

MINI REVIEW

Genetics of drug-induced liver injury: Current knowledge and future prospects

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Abstract

Idiosyncratic drug-induced liver injury (DILI) remains an important clinical problem, both during drug development and the prescription of a range of licensed drugs. Although rare, the consequences are serious. Ongoing studies on genetic risk factors for DILI, especially genomewide association studies, have resulted in the identification of a number of genetic risk factors, including particular HLA alleles and a few non-HLA genes, both immune-related and metabolic. Some non-HLA associations, such as N-acetyltransferase 2 in isoniazid DILI and interferon regulatory factor 6 in interferon-beta DILI are likely to be drug-specific due to the role of the associated gene, but there is also evidence for polygenic susceptibility involving pathways such as oxidative and endoplasmic reticulum stress and mitochondrial function for DILI induced by multiple drugs. Increased knowledge of genetic risk factors should assist in better understanding underlying DILI mechanisms and help improve methods for identifying hepatotoxic drugs early in development. HLA allele-specific T cell proliferation together with in silico prediction of drug binding to specific HLA proteins have confirmed genetic findings for certain common causes of DILI. However, studies in hepatocytes exposed to high drug concentrations suggest toxicity that is not dependent on genotype also occurs. It seems likely that susceptibility to DILI involves several genetic risk factors combining with other factors that affect drug levels. Despite recent progress in detecting genetic risk factors for DILI, low positive predictive values mean that general implementation of genotyping prior to prescription of potentially hepatotoxic drugs is not useful currently.

INTRODUCTION

Idiosyncratic drug-induced liver injury (DILI) remains an important issue, especially during drug development. As reviewed in detail elsewhere, reports of some newly developed drugs causing hepatotoxicity continue to appear, especially for new drugs used in oncology.¹ In addition,

a relatively large number of older, commonly prescribed drugs are well-established causes of DILI, as demonstrated in a recent survey of DILI causative agents based in Europe.² Idiosyncratic DILI reactions are generally rare (<1 in 1000 patients exposed) but have potentially serious consequences; in a detailed study of patients with acute liver failure, 11% had DILI as an etiology with 64% of these

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either undergoing liver transplantation or dying.³ The genetics of idiosyncratic DILI has been studied in detail using both candidate gene and genomewide association studies (GWAS) for the last 25 years. There is now a relatively large body of knowledge available but, as discussed in detail below, it is still not feasible to predict either individual susceptibility to DILI or likely hepatotoxicity of newly developed drugs based on genetics. Despite these limitations, genetic studies have provided valuable data on underlying mechanisms for idiosyncratic DILI; studies combining genetics and in vitro systems have advanced the field considerably. This paper will consider what is currently known about genetic susceptibility to DILI and also discuss how this knowledge has informed mechanism-based studies. Most of the early work on genetics of DILI was concerned with prescribed drugs but there are recent reports of overlapping risk factors for the development of hepatotoxicity with herbal remedies. Some knowledge on DILI genetic risk factors for biologics is also now available, although the majority of the studies to date are concerned with smaller molecules as causative agents.

GENETIC RISK FACTORS FOR DILI

Human leukocyte antigen (HLA) genotype is currently the most widely reported genetic risk factor for DILI but not all forms of idiosyncratic DILI show HLA associations. In addition, there is increasing evidence that non-HLA genetic risk factors contribute to DILI risk alongside HLA genotype or as the only risk factor. This section considers HLA and non-HLA risk factors separately. However, dividing hepatotoxic drugs solely on the basis of whether they show HLA associations or not is best avoided due to risk factors from both classes being important in several examples.

