Using Genome-Wide Association Studies to Identify Genes Important in Serious Adverse Drug Reactions

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Abstract

Genome-wide association (GWA) studies have detected novel associations for serious, idiosyncratic, adverse drug reactions including liver toxicity, hypersensitivity, skin rash, and myotoxicity. Human leukocyte antigen (HLA) genotype has been established as an important predictor of susceptibility to drug-induced liver injury, including injury with some drugs where immune-related toxicity was not suspected previously. Similarly, GWA studies have shown a key role for HLA genotype in susceptibility to carbamazepine-related skin rash and hypersensitivity. HLA genotype is not a risk factor for all forms of drug-induced liver injury or for myotoxicity or cardiotoxicity. For simvastatin-related myotoxicity, a strong association with *SLCO1B1*, which encodes the hepatic statin uptake transporter, has been detected. Genome-wide studies have not yet found clear associations for drug-induced cardiotoxicity, but for bisphosphonate-induced necrosis of the jaw, polymorphisms in the cytochrome P450 CYP2C8 may predict susceptibility. Larger GWA studies and whole-genome sequencing may provide additional insights into all these toxicities.

INTRODUCTION

A serious adverse drug reaction is defined as an undesirable experience concerned with a particular drug and that leads to any of the following: death or life-threatening event, hospitalization, disability or permanent damage, congenital abnormality or birth defect (1, 2). Such events may occur during drug development or may emerge only when the drug has been licensed. Most serious adverse drug reactions can be classified as either type A, where the underlying mechanism is dose dependent, or type B or idiosyncratic, where the event is not predictable from the normal pharmacology of the drug and is generally independent of dose (3, 4). Idiosyncratic adverse events are generally rarer than type A events, and this lower frequency means that they usually emerge late in the drug development process or after licensing. In the period from 1976 to 2005, 28 different drugs were withdrawn from the market in the United States as a result of idiosyncratic serious adverse reactions (5, 6). In particular, the types of reaction involved cardiotoxicity (including torsades de pointes) (28% of withdrawals), hepatotoxicity (21% of withdrawals), nephrotoxicity (7% of withdrawals), and rhabdomyolysis (7% of withdrawals). Additional, more minor, contributions from other toxicities included skin rash and hemolytic anemia.

In addition to these high-profile withdrawals of otherwise valuable drugs, there are a number of examples of licensed drugs that give rise, though only on rare occasions, to serious adverse reactions. Usually, the label includes a warning regarding the possibility of an adverse reaction. These drugs continue to be prescribed, often because of an absence of effective alternatives. There is also increasing interest in developing screening tests that would enable researchers to predict which patients are at risk of suffering adverse drug reactions. Such a development may potentially allow for the reintroduction of some valuable drugs that had been withdrawn previously; this development may also help avoid some of the current serious adverse reactions seen with licensed drugs.

The possibility that genetic tests could be developed for certain types of serious adverse reactions has been investigated for at least the past 20 years (6). There is now considerable evidence that genetic factors contribute to susceptibility to these reactions (6, 7), although it is important to stress that other factors may also contribute. The development of genome-wide association (GWA) studies and their successful application to the identification of novel susceptibility genes for several complex polygenic diseases (8) resulted in an interest in applying GWA studies to the area of serious adverse drug reactions. There are specific problems in doing this: For example, the rarity of serious adverse reactions means that multicenter studies, often involving several countries, may be needed to recruit adequate numbers of cases. Furthermore, a uniform phenotype including clear causality must also be ensured. Nonetheless, a number of GWA studies on serious adverse drug reactions have now been completed and are discussed in detail in this article. Most of these studies relate to either drug-induced hepatotoxicity or hypersensitivity reactions including skin rash, but there are also single studies on drug-induced myotoxicity, cardiotoxicity, and osteonecrosis of the jaw (see **Table 1**). After a general introduction to GWA studies, this review focuses on each type of serious adverse drug reaction for which GWA data are currently available.

GENOME-WIDE ASSOCIATION STUDIES TO IDENTIFY SUSCEPTIBILITY GENES

Until 2004, the main approach to the study of complex disease genetics was the use of candidate-gene case-control studies, with additional family studies possible for some, but not the majority of, diseases. Overall, these studies led to the reproducible identification of only a small number of disease genes (9), because most studies involved relatively small numbers of patients and the polymorphisms chosen for study in candidate genes were often selected arbitrarily. Since 2005,

Table 1 Summary of published genome-wide association studies on serious adverse drug reactions

