Genome-Wide Association Studies for Idiosyncratic Drug-Induced Hepatotoxicity: Looking Back—Looking Forward to Next-Generation Innovation

Zelalem Petros,¹ Eyasu Makonnen,¹ and Eleni Aklillu²

Abstract

Idiosyncratic drug-induced hepatotoxicity is a formidable challenge for rational drug discovery and development, as well as the science of personalized medicine. There is evidence that hereditary factors, in part, contribute to drug toxicity. This expert analysis and review offer the insights gained, and the challenges ahead, for genome-wide association studies (GWASs) of idiosyncratic drug-induced hepatotoxicity. Published articles on genome-wide and subsequent replication studies were systematically searched in the PubMed electronic database. We found that the genetic risk variants that were identified genome-wide, and replication confirmed, are mainly related to polymorphisms in the human leukocyte antigen (HLA) region that include *HLA-DQB1*06:02* for amoxicillin–clavulanate, *HLA-B*57:01* for flucloxacillin, *HLA-DRB1*15:01* for lumiracoxib, and *HLA-DRB1*07:01* for lapatinib and ximelagatran-induced hepatotoxicity. Additionally, polymorphisms in ST6 β -galactosamide α -2, 6-sialyltransferase-1 (*ST6GAL1*), which plays a role in systemic inflammatory response, and variants in intron of family with sequence similarity-65 member-B (*FAM65B*) that play roles in liver inflammation displayed association with flucloxacillin and antituberculosis drug-induced hepatotoxicity, respectively. Taken together, these GWAS findings offer molecular leads on the central role that the immune system plays in idiosyncratic drug-induced hepatotoxicity. We conclude the expert review with a brief discussion of the salient challenges ahead. These include, for example, the need for discursive discovery paradigms that incorporate alternating GWASs and candidate gene studies, as well as the study of the environment, the entire complement of environmental factors, including science and innovation policies that enact on global society and the human host, and by extension, on susceptibility for idiosyncratic drug-induced hepatotoxicity.

Keywords: disruptive innovation, drug discovery and development, drug-induced hepatotoxicity, drug-induced liver injury, GWAS, genome-wide study, translational research

Introduction

IDIOSYNCRATIC DRUG-INDUCED HEPATOTOXICITY (DIH) is defined as an adverse liver reaction, which is unexpected on the basis of the known pharmacology of the administered drugs (Tailor et al., 2015). It is a dose-independent reaction and varies in latency, presentation, and its course (Aithal et al., 2011). Idiosyncratic DIH has a substantial impact on the healthcare system. It contributes to 7–15% of cases of acute liver failure, which often has a worse prognosis, and is characterized by sudden and life-threatening hepatic dysfunction (Lee, 2013; Reuben et al., 2010). Thus, timely diagnosis of DIH and adopting subsequent intervention measures are vital for patient safety.

Idiosyncratic DIH is a common reason for market withdrawal of drugs (Stevens and Baker, 2009). Various classes of drugs can potentially cause idiosyncratic DIH. The most common classes of drugs responsible for the development of DIH include antimicrobials, nonsteroidal anti-inflammatory drugs, central nervous system-acting drugs, anticoagulant medications, herbal supplements, and immune modulator agents (Chalasani et al., 2014; Daly and Day, 2009, 2012; Khoury et al., 2015). Risk factors for DIH are complex, involving environmental factors and host genetics (Kim and Naisbitt, 2016). The exact mechanisms of DIH are still poorly understood, but considered to be multistep and multicellular in nature (Tailor et al., 2015). The suggested mechanisms

¹Department of Pharmacology, School of Medicine, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia.

²Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska University Hospital, Huddinge C1:68, Karolinska Institutet, Stockholm, Sweden.

include direct toxicity, mitochondrial dysfunction, metabolic abnormalities, cellular stress, and immune-mediated reactions (Daly, 2010a; Fredriksson et al., 2014; Yuan and Kaplowitz, 2013).

Interestingly, a taxonomy of multiomics studies has been recently proposed (Pirih and Kunej, 2017). Genetic association studies in prespecified genes of interest (candidate gene approach) or screening the whole genome (genome-wide approach) are the two methods employed to identify variant alleles associated with DIH.