HLA associations

After limited early studies using serological HLA typing, the first report involving direct genotyping for HLA appeared in 2019 and was in a relatively large, well-phenotyped group of cases ($n = 35$) that had suffered DILI due to amoxicillin-clavulanate. A significant association with the HLA class II allele *DRB1*15:01* was detected.⁴ This association has been subsequently well-replicated using both candidate gene and GWAS approaches. As summarized in [Table 1](#) and, in more detail, in [Table S1](#), this landmark finding has been followed up by a relatively large number of further HLA association reports, with HLA associations with DILI due to herbal remedies and biologics now detected in addition to small molecule

TABLE 1 Summary of HLA associations with drug and herbal remedy-induced liver injury

HLA allele	Compound
<i>A*02:01</i>	Amoxicillin-clavulanate
<i>A*31:01</i>	Carbamazepine
<i>A*33:01</i>	Terbinafine, fenofibrate, ticlopidine
<i>A*33:03</i>	Ticlopidine
<i>A*34:02</i>	Allopurinol
<i>B*13:01</i>	Dapsone
<i>B*14:01-C*08:02</i>	Trimethoprim-sulfamethoxazole
<i>B*35:01</i>	<i>Polygonum multiflorum</i> , green tea
<i>B*35:02</i>	Minocycline
<i>B*39:01</i>	Infliximab
<i>B*53:01</i>	Allopurinol
<i>B*57:01</i>	Flucloxacillin, pazopanib
<i>B*57:02</i>	Various anti-HIV and anti-TB drug combinations
<i>B*57:03</i>	Flucloxacillin, various anti-HIV, and anti-TB drug combinations
<i>B*58:01</i>	Allopurinol
<i>B*39:01</i>	Infliximab
<i>C*03:02</i>	Methimazole
<i>DRB1*07:01</i>	Ximelagatran, lapatinib
<i>DRB1*11:04</i>	Nitrofurantoin
<i>DRB1*15:01</i>	Lumiracoxib, amoxicillin-clavulanate
<i>DRB1*15:02</i>	Amoxicillin-clavulanate
<i>DRB1*16:01</i>	Flupirtine

Note: Adapted from ref. 30. More detail is provided in [Table S1](#).

Abbreviation: TB, tuberculosis.

pharmaceuticals. A few general conclusions can be made from the data in these tables: (i) there is no single HLA allele associated with DILI risk generally but certain HLA genotypes are well-represented in the list and associated with DILI due to drugs with chemically different structures (e.g., DILI due to either amoxicillin-clavulanate or lumiracoxib) which are chemically very different shows a *DRB1*15:01* association; (ii) the observed associations may extend across HLA alleles (e.g., an association with flucloxacillin DILI was found both with *B*57:01* and the allele *B*57:03*) which forms part of the same HLA allele group as *B*57:01* but is much rarer; (iii) HLA associations are seen for all three common DILI phenotypes (hepatocellular, mixed, and cholestatic) and are not particularly specific for individual phenotypes. For example, DILI due to amoxicillin-clavulanate most commonly shows a mixed or cholestatic phenotype whereas DILI due to lumiracoxib was almost always hepatocellular but DILI cases due to either drug show strong associations with *DRB1*15:01*;

(iv) the population carrier frequency for most of the HLA allele risk factors for DILI is in the range 1%–10% in the populations studied except that the two HLA risk alleles for amoxicillin-clavulanate DILI have a higher carrier frequency in both the European population already studied as well as other populations worldwide (see Table S1). This results in a relatively low odds ratios (2–3 for each allele) for development of this form of DILI compared with some other forms of DILI where the presence of the “at risk” allele typically results in odds ratios greater than 10.