Type of toxicity	Number of published studies	Drugs involved	Genes implicated	Highest level of significance (lowest p value)	Reference(s)
Liver	4	Ximelagatran, Flucloxacillin, Lumiracoxib, Amoxicillin-clavulanate	HLA classes I and II	8.7×10^{-33}	37, 39, 40, 42
Skin and hypersensitivity	3	Carbamazepine plus miscellaneous agents	*HLA-A*	1.2×10^{-13}	58, 59, 62
Myotoxicity	1	Simvastatin	*SLCO1B1*	4.0×10^{-9}	68
QT prolongation	1	Iloperidone	*CERKL*	2.8×10^{-6}	78
Osteonecrosis of the jaw	1	Pamidronate, zoledronic acid	*CYP2C8*	6.2×10^{-6}	80

the availability of comprehensive data on variability in human genes from the HapMap (10) together with the development of methods allowing very large numbers of single-nucleotide polymorphisms (SNPs) to be genotyped simultaneously (11) have revolutionized the study of complex disease genetics. Using the HapMap information, researchers have covered the majority of common (>5%) variability in the human genome by genotyping sets of cases and controls for large numbers (typically 500,000 to 1,000,000) of different SNPs in GWA studies. A particular advantage of GWA studies over candidate-gene studies is their open nature because the genotyping is performed for polymorphisms in all genes, not simply those that are obvious candidates for effects on the disease of interest. Because large numbers of polymorphisms are being genotyped, it is necessary to analyze the results using statistical tests that correct appropriately for the large number of assays being performed, but these methods are now well established. Manolio et al. (12) and Hardy & Singleton (13) provide more detailed description of all aspects of GWA.

In GWA studies on common complex genetic diseases, typically at least 1,000 cases and 1,000 controls need to be studied to detect the relatively low odds ratios seen for most SNPs affecting disease susceptibility, as found in, for example, type II diabetes and breast cancer (14, 15). GWA studies involving similarly large numbers of cases have also been successfully performed in relation to drug response, including responses to warfarin (16), acenocoumarol (17), and clopidogrel (18). However, for studies on serious idiosyncratic adverse drug reactions, which may typically occur at frequencies of 1 in 10,000 or 100,000 patients treated (3), finding sufficient cases for GWA studies is more difficult. Though investigators have set up several large networks to enable large numbers of cases with serious adverse drug reactions to be recruited (19–21), the GWA studies reported to date include several hundred cases at most; thus, the power to detect small effects is limited. GWA findings are normally confirmed using a replication cohort (13), usually of similar size to or greater size than the original group of cases studied, which is particularly difficult given the challenges of finding sufficient cases for the initial study. In spite of these limitations, some progress in understanding genetic susceptibility to serious adverse drug reactions has been made (**Table 1**).

LIVER-RELATED ADVERSE DRUG REACTIONS

Idiosyncratic hepatotoxicity relating to drug exposure is usually referred to as drug-induced liver injury (DILI), a rare but clinically important problem. Drugs that give rise to this toxicity are

structurally diverse and belong to a number of different therapeutic classes, but certain antimicrobial agents and nonsteroidal anti-inflammatory drugs are among the most common causes of idiosyncratic DILI (22–24). One U.S.-based survey suggested that DILI accounts for 20% of all hospital admissions due to severe liver injury and 50% of acute liver failure cases, 75% of which require liver transplantation (25). DILI is also the most common reason that clinical trials of new therapeutic agents are terminated (26). Many different drugs can cause DILI, with the precise pattern of injury varying between drugs. Typically, DILI reactions are classified as hepatocellular when the injury is focused on the hepatocyte and cholestatic when the damage occurs at the hepatocyte canalicular membrane or further downstream in the biliary tree (27). The underlying mechanism by which DILI develops is likely to be complex but may involve both direct toxic effects by the drug, for example, involving oxidative stress or cellular damage, and, for some drugs, formation of reactive intermediates resulting in either direct toxicity or an inappropriate immune response (28).

The first study on a possible genetic association for DILI susceptibility appeared more than 20 years ago as a report showing an increased incidence in frequency of certain human leukocyte antigen (HLA) class II serotypes among DILI cases compared with controls (29). These cases included DILI induced by several drugs. A number of further reports of associations with particular HLA serotypes and genotypes followed, including, in particular, two independent reports suggesting that the HLA class II allele *DRB1*1501* was a risk factor for DILI induced by the antimicrobial agent, amoxicillin-clavulanate (30, 31). This form of DILI has been suggested to relate predominantly to the clavulanic acid component of the drug (32), though this has still not been demonstrated directly. Candidate-gene association studies have also led to the detection of several other associations with non-HLA genes, either for DILI due to individual drugs (33, 34) or for cases of this adverse drug reaction linked to a range of different drugs (35, 36).

