotyping for HLA B*5701 prior to the prescription of abacavir in whites is a cost-effective strategy. An issue to consider here is what test characteristics (ie, predictive accuracy) are required before a test can be implemented into clinical practice. Given the potential severity of abacavir hypersensitivity, it has been suggested that only a test that is 100% predictive in all populations would be clinically useful. However, it has to be conceded that even the current test characteristics are striking and exceed those of many other tests that are widely used today, and perhaps we may have to be more modest in our requirements to introduce pharmacogenetics into clinical practice.³³

CARBAMAZEPINE HYPERSENSITIVITY

CBZ is a widely used anticonvulsant that can cause rashes in up to 10% of patients, and in occasional cases, this may be the precursor to the development of a hypersensitivity syndrome characterized by systemic manifestations such as fever and eosinophilia.^{23,34} Rarely, CBZ can induce blistering skin reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis, 2 conditions associated with a high fatality rate.³⁵ There is now increasing laboratory evidence to show that CBZ hypersensitivity is a T-cell mediated disease.^{36,37} However, whether maculopapular eruptions, hypersensitivity syndrome, and the blistering rashes are of similar pathogenesis or diseases with different pathogenesis is unclear.

Although the mechanism of CBZ hypersensitivity is poorly understood, it has been postulated that metabolites and not the parent drug are the causal agents.⁴ Evidence for this has come from in vitro studies. CBZ can be metabolized to stable, cytotoxic, and protein-reactive metabolites.³⁸ The metabolism of CBZ in man, and experimental animals, is

complex. The major route of metabolism both in vitro and in vivo is 10,11-epoxidation to CBZ-10,11-epoxide (which is itself a drug).^{39,40} Detoxication products from the postulated arene oxide have been detected in rat bile⁴¹ and suggested to be present in human urine.⁴² Although other reactive metabolites have been postulated,⁴³ evidence of the possible role of arene oxides, taken together with findings from the in vitro lymphocyte cytotoxicity assay, suggested that patients may have a detoxification defect.^{4,44} This led to analysis of the microsomal epoxide hydrolase gene, which failed to identify any specific polymorphisms that were associated with CBZ hypersensitivity in 2 separate cohorts of patients.^{45,46} In addition, so far, studies have failed to identify any association of CBZ hypersensitivity with polymorphisms in genes encoding enzymes involved in the metabolism and bioactivation of CBZ, and the bioinactivation of its postulated reactive metabolites.³⁴

In view of the lack of association of CBZ hypersensitivity with gene polymorphisms in its drug metabolizing enzymes, subsequent studies have focused on the role of the MHC. This has led to the finding that CBZ hypersensitivity syndrome, but not mild maculopapular eruptions, is associated with the haplotype TNF2-DR3-DQ2.⁴⁷ This locus may thus either determine severity of the reaction or alternatively the milder reactions have a different pathogenesis, and thus different predisposing genes, than the more severe reactions. This finding has also been borne out in more recent studies in an extensive analysis of the heat shock protein (HSP) locus, which has shown that severe but not mild CBZ hypersensitivity reactions are associated with 3 SNPs in the HSP-70 locus, 2 in HSP70-1 and one in HSPA1L.⁴⁸ It is not possible at this stage to state whether the associations identified so far represent causal variants or are in linkage disequilibrium with a causal variant in another gene in the MHC. It does however seem likely that the causal variant for CBZ hypersensitivity in whites resides on the ancestral haplotype 8.1 (Table 3).

Of interest, a recent study in a Han Chinese population from Taiwan has shown that HLA-B*1502 may act as a genetic marker for CBZ-induced SJS, with an odds ratio that was greater than 2504.⁴⁹ All patients with SJS carried the

HLA-B*1502 allele, but this was only observed in 3% of tolerant patients. This is an extremely important finding that suggests that in the Han Chinese population, testing for HLA-B*1502 (where it has a prevalence of 7% compared with 2% in whites) may prevent CBZ-induced SJS. A formal cost-effective analysis has not been undertaken; however, given the relative rarity of SJS, it may be considered not to be economically feasible despite the strength of the association with HLA-B*1502. The findings in Han Chinese cannot be extrapolated to whites: in our population of whites (including 2 patients with SJS), we have not shown an association with HLA-B*1502 (Alfirevic, unpublished data, 2006). Whether this is related to differences in the linkage disequilibrium pattern or in clinical manifestations between the 2 cohorts is not clear at this stage.