Candidate gene association studies

Until recently, candidate gene association studies (CGASs) have been the most widely used approach, where DNA samples from cases and controls (treatment tolerants) were genotyped for single-nucleotide polymorphisms (SNPs) in specific gene, for which prior knowledge suggested a role in the pathogenesis or has functional relevance (Hirschhorn et al., 2002). Various CGASs have identified susceptibility variants for idiosyncratic DIH linked to genes related to pharmacokinetics, oxidative stress, and immune response (Daly and Day, 2009, 2012; Russmann et al., 2010; Urban et al., 2014).

For instance, association of polymorphisms in N-acetyltransferase 2 (*NAT2*) (Cho et al., 2007; Du et al., 2013; Huang et al., 2002; Ohno et al., 2000; Possuelo et al., 2008; Yimer et al., 2011), cytochrome P450 family-2 subfamily-E member-1 (*CYP2E1*) (Deng et al., 2012; Huang et al., 2003; Vuilleumier et al., 2006), glutathione S-transferases M1 (*GSTM1*) (Huang et al., 2007; Li et al., 2013; Roy et al., 2001), uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) (Chang et al., 2012), ATP-binding cassette subfamily-B member-1 (*ABCB1*) (Yimer et al., 2011), solute carrier organic anion transporter family member-1B1 (*SLCO1B1*) (Chen et al., 2015a; Li et al., 2012), mitochondrial superoxide dismutase (*SOD2*) (Huang et al., 2007), and nuclear factor erythroid 2-related factor 2 (*Nrf2*) signaling pathway (Nanashima et al., 2012) genes with antituberculosis DIH has been reported previously.

Genetic factors for increased risk of developing idiosyncratic DIH in other classes of drugs include polymorphisms in genes encoding *UGT2B7* and ATP-binding cassette subfamily-C member-2 (*ABCC2*) with diclofenac (Daly et al., 2007), *GSTM1* and *GSTT1* with amoxicillin-clavulanate (AC) and troglitazone (Lucena et al., 2008), cytochrome P450 2B6 (*CYP2B6*) with efavirenz-based antiretroviral therapy (ART) (Mugusi et al., 2012; Yimer et al., 2011, 2012), and *ABCB1* with nevirapine (Haas et al., 2006).

Polymorphisms in the human major histocompatibility complex (MHC) gene cluster, referred to as the human leukocyte antigen (HLA), have been demonstrated to contribute to risk of developing idiosyncratic DIH (Grove and Aithal, 2015). HLA alleles identified through CGASs include *HLA-DQB1*02:01* and *DQB1*05:05* for antituberculosis drugs (Chen et al., 2015b; Sharma et al., 2002); *HLA-B*58:01* and *DRB1*01:02* for nevirapine-containing antiretroviral regimens (Ostrov et al., 2012; Phillips et al., 2013); *HLA-DRB1*15:01*, *DQB1*06:02*, *A*02:01*, and *DRB5*01:01* for AC (Andrade et al., 2004; Drago et al., 2014; Hautekeete et al., 1999; O'Donohue et al., 2000; Stephens et al., 2013), and *HLA-A*33:01* for ticlopidine (Hirata et al., 2008)-induced DIH.

Although CGASs have been able to identify genetic risk factors that are known to contribute to susceptibility to

common diseases and pharmacogenetic traits, this approach has some drawbacks (Daly and Day, 2001, 2009; Russmann et al., 2010). The major limitation is that the selection of candidate genes is hypothesis driven based on the current understanding of disease pathogenesis. Hence, genetic variants related to unknown mechanisms that have relevance to disease susceptibility cannot be detected. CGASs rely on the analysis of limited number of SNPs and do not usually consider regions that regulate gene expression and thus lack comprehensiveness (Russmann et al., 2010). In addition, in some CGASs, inconsistent results were reported. In this sense, the genome-wide approach could have a good potential to understand the trait of interest (Hirschhorn and Daly, 2005) and is increasingly being applied in the areas of pharmacogenomics.

Genome-wide association studies

Genome-wide association studies (GWASs) are genetic association studies in which a large number of markers that capture a significant proportion of common genetic variations in the genome are genotyped in a set of DNA samples that are informative for a given trait (McCarthy et al., 2008). The goal of GWASs is to identify DNA sequence variants that affect an individual's risk to a disease or response to drug treatment through detection of associations between allele or genotype frequencies and trait status. In contrast to CGASs, GWASs investigate the possible association of genetic variations throughout the entire human genome and therefore represent comprehensive and unbiased scan of the genome (Daly, 2012; Karlsen et al., 2010).