GWA approaches have now been used to investigate susceptibility to hepatotoxicity in four studies, each involving different drugs associated with DILI (see **Table 2** for a summary). Slightly unexpectedly, all four studies have shown statistically significant associations with particular HLA class I or II alleles, suggesting that T cell responses contribute to the toxicity, but no significant

Table 2 Genome-wide association studies on drug-induced liver injury

Drug	Number of cases	SNP(s)[a] showing lowest p value	p value[b]	Odds ratio (95% CI)[b]	Gene and allele tagged by SNP	Reference
Ximelagatran	74	rs2858869	6.0×10^{-6}	Not done	*HLA-DRB1*0701-DQA1*0201*	37
Flucloxacillin	51	rs2395029	8.7×10^{-33}	45 (19.4–105)	*HLA-B*5701*	39
Lumiracoxib	41	rs9270986	2.8×10^{-10}	5.3 (3.0–9.2)	*HLA-DRB1*1501-DQB1*0602*	40
Amoxicillin-clavulanate	201	rs9274407	4.8×10^{-14}	3.1 (2.3–4.2)	None	42
		rs9267992	6.8×10^{-13}	3.1 (2.3–4.2)	None	
		rs3135388	3.5×10^{-11}	2.8 (2.1–3.8)	*HLA-DRB1*1501-DQB1*0602*	
		rs2523822	1.8×10^{-10}	2.3 (1.8–2.9)	*HLA-A*0201*	

[a]SNP, single-nucleotide polymorphism.
[b]Based on allele frequency for SNP.

genome-wide non-HLA associations were detected in any of the studies. The association with HLA is not unexpected for amoxicillin-clavulanate, as this had been demonstrated previously by two smaller candidate-gene association studies (30, 31).

The earliest of the four GWA studies relating to DILI focused on the direct thrombin inhibitor ximelagatran, which was developed as a potential replacement for warfarin and other coumarin anticoagulants but was withdrawn by the manufacturers in 2006 (37). This drug was associated with raised alanine aminotransferase (ALT) levels (transaminitis) among some patients, though this elevation was relatively small in most, but not all, affected individuals. A GWA study performed on 74 cases of transaminitis linked to ximelagatran was the earliest reported GWA on any serious adverse reaction. This study involved a set of 266,000 SNPs, whereas the three more recent studies involved between 700,000 and 1,000,000 SNPs. The study on ximelagatran also involved genotyping for a range of additional candidate genes to increase coverage of key SNPs and separate HLA genotyping. Both GWA and candidate SNPs were tested for association with raised ALT rather than a control group. The GWA study failed to detect any significant GWAs, but a relatively low p value (6.0×10^{-6}) was obtained for a SNP in the HLA class II *DRB1* gene. Further direct HLA typing confirmed a significant association between the level of ALT increase and *HLA-DRB1*0701* ($p = 4 \times 10^{-5}$) (37).

This first slightly limited, though interesting, study on a form of DILI involving GWA was followed by a study on flucloxacillin-related DILI. Flucloxacillin is an example of a drug prescribed commonly in a number of countries worldwide but which is associated occasionally (in <1 in 10,000 patients prescribed the drug) with DILI (38). The DNA samples studied were from 51 patients of Northern European ethnic origin who had suffered moderate to severe DILI with a clear causal link to flucloxacillin (39). The GWA study involved genotyping of these cases and matched populations controls for approximately 900,000 SNPs. A number of SNPs in the major histocompatibility complex (MHC) region of chromosome 6 where HLA genes are located showed genome-wide significant p values, with the top SNP in the *HCP5* gene showing a p value of 8.7×10^{-33}. This SNP is in strong linkage disequilibrium with the class I HLA allele *B*5701*. Direct HLA typing confirmed that carriage of *B*5701* was a strong risk factor for flucloxacillin-related DILI {odds ratio 80.6 [95% confidence interval (CI) 23–285] based on carriage of at least one *B*5701* allele}; this finding was also duplicated in a replication cohort of 16 further cases. Despite the strong association, only 1 in 500 to 1,000 *B*5701*-positive individuals prescribed flucloxacillin are predicted to develop DILI, so genotyping for this allele prior to flucloxacillin prescription is unlikely to be a useful pharmacogenetic test. It does, however, have potential as a diagnostic in suspected DILI cases (39).

A more recent, slightly smaller GWA study involved 41 cases of DILI collected during a phase III clinical trial of the nonsteroidal anti-inflammatory drug lumiracoxib, which has recently been withdrawn from the market in a number of countries owing to a relatively high incidence (approximately 2.6%) of raised ALT levels in users (40). The 41 DILI cases, together with lumiracoxib-exposed controls who had not suffered DILI, were genotyped for approximately 700,000 SNPs. A number of SNPs in the MHC region showed genome-wide significance, with the lowest p value at 4.4×10^{-12}. As with the entirely separate flucloxacillin DILI study, further HLA typing was performed, and a clear association with the HLA class II allele *DRB1*1501* was detected (odds ratio 5.0, 95% CI 3.6 –7.0). Though the overall HLA association for lumiracoxib DILI was less strong than that for flucloxacillin DILI, typing for a particular HLA allele (*DQA1*0102*) in linkage disequilibrium with *DRB1*1501* prior to prescription may help prevent doctors from prescribing lumiracoxib to the 34% of Europeans positive for this allele. This interesting approach is being considered as a possible means of reintroducing lumiracoxib to the market worldwide. By genotyping, the incidence of DILI in lumiracoxib users could drop to less than 1% by excluding those positive for *DQA1*0102* (40, 41).