THE ENVIRONMENT AND DRUG HYPERSENSITIVITY

Despite the increasing evidence that genetic factors predispose to drug hypersensitivity, we should not discount the role of environmental factors. The best example of this is the role of viral infections in predisposing to drug hypersensitivity. For instance, in patients with Epstein-Barr virus induced infectious mononucleosis, the risk of rash with amoxicillin is increased by a factor of 58.⁵⁰ An increase in the frequency of hypersensitivity has also been observed in HIV patients treated with the combination of sulfamethoxazole (SMX) and trimethoprim. In HIV-negative patients, the frequency of hypersensitivity with the combination product is less than 3%, while in HIV-positive patients, it increases to 30%.⁵¹ Of interest, while slow acetylator phenotype is a risk factor for the development for hypersensitivity in HIV-negative patients,⁵² neither acetylator phenotype nor genotype has shown to predispose to SMX hypersensitivity in HIV-positive patients.⁵³⁻⁵⁵ Furthermore, convincing genetic associations have also not been demonstrated with other enzymes involved in the bioactivation of SMX to its toxic hydroxylamine and nitroso metabolites, and their detoxification.⁵⁴ Unlike abacavir and CBZ, an association with SMX hypersensitivity in HIV-positive patients with MHC genes has also not been identified (Table 3; Vilar et al, unpublished data, 2005). Thus, the 10-fold increase in the frequency of SMX hypersensitivity in HIV-positive patients cannot simply be attributed to conventional genetic factors. Whether this is due to the “danger” posed by concomitant HIV infection (ie, an environmental factor),⁵⁶ or whether there is an interaction with novel genetic factors is unclear at present and requires further investigation.

FUTURE PERSPECTIVES AND CONCLUSION

As our knowledge of the human genome improves, we will undoubtedly identify novel genetic predisposing factors for drug hypersensitivity reactions. All the studies to date have used a candidate gene approach. Clearly this is limited by

our knowledge of the mechanisms of drug hypersensitivity. The technology to identify genetic variants across the whole genome is advancing rapidly, and the next stage of genetic investigation will be to perform an unbiased assessment of predisposition through whole genome scanning.⁵⁶ Before we can progress to this stage, however, several important issues will need to be considered and resolved, as follows:

1. Most drug hypersensitivity reactions are relatively rare, and conventional power calculations suggest that up to 1000 patients may be required.⁵⁷ It is very unlikely that a single center, let alone a single country, will be able to identify this number of cases, and therefore multicenter multinational collaborations are going to be essential. In addition, we need to develop better methods to identify and bank DNA samples from patients with drug hypersensitivity as and when they arise—this applies to both clinical trials and in routine clinical practice.
2. It is clear that drug hypersensitivity reactions vary in their severity and the pattern of clinical manifestations. Therefore, accurate phenotypic characterization of patients is going to be crucial. An important point to consider with respect to phenotype is whether the varying manifestations represent the same disease process, or different diseases altogether, as this will impact on the statistical power to identify the genetic predisposing factors. Clearly it is also possible that the genetic predisposition to the phenotypic manifestations may be drug-specific. Thus, in the studies in Han Chinese, while HLA-B*1502 acts as a marker for CBZ-induced SJS only,⁴⁹ with allopurinol, the genetic predisposing factors seem to be relatively similar irrespective of whether the patient developed hypersensitivity syndrome or SJS.⁵⁸
3. The incidence of hypersensitivity may vary in different populations treated with the same drug. For example, thiacetazone-induced hypersensitivity seems to be a particular problem in black patients,⁵⁹ while SMX hypersensitivity seems to be more common in whites than in blacks.⁶⁰ This has clear implications for genetic investigations in that the identification of a genetic predisposing factor may only be relevant for one ethnic group, and it may not be possible to extrapolate the findings to other populations. This is perhaps best exemplified by abacavir hypersensitivity, where HLA-B*5701 acts as a predisposing factor in white patients, but not at all in black patients.²⁸