GWAS allows the identification of novel susceptibility variants that may provide a better biological understanding of phenotypes (Motsinger-Reif et al., 2013). Such studies enable to elucidate the involvement of multiple genes or previously unrecognized biological pathways in disease development (Manolio, 2013). GWASs are particularly suitable for simultaneous identification of several common risk variants in a single study and are thus relevant for complex traits where the concerted action of several risk factors contributes to the observed phenotype (Russmann et al., 2010).

The availability of comprehensive data on human genetic variation from Human Genome and International Haplotype Mapping (HapMap) projects (International-HapMap Consortium, 2005; Wang et al., 2005) together with high-throughput genotyping technologies that allow large numbers of SNPs to be genotyped simultaneously has made GWASs technically feasible. The HapMap project has already genotyped millions of SNPs on samples representing the European, African, and Asian populations; and the data characterized the patterns of linkage disequilibrium (LD) across the genome (International-HapMap Consortium, 2005). Once the patterns of LD are known for a given region of the genome, a minimal set of correctly chosen variants (tag SNPs) can thereby serve as a proxy for many others and provide adequate information about most of the common variations within the genomic region (Hirschhorn and Daly, 2005).

A case-control study is the most frequently used study design for GWASs in which allele or genotype frequencies in patients with the disease of interest are compared with those in a disease-free group (Pearson and Manolio, 2008). The major steps involved in GWASs include (1) careful selection

of cases and controls from a population; (2) isolation of DNA, SNP genotyping, and quality control measures to enrich the dataset; (3) appropriate statistical tests to identify differences in allele and genotype frequencies between cases and controls; (4) careful interpretation of the results, and (5) replication of the findings with an independent cohort.

GWAS-identified and replication-confirmed genetic risk variants can have impacts on clinical medicine through prediction of outcomes or through elucidation of underlying biology (Hirschhorn and Gajdos, 2011; Manolio, 2013; McCarthy et al., 2008). Much of the immediate focus is for genetic testing that utilizes common variants as biomarkers to predict disease, to monitor disease progression and treatment response, or to avoid serious adverse drug reactions and thus advance clinical care through personalized medicine (McCarthy et al., 2008). On the other hand, identification of genetic loci and the relevant genes at those loci can help to describe new biological pathways and therapeutic targets, which can, in turn, provide clues for the development of novel preventive and treatment approaches (Hirschhorn and Gajdos, 2011).

It is now possible and indeed the norm to conduct GWASs to find associations between disease phenotypes and genetic variants that may predispose to the diseases. The successful applications in identifying novel susceptibility genes for complex diseases showed an interest in applying GWASs to identify genetic variants for pharmacogenomic traits such as idiosyncratic DIH (Stankov et al., 2013). The objective of this review is therefore to provide an overview on GWASs that identified genetic risk variants for idiosyncratic DIH and discuss the prospects and associated challenges.

Literature Review

Published reports were systematically searched in electronic databases of Medline (source PubMed). The search phrases used include “GWAS for drug-induced hepatotoxicity,” “GWAS for drug-induced liver injury (DILI),” and “GWAS for drug-induced liver damage” to identify published articles that included data on GWASs for idiosyncratic DIH. The methodology for the inclusion criteria was studies published as original articles and studies with subsequent replications. There were no restrictions on the class of drugs, doses, and routes of drug administration. The search yielded 18 articles; of these, 10 were included in the review.

Analysis of the Topline Findings

To date, a few GWASs have investigated genetic associations with idiosyncratic DIH (Cao et al., 2015; Daly et al., 2009; Kindmark et al., 2008; Lucena et al., 2011; Parham et al., 2016; Petros et al., 2016; Singer et al., 2010; Spraggs et al., 2011; Urban et al., 2012). The top associated SNPs are summarized in Table 1.

Amoxicillin-clavulanate-induced hepatotoxicity

AC is a commonly prescribed antimicrobial drug worldwide. The drug is well tolerated, but rarely DIH could occur due to the clavulanate component (Lucena et al., 2011). GWASs on susceptibility to AC-induced hepatotoxicity with 201 cases and 532 controls using 822,927 SNPs showed association with many loci in the HLA region (Lucena et al., 2011).

The strong associations of rs9274407 ($p = 4.8 \times 10^{-14}$), which is correlated with rs3135388, a tag SNP of *HLA-DRB1*15:01-DQB1*06:02*; and rs2523822 ($p = 1.8 \times 10^{-10}$), which is in LD with *HLA-A*02:01*, were reported. A subsequent replication study using high-resolution genotyping on 177 cases and 219 controls confirmed associations of *HLA-A*02:01* ($p = 1.9 \times 10^{-6}$) and *HLA-DQB1*06:02* ($p = 4.6 \times 10^{-10}$) with AC-induced hepatotoxicity (Lucena et al., 2011).