The largest GWA study on DILI so far reported relates to the drug amoxicillin-clavulanate (mentioned above). Amoxicillin-clavulanate-related DILI has a number of features in common with flucloxacillin-related DILI in terms of frequency and type of liver injury. It also provides another example of a widely prescribed drug showing occasional liver toxicity. In a study of 201 DILI cases of European ethnic origin with ethnically matched population controls, representing the largest GWA study on DILI reported to date, genome-wide significance was again seen in the MHC region (42). The most significant SNPs (lowest p value $= 4.8 \times 10^{-14}$) localized to both the HLA class I and class II regions, whereas the previous GWA studies had found associations within only either class I or class II. Detailed HLA typing provided evidence that both *DRB1*1501-DQB1*0602* and *A*0201* were risk factors for development of DILI [odds ratios 3.3 (95% CI 2.0–5.7) and 2.2 (95% CI 1.6–3.2), respectively] and that there was a statistically significant genetic interaction between these alleles increasing the risk of DILI in individuals positive for both. The *DRB1*1501-DQB1*0602* association was in agreement with previous reports (30, 31), but the *A*0201* association was novel (42). These data are significant, but as with the findings for flucloxacillin, overall positive predictive value is low and the only possible use of genotyping for the risk factors described here would be for diagnostic purposes.

Though some DILI cases show features such as rash and/or eosinophilia that may indicate an HLA or other immune system association, only a minority of cases overall show such features. One particular feature of the DILI GWA study findings is that apparent associations with the HLA haplotype *DRB1*1501-DQB1*0602-DQA1*0102* have been detected for both amoxicillin-clavulanate and lumiracoxib-related DILI (40, 42). These compounds showing similar HLA associations for DILI are not obviously structurally similar (see **Figure 1**). In addition, there are phenotypic differences in the pattern of liver injury observed with the two drugs (40, 42). The association between *HLA-B*5701* and flucloxacillin-induced DILI is also seen for abacavir-induced hypersensitivity reactions that normally do not affect the liver (43), but the positive predictive value for *B*5701* in abacavir hypersensitivity is considerably higher than that for flucloxacillin DILI (39). There is also no obvious structural similarity between flucloxacillin and abacavir (**Figure 1**).

All four GWA studies on DILI involved smaller numbers of cases (between 41 and 201) than have been studied in GWA investigations on complex diseases. This has still enabled the detection of the relatively strong HLA associations seen for these drug reactions, but the power to detect weaker associations, perhaps involving non-HLA genes, is more limited. In addition, in a recent study on DILI relating to the anticancer drug lapatanib, an initial GWA study failed to detect any genome-wide significant associations, but in further candidate-gene analysis, a significant association was found with the HLA class II allele *DQA1*0201* (44), which forms part of the haplotype also associated with ximelagatran transaminitis (37). As with the other examples of HLA alleles associated with serious adverse drug reactions, these two compounds are not structurally related (**Figure 1**).

The mechanism underlying the HLA associations seen in DILI remains unclear. GWA studies have covered a wide range of genetic markers across the MHC region, and the strongest associations have been localized to specific class I and II HLA genes. However, although there is still no direct evidence that these gene products are causal, the parent drug or a metabolite either may interact directly with specific HLA class I or II proteins in an antigen presentation reaction to T cells or may form a covalent complex with intracellular proteins that is then cleaved, recognized specifically by certain HLA molecules, and presented to T cells.

Most of the drugs shown in **Figure 1** are subject to metabolism, though data on whether clavulanic acid undergoes enzyme-mediated metabolism are limited (45, 46). However, for DILI related to the drugs on which GWA studies have been performed, no association between DILI and genes concerned with drug disposition has been detected, despite the excellent representation