4. The ultimate aim of pharmacogenetics is to predict the response to the drug before the patient takes the drug. With respect to drug hypersensitivity, the aim would therefore be to prevent these reactions through preprescription genotyping. Two important aspects need to be considered here. First, what level of predictive accuracy will be acceptable to patients and clinicians before the test is used? It is unlikely that we will achieve 100% predictive accuracy with any pharmacogenetic test.³³ To this end, it is interesting to note that the phenotypic in vitro cytotoxicity assay¹² actually has better predictive values than any genotypic marker identified so far, as least with respect to the use of CBZ in whites.^{4,44} Second, given that predisposition is likely to be multigenic, is it going to be cost effective to screen patients prior to starting the drug, especially when the background incidence of the hypersensitivity reaction is low? Such information will be needed to convince those responsible for holding scarce health-care resources to invest in such testing.

CONCLUSION

In conclusion, there is increasing evidence to show that drug hypersensitivity reactions are genetically determined. Identification of such factors is important, not only to realize the prospect of developing preventive strategies but also to learn about the mechanisms of these reactions, which may ultimately lead to other preventive strategies through better drug design and to better treatment strategies for patients who develop the reactions. The success of this area of research is going to be critically dependent on the identification and careful phenotyping of patients with such reactions, which is only likely to be achieved through international collaborations.

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REFERENCES

1. Rawlins MD, Thompson JW. Mechanisms of adverse drug reactions. In: Davies DM, ed. *Textbook of Adverse Drug Reactions*. Oxford, UK: Oxford University Press; 1991:18-45.
2. Demoly P, Gomes ER. Drug hypersensitivities: definition, epidemiology and risk factors. *Allergy Immunol (Paris)*. 2005;37:202-206.
3. Chadwick D, Shaw MDM, Foy P, Rawlins MD, Turnbull DM. Serum anticonvulsant concentration and the drug-induced skin eruptions. *J Neurol Neurosurg Psychiatry*. 1984;47:642-644.

4. Shear NH, Spielberg SP, Cannon M, Miller M. Anticonvulsant hypersensitivity syndrome: in vitro risk assessment. *J Clin Invest*. 1988;82:1826-1832.
5. Pirmohamed M, Naisbitt DJ, Gordon F, Park BK. The danger hypothesis: potential role in idiosyncratic drug reactions. *Toxicology*. 2002;181-182:55-63.
6. Strachan DP, Wong HJ, Spector TD. Concordance and interrelationship of atopic diseases and markers of allergic sensitization among adult female twins. *J Allergy Clin Immunol*. 2001;108:901-907.
7. Edwards SG, Hubbard V, Aylett S, Wren D. Concordance of primary generalized epilepsy and CBZ hypersensitivity in monozygotic twins. *Postgrad Med J*. 1999;75:680-681.
8. Johnson-Reagan L, Bahna SL. Severe drug rashes in 3 siblings simultaneously. *Allergy*. 2003;58:445-447.
9. Peyrieere H, Nicolas J, Siffert M, Demoly P, Hillaire-Buys D, Reynes J. Hypersensitivity related to abacavir in 2 members of a family. *Ann Pharmacother*. 2001;35:1291-1292.
10. Pellicano R, Silvestris A, Iannantuono M, Ciavarella G, Lomuto M. Familial occurrence of fixed drug eruptions. *Acta Derm Venereol*. 1992;72:292-293.
11. Gennis MA, Vemuri R, Burns EA, Hill JV, Miller MA, Spielberg SP. Familial occurrence of hypersensitivity to phenytoin. *Am J Med*. 1991;91:631-634.
12. Spielberg SP, Gordon GB, Blake DA, Goldstein DA, Herlong HF. Predisposition to phenytoin hepatotoxicity assessed in vitro. *N Engl J Med*. 1981;305:722-727.
13. Park BK, Pirmohamed M, Kitteringham NR. Idiosyncratic drug-reactions: a mechanistic evaluation of risk-factors. *Br J Clin Pharmacol*. 1992;34:377-395.
14. Pirmohamed M, Park BK. Genetic susceptibility to adverse drug reactions. *Trends Pharmacol Sci*. 2001;22:298-305.
15. Perry HM, Tan EM, Carmody S, Sakamota A. Relationship of acetyl transferase activity to antinuclear antibodies and toxic symptoms in hypertensive patients treated with hydralazine. *J Lab Clin Med*. 1970;76:114-125.
16. Batchelor JR, Welsh KI, Tinoco RM, et al. Hydralazine-induced systemic lupus erythematosus: influence of HLA-DR and sex on susceptibility. *Lancet*. 1980;1:1107-1109.
17. Naisbitt DJ, Pirmohamed M, Park BK. Immunopharmacology of hypersensitivity reactions to drugs. *Curr Allergy Asthma Rep*. 2003;3:22-29.
18. Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. *Nature*. 2001;409:860-921.
19. Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. *Science*. 2001;291:1304-1351.
20. Tsunoda T, Lathrop GM, Sekine A, et al. Variation of gene-based SNPs and linkage disequilibrium patterns in the human genome. *Hum Mol Genet*. 2004;13:1623-1632.
21. Walsh EC, Mather KA, Schaffner SF, et al. An integrated haplotype map of the human major histocompatibility complex. *Am J Hum Genet*. 2003;73:580-590.
22. Symonds W, Cutrell A, Edwards M, et al. Risk factor analysis of hypersensitivity reactions to abacavir. *Clin Ther*. 2002;24:565-573.
23. Vittorio CC, Muglia JJ. Anticonvulsant hypersensitivity syndrome. *Arch Intern Med*. 1995;155:2285-2290.
24. Hetherington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. *Clin Ther*. 2001;23:1603-1614.