Despite these mainly strong HLA associations with DILI, genotyping for the various HLA alleles listed shows a lower positive predictive value when compared with certain other established HLA predictors for adverse drug reactions more generally. In particular, to prevent abacavir hypersensitivity reactions, genotyping for *HLA-B*57:01* is now mandated in many countries prior to prescription of this drug. One in every two patients carrying *B*57:01* will develop serious hypersensitivity when abacavir is administered. However, although *B*57:01* is also a risk factor for flucloxacillin-induced DILI, it is estimated that only one in every 500 patients positive for this allele and prescribed this antimicrobial develop symptoms of DILI.⁵ This low positive predictive value makes testing prior to flucloxacillin prescription of limited value, although use of the test does show a high negative predictive value which makes it potentially useful for flucloxacillin DILI diagnosis. For the other HLA-drug associations summarized in Tables 1 and S1, the positive predictive value of genotyping is lower than that for *B*57:01* in relation to flucloxacillin DILI. The question of whether a polygenic risk score based not only on HLA genotype but additional non-HLA genetic risk factors is useful is discussed below.

Many of the drugs listed in Table 1 feature prominently in surveys of DILI due to prescribed drugs. In general, detection of an HLA association with DILI can be made using as few as 15 cases providing a large number of controls are also analyzed.⁶ The availability of relatively large numbers of DILI cases due to particular drugs (see for example ref. 7) has enabled the conclusion that an HLA association is unlikely for a number of well-established causes of DILI based on at least 15 adjudicated DILI cases being available (see Table 2).

Non-HLA gene associations

In parallel with the studies describing HLA associations with DILI, a number of signals from non-HLA genes have also been reported. In general, the reported associations involve either genes relevant to drug disposition or the immune response. Many of the reported associations are based on candidate gene studies on small numbers of

TABLE 2 Drugs causing DILI with no detectable HLA association

Isoniazid
Diclofenac
Azathioprine and other thiopurines
Ciprofloxacin and other fluoroquinolones
Atorvastatin and other statins
Nimesulide
Interferon beta
Fasiglifam (TAK-875)

Note: Based on >15 cases available for study but no detectable significant signal in HLA region.^{7,11,12,16}

Abbreviation: DILI, drug-induced liver injury.

cases without replication cohorts and will not be discussed further here. However, some interesting signals have emerged from recent GWAS on large cohorts. A GWAS involving 862 European cases of DILI due to a large number of different prescribed drugs found a genomewide significant signal in an intergenic region of chromosome 2 and, for hepatocellular DILI cases only, a signal on chromosome 4 in the *LRBA* gene in addition to a HLA signal.⁷ However, neither non-HLA signal could be replicated in a smaller replication cohort. This cohort of 862 cases was then included in a new enlarged cohort of 1806 European cases which were meta-analyzed with smaller numbers of African-American and Hispanic cases.⁸ The study, as was expected, found a highly significant HLA association but also found a second genomewide significant signal on chromosome 1 representing a nonsynonymous polymorphism in *PTPN22*, a gene encoding a phosphatase enzyme that contributes to B and T cell responses. This polymorphism is a risk factor for certain autoimmune diseases and is functionally significant in terms of effect on activity for the phosphatase enzyme encoded by this gene. The *PTPN22* signal was generated particularly from cases due to amoxicillin-clavulanate in the cohort with a smaller contribution from DILI cases due to terbinafine, sulfamethoxazole-trimethoprim, and a few other drugs. Importantly, the *PTPN22* signal was replicated in an independent cohort of 113 Icelandic DILI cases.

A further non-HLA signal for amoxicillin-clavulanate DILI was detected by using transcriptome-wide association performed on liver tissue (TWAS) combined with GWAS on 444 amoxicillin-clavulanate DILI from the GWAS reported by Cirulli and colleagues.^{8,9} TWAS showed a significant association of DILI risk with reduced liver expression of *ERAP2*, which codes for an enzyme that trims peptides for presentation by class 1 HLA proteins. Genotyping of a replication cohort for the main polymorphism in *ERAP2* responsible for the TWAS signal confirmed significance. As suggested recently, a combined

polygenic risk score involving the two HLA alleles associated with amoxicillin-clavulanate DILI together with the *PTPN22* and *ERAP2* variants may be a useful predictor of susceptibility to this adverse reaction or at least useful as a diagnostic tool.¹⁰

In a separate GWAS concerned entirely with DILI induced by interferon beta, a genome-wide significant signal was detected for an apparently functionally significant polymorphism close to the gene *IRF6* (interferon regulatory factor 6).¹¹ This association has not been observed for DILI induced by other drugs and it seems likely to be specific for interferon in view of the direct biological association.