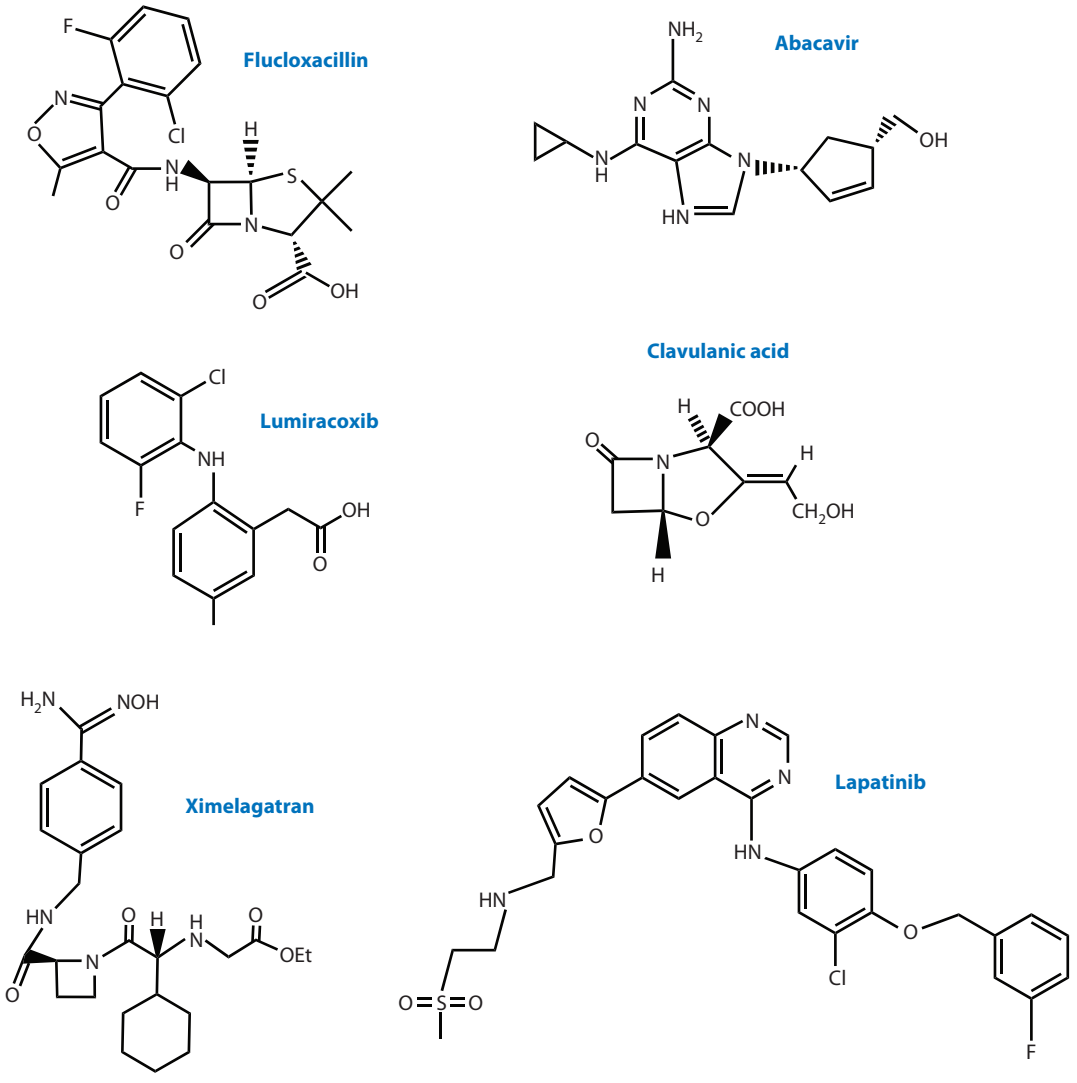

Figure 1

Chemical structures of drugs showing human leukocyte antigen (HLA) associations with drug-induced liver injury. The structures of ximelagatran, flucloxacillin, lumiracoxib, clavulanic acid, and lapatanib are indicated. Also shown is the structure of abacavir, which does not give rise to liver injury but does give rise to hypersensitivity reactions that, similar to flucloxacillin-induced liver injury, are also associated with *HLA-B*5701*.

of relevant SNPs on the platforms used for genotyping. It remains possible that only rare variants in these genes are relevant or that there is inadequate power to detect associations with more common variants given the small effect sizes and the relatively small numbers of cases included in the GWA studies.

Though HLA-related SNPs were the only SNPs showing genome-wide significance in the published GWA studies, two of the studies detected some additional SNPs showing possible associations. In particular for flucloxacillin DILI, the analysis suggested that a gene that has a possible role in B cell immune responses and is expressed in the liver, ST6 β-galactosamide

α-2,6-sialyltranferase 1 (*ST6GAL1*) (47), also contributed to flucloxacillin toxicity. To observe genome-wide significance for the *ST6GAL1* SNP, it was necessary to exclude any samples that were negative for *B*5701* (39). In the GWA study on amoxicillin-clavulanate DILI (42), additional analyses were performed to assess the contribution of SNPs relevant to drug disposition and to autoimmune disease. As discussed above, no significant associations with the SNPs in genes relevant to drug disposition were detected, but when the SNPs relevant to autoimmune disease were examined, two SNPs in *PTPN22*, which encodes the lymphoid-specific protein tyrosine phosphatase, nonreceptor type 22 involved in T-cell-receptor signaling, showed relatively low p values that remained statistically significant after correction for multiple testing.