25. Mallal S, Nolan D, Witt C, et al. Association between presence of *HLA-B*5701*, *HLA-DR7*, and *HLA-DQ3* and hypersensitivity to HIV-1 reverse transcriptase inhibitor abacavir. *Lancet*. 2002;359:727-732.
26. Martin AM, Nolan D, Gaudieri S, et al. Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant. *Proc Natl Acad Sci USA*. 2004;101:4180-4185.
27. Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet*. 2002;359:1121-1122.
28. Hughes AR, Mosteller M, Bansal AT, et al. Association of genetic variations in HLA-B region with hypersensitivity to abacavir in some, but not all, populations. *Pharmacogenomics*. 2004;5:203-211.
29. Hughes DA, Vilar FJ, Ward CC, Alfievic A, Park BK, Pirmohamed M. Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity. *Pharmacogenetics*. 2004;14:335-342.
30. Dodd CC, Naisbitt DJ, Vilar FJ, et al. Abacavir hypersensitivity in human immunodeficiency virus-positive patients: demonstration of the presence of drug-specific lymphocyte proliferation in vitro. *Br J Clin Pharmacol*. 2003;55:421.
31. Phillips EJ, Wong GA, Kaul R, et al. Clinical and immunogenetic correlates of abacavir hypersensitivity. *AIDS*. 2005;19:979-981.
32. Walsh JS, Reese MJ, Thurmond LM. The metabolic activation of abacavir by human liver cytosol and expressed human alcohol dehydrogenase isozymes. *Chem Biol Interact*. 2002;142:135-154.
33. Lindpaintner K. The importance of being modest: reflections on the pharmacogenetics of abacavir. *Pharmacogenomics*. 2002;3:835-838.
34. Leeder JS. Mechanisms of idiosyncratic hypersensitivity reactions to antiepileptic drugs. *Epilepsia*. 1998;39:S8-S16.
35. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. *Lancet*. 1999;353:2190-2194.
36. Mauri-Hellweg D, Bettens F, Mauri D, Brander C, Hunziker T, Pichler WJ. Activation of drug-specific CD4(+) and CD8(+) T cells in individuals allergic to sulfonamides, phenytoin, and CBZ. *J Immunol*. 1995;155:462-472.
37. Naisbitt DJ, Britschgi M, Wong G, et al. Hypersensitivity reactions to CBZ: characterization of the specificity, phenotype, and cytokine profile of drug-specific T-cell clones. *Mol Pharmacol*. 2003;63:732-741.
38. Pirmohamed M, Kitteringham NR, Guenther TM, Breckenridge AM, Park BK. An investigation of the formation of cytotoxic, protein-reactive, and stable metabolites from CBZ in vitro. *Biochem Pharmacol*. 1992;43:1675-1682.
39. Tybring G, von Bahr C, Bertilsson L, Collste H, Glaumann H, Solbrand M. Metabolism of CBZ and its epoxide metabolite in human and rat liver in vitro. *Drug Metab Dispos*. 1981;9:561-564.
40. Kroetz DL, Kerr BM, McFarland LV, Loiseau P, Wilensky AJ, Levy RH. Measurement of in vivo microsomal epoxide hydrolase activity in white subjects. *Clin Pharmacol Ther*. 1993;53:306-315.
41. Madden S, Maggs JL, Park BK. Bioactivation of CBZ in the rat in vivo: evidence for the formation of reactive arene oxide(s). *Drug Metab Dispos*. 1996;24:469-479.
42. Lertratanakoon K, Horning MG. Metabolism of CBZ. *Drug Metab Dispos*. 1982;10:1-10.