A complex polygenic risk score for DILI more generally has been developed using data based on the GWAS involving 862 Europeans by Nicoletti and colleagues⁷ described above. This is of particular interest because the risk scores developed are intended as a general tool for DILI susceptibility prediction.¹² The study developed three different scores which were based on genomic data from: (i) the entire cohort, (ii) hepatocellular DILI cases only, and (iii) cholestatic and mixed DILI cases only. The scores were each based on genotype for approximately 28,000 different single nucleotide polymorphisms (SNPs). The cholestatic-mixed score was significantly higher in cases of DILI due to the hepatotoxic drug fasiglifam compared with controls, whereas the total and hepatocellular scores did not show this difference. In addition, the cholestatic-mixed score was predictive for both flucloxacillin and amoxicillin-clavulanate DILI using cases that were not included in the original GWAS. The variants included in the significant risk score are enriched in genes relevant to oxidative and endoplasmic reticulum stress together with mitochondrial function. These pathways are plausible contributors to DILI, although, to date, specific genetic variants relevant to these pathways have not been shown reliably to contribute as individual risk factors. Further studies on these polygenic risk scores are needed to fully assess their relevance and usefulness.

Another example of a gene-drug relationship for DILI concerns the anti-tuberculosis agent isoniazid and the gene encoding the main enzyme involved in its metabolism *NAT2*. Reports that phenotype and/or genotype for *NAT2* affects susceptibility to DILI due to this drug have appeared over an extended period since the mid-1970s.¹³ Up until recently, a clear consensus on the precise relationship of *NAT2* genotype with DILI susceptibility had not emerged with many studies published but mainly based on the very small numbers of cases or a DILI phenotype not considered to be clinically severe. A recent GWAS involving 79 cases of isoniazid-related DILI on a well phenotyped cohort from Thailand detected a genome-wide significant signal at the *NAT2* locus on chromosome 8 with

a polymorphism tagging slow acetylation increasing risk of this form of DILI.¹⁴ No other genome-wide significant risk signals were detected. Slow acetylation due to *NAT2* deficiency is seen at a frequency of approximately 10% in Thais, which is similar to that in other east Asian populations. A candidate gene study based in Taiwan had earlier reported broadly similar findings.¹⁵ Up until recently, the relationship between *NAT2* genotype and DILI due to isoniazid in other ethnic groups has been less clear and a recent GWAS involving meta-analysis of European and Indian isoniazid DILI cases failed to detect any genome-wide significant signals.¹⁶ However, when *NAT2* genotypes were assigned from the GWAS data the *NAT2* alleles *NAT2*6* and **7*, which are the main alleles associated with slow acetylation in East Asians, were also found to be risk factors in homozygotes and compound heterozygotes in the European and Indian cases. Importantly, another allele *NAT2*5*, which is rarely seen in East Asians but is common in Europeans and generally considered to be an additional slow acetylator allele, was not a risk factor and may have some protective effects. Some recent in vitro data suggests that the enzyme encoded by *NAT2*5* shows higher activity than either **6* or **7* in findings which are consistent with the observations seen in recently in DILI cases.¹⁷ The possibility of dosing with isoniazid based on genotype has been investigated in a clinical trial based in Japan.¹⁸ Results of that trial were supportive of this approach but more complex dosing guidelines might be needed for populations where *NAT2*5* is common.