To date, GWA studies on DILI have focused either on drugs that are very widely prescribed and occasionally give rise to DILI (flucloxacillin and amoxicillin-clavulanate) or are either newly licensed or still in development with a liability to give rise to DILI detected during clinical trials (ximelagatran and lumiracoxib). Assembling suitably sized groups of DILI cases due to other drugs occasionally associated with DILI such as specific NSAIDs, statins, and certain other antimicrobials to enable further GWA studies to be performed with adequate statistical power is more challenging, though achievable via international collaboration. Whether the HLA genotype will be the strongest risk factor for DILI linked to these other drugs is still unclear. There is evidence from candidate-gene association studies that drug-metabolism genes contribute to susceptibility to some forms of DILI, for example, *NAT2* in the case of isoniazid-related DILI (reviewed in Reference 48). It would be of value if such findings could be confirmed by GWA studies.

HYPERSENSITIVITY AND SKIN REACTIONS

A hypersensitivity reaction is an inappropriate immune reaction to an otherwise nontoxic agent. The manifestations of hypersensitivity reactions are broad. Certain forms of DILI, as discussed above, can be regarded as hypersensitivity reactions, for example, flucloxacillin and coamoxiclav-induced liver injury. Skin reactions, which may also involve other organs such as the liver, lungs, or kidneys, are the most common type of drug-induced hypersensitivity reactions (49).

The antiretroviral drug abacavir is associated with hypersensitivity: Up to 8% of patients prescribed this drug suffer symptoms including fever, malaise, gastrointestinal symptoms, and internal organ involvement (49). Skin rash is also seen in many affected individuals. As discussed in more detail in Liver-Related Adverse Drug Reactions (section above), almost all individuals who suffer abacavir hypersensitivity are positive for *HLA-B*5701*, the HLA allele also associated with flucloxacillin-induced liver injury. However, the association between abacavir-induced hypersensitivity and *B*5701* was established by candidate-gene association analysis, not by a GWA study (43).

Carbamazepine, a widely used anticonvulsant, causes skin rash in up to 10% of patients, and occasionally, this may progress to a hypersensitivity syndrome (50, 51) that can include rare blistering skin reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and also hepatitis (52). Using HLA as a candidate gene, a study in patients from Taiwan has shown a very strong association between *HLA-B*1502* and carbamazepine-induced SJS (53). However, in Europeans (54, 55) and Japanese (56), the allele frequency of *HLA-B*1502* is lower, and no association for development of Stevens-Johnson syndrome has been shown for this allele. A range of other drugs including other anticonvulsants such as phenytoin and lamotrigine, allopurinol and sulfonamide antimicrobial agents may also rarely give rise to hypersensitivity reactions involving skin and other tissues. In the case of allopurinol, a highly significant association between *HLA-B*5801* and both hypersensitivity and SJS/TEN reactions induced by this drug has been detected by candidate-gene studies in a range of ethnic groups (55, 57).

Recently, three GWA studies on drug-induced skin rash have added to the existing data obtained from candidate-gene association studies discussed above. The first involved 53 Japanese cases of carbamazepine-induced skin rash, including cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug-induced hypersensitivity syndrome (58). The strongest association was seen with a SNP in strong linkage disequilibrium with *HLA-A*3101*. Detailed HLA typing confirmed the association with *HLA-A*3101* and the expected lack of association with *HLA-B*1502* in this population. The *HLA-A*3101* association was also confirmed in a replication cohort of 61 cases (58); the allele is a risk factor for both SJS/TEN and hypersensitivity reactions, unlike the association between *HLA-B*1502* and carbamazepine toxicity in Chinese, which is more specific to SJS/TEN. In a second GWA study of patients of European ethnic origin, a similar *HLA-A*3101* association for carbamazepine hypersensitivity was detected, which again related to both hypersensitivity and SJS/TEN (59). The European GWA study involved 65 cases and was replicated in a further 145 cases. Both studies showed odds ratios in excess of 10 for hypersensitivity reactions and 25 for SJS/TEN. In addition, relatively high specificity and sensitivity values were estimated, suggesting that genotyping for *HLA-A*3101* prior to carbamazepine prescription would be cost effective in preventing hypersensitivity reactions (59), as already is the case for *HLA-B*1502* typing in Han Chinese and some other ethnicities (60).

These findings are also of considerable interest in terms of the biological basis for hypersensitivity reactions, indicating that more than one HLA class I gene product is able to present an antigen complex including carbamazepine or a metabolite to cytotoxic T cells, possibly owing to overlap in peptide-binding specificity (61).