The results of the study were consistent with two earlier CGASs that reported *HLA-DRB1*15:01-DQB1*06:02* in 57% of cases, but in only 12% of controls (Hautekeete et al., 1999), and *HLA-DRB1*15:01* in 70% of cases, but in only 20% of controls (O'Donohue et al., 2000). The *HLA-DRB1*15:01* allele was implicated in DIH associated with both AC and lumiracoxib GWASs (Lucena et al., 2011; Singer et al., 2010). This is an example of a similar HLA allele risk profile for idiosyncratic DIH resulting from two structurally different drugs, but may represent a common immunological pathway for idiosyncratic DIH.

Antituberculosis drug-induced hepatotoxicity

Recently, we carried out a GWAS consisting of 48 DIH cases and 354 treatment tolerant Ethiopian tuberculosis patients treated with first-line antituberculosis drugs to identify genetic variants associated with antituberculosis drug-induced hepatotoxicity (Petros et al., 2016). It was the first published GWAS for antituberculosis drug-induced hepatotoxicity in an African population. The top SNPs in the GWAS after adjustment for covariates were rs10946739 ($p = 4.1 \times 10^{-6}$) and rs10946737 ($p = 9.7 \times 10^{-6}$) located in the intron region of family with sequence similarity-65 member-B (*FAM65B*). In the combined analysis (pooled subjects of GWAS and replication cohorts), the top SNP was rs10946737 ($p = 4.4 \times 10^{-6}$) located in the same intron region of *FAM65B*. A small replication cohort supported the GWAS finding, although the data did not reach statistical significance.

The *FAM65B* gene encodes a cytoplasmic protein that plays a role in myoblast differentiation and it is transiently upregulated during early stage of the process (Yoon et al., 2007). *FAM65B* is expressed in the hepatocytes, gall bladder, and bile duct, and a recent study indicated that *FAM65B* plays roles in liver inflammation (Stoyanov et al., 2015). The GWAS on the antituberculosis drug-induced liver injury also identified a cluster of SNPs in the intron of ATP/GTP-binding protein-like 4 (*AGBL4*) suggestive of genome-wide significant association (Petros et al., 2016). Although further analysis is required to clarify the functional importance of *FAM65B* and *AGBL4*, the study demonstrated the potential of GWASs to discover genetic risk factors that mediate DIH due to antituberculosis drugs.

Flucloxacillin-induced hepatotoxicity

Flucloxacillin is widely used for the treatment of staphylococcal infections; however, it has been associated with cholestatic type of hepatotoxicity (Daly, 2010b). In a GWAS involving 51 cases and 282 controls covering 666,399 SNP markers, a strong association was identified with rs2395029 ($p = 8.7 \times 10^{-33}$), which is in complete LD with *HLA-B*57:01* (Daly et al., 2009). Furthermore, HLA genotyping showed that 84% of patients with flucloxacillin-induced hepatotoxicity carried the *HLA-B*57:01* allele compared with just 5%

TABLE 1. GENETIC SUSCEPTIBILITIES FOR IDIOSYNCRATIC DRUG-INDUCED HEPATOTOXICITY IDENTIFIED THROUGH GENOME-WIDE ASSOCIATION STUDIES AND SUBSEQUENT REPLICATION STUDIES