MECHANISTIC STUDIES BASED ON GENOMIC DATA

Despite the good progress made recently in identifying genetic risk factors for idiosyncratic DILI and recognition of the important contribution to risk by HLA and certain other genotypes, the underlying mechanism for development of DILI is still not completely understood, as discussed recently.¹⁹ In particular, there is still a need to develop reliable cell-based systems useful for predicting DILI risk early in drug development. Progress on this aspect has been made and some approaches now available incorporate genomic data. Studies involving either isolated T cells or peripheral blood mononuclear cells cultured with autologous antigen-presenting cells in the presence of the drug causing the adverse reaction were originally performed to determine the mechanism underlying the abacavir hypersensitivity association with *HLA-B*57:01* and were subsequently performed to study other associations, such as that between carbamazepine-induced skin rash and *HLA-B*15:02*.²⁰ HLA-restricted cell proliferation and production of

inflammatory cytokines is the end point used. This approach has also been used successfully to show HLA specific proliferation in T cells positive for *HLA-B*57:01* and flucloxacillin.²¹ Broadly similar cell-based studies showing HLA-specific responses for well-established causes of DILI with an HLA association have been reported for amoxicillin-clavulanic acid²² and ticlopidine,²³ but not for lapatinib.²⁴ Some of these studies found the reaction only when T cells from DILI cases were used but, in some cases, it was also possible to induce proliferation in an HLA genotype-specific manner in drug-naïve cases. In parallel with this approach, molecular modeling studies involving either the DILI-causing agent or a metabolite and the HLA risk factor protein suggest a direct interaction between drug or metabolite and the HLA molecule similar to that already established to occur for *B*57:01* and abacavir²⁰ have been performed. These studies suggest an ionic interaction between HLA protein and drug may occur for minocycline and trimethoprim-sulfamethoxazole.^{25,26} Because for most drugs causing DILI, only a small proportion of individuals who are drug exposed and positive for the at-risk genotype develop toxicity, it remains possible that stimulation of a T cell response is not sufficient to generate detectable toxicity in vivo with other events also contributing. Studies describing direct toxic effects in cultured human hepatocytes involving oxidative and endoplasmic reticulum stress together with effects on other cellular processes, such as alterations in bile acid homeostasis with flucloxacillin, amoxicillin, and clavulanic acid when very high concentrations of the drugs are added,^{27,28} are consistent with overall susceptibility involving multiple signals, some of which would be genetically determined. These findings are also broadly in line with those from the recent study proposing a polygenic risk score for DILI.¹²

CONCLUSIONS AND FUTURE DIRECTIONS

There is now a good body of knowledge available on genetics of DILI, mainly from GWAS, but our understanding both of the genetic basis and the underlying mechanism is still not comprehensive. Current knowledge can be used for diagnostic purposes, such as performing *HLA-B*57:01* genotyping in patients showing symptoms of DILI who has been exposed recently to flucloxacillin or multiple genes in the case of amoxicillin-clavulanate.¹⁰

Increasing routine genome sequencing or use of genotyping panels in patients means that genomic data relevant to DILI risk may be available in some electronic medical records. This information could be used in the future to

inform prescribing, especially in situations where an alternative drug which is less likely to induce DILI in an individual patient is available.

Further genomic studies on DILI may be feasible and studies that may facilitate this involving further patient recruitment are in progress. Although most “low hanging fruit” in the form of risk factors, such as common HLA alleles, have probably now been identified, it is very likely that both common variants with a small effect on risk and rare variants with larger effects on risk can be detected if the sample size is increased. Both types of risk factors are important, especially in the case of DILI where the rarity of the condition makes it more likely that rare variants make a contribution to overall risk. The value of exome sequencing of large cohorts to identify rare variants that contribute to chronic liver disease risk has recently been well-demonstrated.²⁹ A similar approach in DILI is possible but confirming associations of this type from exome sequencing is challenging due to the rarity of DILI compared with the chronic liver diseases, such as alcoholic and non-alcoholic fatty liver disease investigated in the recent study.

In summary, despite good progress recently on understanding the genetics of idiosyncratic DILI, further studies are needed before widespread implementation of pre-prescription genotyping to prevent DILI reactions is feasible.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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