The third GWA study on drug-induced skin injury was in a European population consisting of 96 cases of SJS or TEN induced by a variety of different drugs including the anticonvulsant lamotrigine and the antimicrobial cotrimoxazole (62). Only 3 cases related to carbamazepine exposure. For this heterogeneous group, no genome-wide significance was obtained for any individual SNP marker. When subgroup analysis was performed for lamotrigine and cotrimoxazole, a signal with a relatively low, though not genome-wide significant, p value was seen for lamotrigine in a SNP adjacent to the *ADAM22* gene, but no obvious possible associations were seen for cotrimoxazole. As *ADAM22* was suggested previously to be a susceptibility gene for epilepsy, the association in the lamotrigine cases may relate to an increased frequency in epilepsy cases compared with population controls rather than an actual drug-induced skin injury association. The failure to see any overall statistical significance in this GWA study suggests that genetic risk factors for drug-induced skin injury may be drug specific.

DRUG-INDUCED MYOPATHY

A number of different drugs are associated with myopathy, which usually involves subacute manifestation of myopathic symptoms such as muscle weakness, myalgia, creatine phosphokinase (CPK) elevation, or myoglobinuria. The precise disease phenotype is somewhat dependent on the individual drug (63). Most cases are not serious and are readily reversible by drug withdrawal, but a more severe form of disease resulting in rhabdomyolysis followed by death also occurs rarely.

Despite being very effective drugs that are used successfully worldwide, statins can cause muscle toxicity. As with other myotoxic drugs, this manifests as an asymptomatic rise in CPK but can be more serious on rare occasions. The mechanism by which statins give rise to toxicity is still not completely clear, but increasing evidence indicates an induction of expression of the protein atrogin-1 in affected muscle tissue leading to muscular atrophy, possibly because of inhibition of geranylgeranyl isoprene unit transfer by statins (64). Drug interactions seem to be an important contributor to statin-induced myopathy, but there is also increasing evidence for a role for genetic

polymorphisms relevant to their metabolism and transport in susceptibility to toxicity (65) and more limited evidence that genes encoding proteins relevant to muscular function may contribute (66, 67). Unlike the case with DILI, there is currently no evidence for a role for the immune system in susceptibility to myopathy induced by either statins or other drugs.

Understanding the genetic basis of susceptibility to simvastatin-induced myopathy was greatly increased by a GWA study of 85 cases of myopathy and 90 simvastatin-exposed controls without evidence of myopathy (68). The cases and controls were all of European ethnic origin. A highly significant association ($p = 4 \times 10^{-9}$) was seen for a single SNP in *SLCO1B1* with an odds ratio of 4.5 per copy of the variant allele. This effect was confirmed in 21 cases of myopathy from a separate replication cohort. *SLCO1B1* encodes an anionic drug transporter located on the sinusoidal face of the hepatocyte, which is the main inward transporter for a number of different statins (65). The significant SNP was in strong linkage disequilibrium with a nonsynonymous SNP in the *SLCO1B1*15* allele (also present in the rarer *SLCO1B1*5* allele) that is associated with higher plasma levels of statins owing to impaired transport (69). This association is, therefore, very biologically plausible. The significant polymorphism is common with a variant allele frequency of 0.13 in European populations, but possession of the variant allele explains only approximately 18% of attributable risk, with substantial numbers of myopathy cases homozygous wild type for *SLCO1B1*. The study had limited power to detect variants with a smaller effect than that of *SLCO1B1*, but no suggestion of significant effects for a list of candidate genes studied in more detail was obtained. There is a need for further larger studies with power to detect smaller effects to explain a higher proportion of risk for this toxicity. The association of muscle injury with *SLCO1B1*15* has recently been confirmed for milder toxicity and several different statins in a candidate-gene study (70). In addition, in a large study of individuals with type II diabetes who were receiving statins, carriage of the *SLCO1B1*15* allele was associated with a significantly increased risk of "statin intolerance," which was defined by either biochemical abnormalities and a change in prescription including discontinuation or a change in prescription alone (71).