43. Lillibridge JH, Amore BM, Slattery JT, et al. Protein-reactive metabolites of CBZ in mouse liver microsomes. *Drug Metab Dispos*. 1996;24:509-514.
44. Pirmohamed M, Graham A, Roberts P, et al. CBZ hypersensitivity: assessment of clinical and in vitro chemical cross-reactivity with phenytoin and oxcarbazepine. *Br J Clin Pharmacol*. 1991;32:741-749.
45. Gaedigk A, Spielberg SP, Grant DM. Characterization of the microsomal epoxide hydrolase gene in patients with anticonvulsant adverse drug reactions. *Pharmacogenetics*. 1994;4:142-153.
46. Green VJ, Pirmohamed M, Kitteringham NR, et al. Genetic-analysis of microsomal epoxide hydrolase in patients with CBZ hypersensitivity. *Biochem Pharmacol*. 1995;50:1353-1359.
47. Pirmohamed M, Lin K, Chadwick D, Park BK. TNFalpha promoter region gene polymorphisms in CBZ- hypersensitive patients. *Neurology*. 2001;56:890-896.
48. Alfievic A, Mills T, Harrington P, et al. Serious CBZ-induced hypersensitivity reactions associated with the HSP70 gene cluster. *Pharmacogenetics and Genomics*. In press.
49. Chung W-H, Hung S-I, Hong H-S, et al. Medical genetics: a marker for Stevens-Johnson syndrome. *Nature*. 2004;428:486.
50. van der Linden PD, van der Lei J, Vlug AE, Stricker BH. Skin reactions to antibacterial agents in general practice. *J Clin Epidemiol*. 1998;51:703-708.
51. Koopmans PP, van der Ven AJAM, Vree TB, van der Meer JWM. Pathogenesis of hypersensitivity reactions to drugs in patients with HIV-infection: allergic or toxic. *AIDS*. 1995;9:217-222.
52. Rieder MJ, Shear NH, Kane A, Tang BK, Spielberg SP. Prominence of slow acetylator phenotype among patients with sulfonamide hypersensitivity reactions. *Clin Pharmacol Ther*. 1991;49:13-17.
53. Wolkenstein P, Lorient MA, Aractingi S, Cabelguenne A, Beaune P, Chosidow O. Prospective evaluation of detoxification pathways as markers of cutaneous adverse reactions to sulphonamides in AIDS. *Pharmacogenetics*. 2000;10:821-828.
54. Pirmohamed M, Alfievic A, Vilar J, et al. Association analysis of drug metabolizing enzyme gene polymorphisms in HIV-positive patients with co-trimoxazole hypersensitivity. *Pharmacogenetics*. 2000;10:705-713.
55. Alfievic A, Stalford AC, Vilar FJ, Wilkins EGL, Park BK, Pirmohamed M. Slow acetylator phenotype and genotype in HIV-positive patients with sulphamethoxazole hypersensitivity. *Br J Clin Pharmacol*. 2003;55:158-165.
56. Pirmohamed M, Naisbitt DJ, Park BK. The danger hypothesis: inflammation and idiosyncratic toxicity. *Toxicology*. 2001;164:5.
57. Palmer LJ, Cardon LR. Shaking the tree: mapping complex disease genes with linkage disequilibrium. *Lancet*. 2005;366:1223-1234.
58. Hung SI, Chung WH, Liou LB, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci USA*. 2005;102:4134-4139.
59. Nunn P, Kibuga D, Gathua S, et al. Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet*. 1991;337:627-630.
60. Chintu C, Bhat GJ, Walker AS, et al. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. *Lancet*. 2004;364:1865-1871.