DRUG-INDUCED LONG QT SYNDROME

As discussed in the Introduction (section above), cardiotoxicity is currently the most common reason for withdrawal of licensed drugs from the market. Examples of such drugs come from a variety of different classes including antipsychotics, antihistaminics, and antimicrobials. In susceptible individuals, these drugs are associated with delay of cardiac repolarization, which can be detected by prolongation of the QT interval on an electrocardiogram (ECG), and onset of a form of ventricular tachycardia called torsades de pointes (also detectable by ECG), which can lead to ventricular fibrillation and death (for a detailed review, see Reference 72). QT interval prolongation is an imperfect marker for the arrhythmic potential of a drug, given than many drugs prolong the QT interval but do not progress to arrhythmia, but it is currently the only available measure. QT prolongation can either be an inherited congenital disease or an acquired form that is triggered by exposure to environmental factors including certain drugs. There is considerable evidence to suggest that drugs associated with QT prolongation affect cardiac ion channels. In addition, the causative mutations associated with rare congenital long QT syndromes are often found in genes encoding ion channels (72). To date, GWA studies have focused on factors affecting QT length in populations, not drug-induced long QT (73–75). However, findings from these studies have resulted in the identification of SNPs in more than 10 different genes including the nitric oxide synthase 1 (NOS1) regulator *NOS1AP*, a range of sodium and potassium channel genes including *SCN5A* and *KCNJ2*, and miscellaneous other genes as important genetic predictors. As a result, these findings may contribute to an increased understanding of genetic

factors underlying susceptibility to drug-induced long QT syndrome. Unusually for a serious adverse drug reaction, there is evidence from family studies that susceptibility to drug-induced QT prolongation is, in part, genetically determined (76). Support for the relevance of GWA studies on population variation in QT length to drug-induced QT prolongation has been given by a finding for verapamil where increased QT prolongation was seen in patients positive for the variant in *NOS1AP* associated with longer QT interval in the general population (77).

The only GWA study on drug-induced QT prolongation thus far reported involved a phase III clinical trial of the antipsychotic drug iloperidone in which 183 patients had QT measurements performed 14 days after the start of drug treatment (78). No genome-wide significant signals were detected, but relatively low p values were obtained for several loci including the *CERKL* gene, which encodes a protein involved in the ceramide pathway, a regulator of currents conducted by potassium channels, and *SLCO3A1*, which may contribute to prostaglandin translocation. No trends toward significance with the SNPs in either ion channels or *NOS1AP* relevant to QT length in the previous studies were detected. There may be value in further GWA studies on patients who have suffered drug-induced QT prolongation from currently prescribed drugs to enable clearer identification of "at risk" genotypes.

BISPHOSPHONATE-INDUCED OSTEONECROSIS OF THE JAW

Bisphosphonates such as pamidronate and zoledronic acid are used widely in the treatment of cancer and osteoporosis to limit loss of bone mass. In some patients, their use is associated with necrotic damage to bone tissue in the jaw, which is often triggered by dental problems (79). In a GWA study involving 25 cases, four SNPs in the cytochrome P450 CYP2C8 gene showed altered frequencies compared with controls that narrowly escaped genome-wide significance (lowest p value was 6.22×10^{-6}) (80). One of the associated SNPs is located in the CYP2C8 promoter region and forms part of a haplotype seen at a frequency of 9.9% in Europeans. The other three associated SNPs are also found within this haplotype as well as in a second, slightly rarer, haplotype. There is some preliminary evidence that this haplotype is associated with lower than average CYP2C8 activity (81, 82). CYP2C8 plays a major role in the metabolism of a small number of drugs (83), but there is no evidence that bisphosphonates undergo metabolism by this or any other cytochrome P450. However, because a more general biological role for CYP2C8 in metabolism of inflammatory mediators (84) and a key role for inflammation in the bisphosphonate-induced osteonecrosis have been proposed (85), this finding is of interest but needs follow-up in a larger number of cases.

CONCLUDING REMARKS

GWA studies have facilitated progress in understanding genetic susceptibility to a range of serious adverse drug reactions. To date, most associations detected are strong and highly significant. Though this seems to be a particular feature of the GWA studies on adverse drug reactions reported so far, it also seems likely that only a proportion of genetic susceptibility is being explained by these strong associations and that additional studies, either larger GWA studies with better power to detect smaller effect sizes or whole-genome sequencing to detect rare genetic variants, will identify additional factors that contribute to risk. In particular, for examples such as flucloxacillin-induced liver injury or statin-induced myopathy, though strong associations have already been detected, the predictive value of the genotypes involved in these associations appears insufficient for their incorporation into routine decisions on prescribing. However, genotyping for the risk factors may be of value in diagnosing these adverse drug reactions. By contrast, the recent findings

of an association between *HLA-A*3101* and carbamazepine hypersensitivity may be translated more generally to the clinic (59), and it has also been proposed that a HLA-typing test could be incorporated into treatment with lumiracoxib (41).

The current findings from GWA studies should also be of value in the design of better model systems to detect idiosyncratic adverse drug reactions during drug development. For example, the potential importance of T cell responses in DILI is now much clearer, even though the underlying biology is still not understood, but multicellular systems involving both hepatocytes and immune cells may be helpful in identifying potentially hepatotoxic drugs. Similar approaches may also be applicable to other immune-related drug toxicities such as skin rash.

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