Drug	Cases/Controls		Nearest gene/allele	p	OR	Reference
	GWAS cohort	Replication cohort				
Amoxicillin-clavulanate	201/532	177/219	<i>HLA-DQB1</i>	4.8×10^{-14}	3.1	Lucena et al. (2011)
			<i>HLA-A*02:01</i>	1.8×10^{-10}	2.3	
			<i>HLA-DQB1*06:02</i>	4.6×10^{-10}	4.2	
			<i>HLA-A*02:01</i>	1.9×10^{-6}	2.2	
Antituberculosis drugs	48/354	27/217	<i>FAM65B</i>	9.7×10^{-6}	4.3	Petros et al. (2016)
			<i>AGBL4</i>	1.0×10^{-2}	2.2	
Flucloxacillin	51/282	23/64	<i>HLA-B*57:01</i>	8.7×10^{-33}	45.0	Daly et al. (2009)
			<i>ST6GAL1</i>	1.4×10^{-8}	4.1	
			<i>HLA-B*57:01</i>	9.0×10^{-19}	80.6	
Lapatinib	34/810 37/286	24/155	<i>HLA-DRB1*07:01</i>	7.8×10^{-11}	NR	Spraggs et al. (2011); Parham et al. (2016)
			<i>HLA-DQB1*02:02</i>	7.0×10^{-3}	2.9	
			<i>HLA-DQA1*02:01</i>	8.0×10^{-5}	9.0	
			<i>HLA-DQB1*02:02</i>	3.0×10^{-4}	6.9	
			<i>HLA-DRB1*07:01</i>	4.0×10^{-4}	6.9	
Lumiracoxib	41/176	98/405 137/577	<i>HLA-DRB1</i>	2.8×10^{-10}	5.3	Singer et al. (2010)
			<i>HLA-DRB1</i>	4.4×10^{-12}	3.4	
			<i>HLA-DRB1*15:01</i>	6.8×10^{-25}	7.5	
			<i>HLA-DQB1*06:02</i>	1.1×10^{-22}	6.9	
			<i>HLA-DRB5*01:01</i>	1.6×10^{-20}	7.2	
			<i>HLA-DQA1*01:02</i>	1.2×10^{-18}	6.3	
Platinum-based chemotherapy	246/83	244/131	<i>TRPM2</i>	4.9×10^{-5}	3.8	Cao et al. (2015)
			<i>TRPM2</i>	3.9×10^{-2}	1.9	
Ximelagatran	74/130	10/16	<i>HLA-DQA1</i>	7.3×10^{-8}	4.6	Kindmark et al. (2008)
			<i>HLA-DQB1</i>	2.0×10^{-7}	2.8	
			<i>HLA-DQA1*02</i>	6.0×10^{-6}	9.5	
			<i>HLA-DRB1*07</i>	9.1×10^{-6}	4.4	
Multiple drugs (Diclofenac)	783/3001		<i>PPARG</i>	1.0×10^{-8}	11.3	Urban et al. (2012)

AGBL4, ATP/GTP-binding protein-like 4; *FAM65B*, sequence similarity 65 member B; GWAS, genome-wide association studies; HLA, human leukocyte antigen; NR, not reported; OR, odds ratio; *p*, The smallest *p* values in the genome-wide and subsequent replication studies; *PPARG*, peroxisome proliferator-activated receptor gamma; *ST6GAL1*, ST6 β -galactosamide α -2, 6-sialyltransferase-1; *TRPM2*, transient receptor potential cation channel subfamily-M member-2.

of the population controls. Possession of *HLA-B*57:01* allele was associated with an 80-fold increased risk of developing DIH. The association was replicated in a second cohort by direct genotyping (Daly et al., 2009). This finding was of particular interest because the *HLA-B*57:01* association is also seen in abacavir-induced hypersensitivity reactions (Mallal et al., 2002). However, because of a low positive predictive value for DIH prediction, routine genotyping for *HLA-B*57:01* in patients prescribed flucloxacillin is less valuable, although knowledge of the genotype could be useful in diagnosing DIH (Daly et al., 2009).

In carriers of *HLA-B*57:01*, another SNP rs10937275 in *ST6* β -galactosamide α -2, 6-sialyltransferase-1 (*ST6GAL1*) also showed genome-wide significance ($p = 1.4 \times 10^{-8}$) (Daly et al., 2009). *ST6GAL1* encodes Golgi membrane protein that plays roles in glycoprotein modification and is thought to be involved in the generation of cell surface carbohydrate determinants and differentiation antigens that may be necessary for lymphocyte function (Bast et al., 1992). Hepatic expression of *ST6GAL1* is elevated as part of the acute-phase inflammatory response and also considered an integral part of systemic inflammatory response. Therefore, like *HLA-B*57:01*,

ST6GAL1 variants might mediate an immunopathogenic mechanism in idiosyncratic DIH.

Lapatinib-induced hepatotoxicity

Lapatinib is a human epidermal growth factor receptor-2 (HER2) inhibitor approved for the treatment of patients with advanced or metastatic breast cancer whose tumors over-express human epidermal growth factor receptor (Geyer et al., 2006). Although clinical experience showed an acceptable safety profile, the drug has been associated with idiosyncratic hepatotoxicity and the genetic basis was explored in two different GWASs (Parham et al., 2016; Spraggs et al., 2011). In the first study, although no statistically significant associations were revealed, several marginal associations with polymorphisms localized in the HLA region were identified near the threshold significance level, suggestive of a likely role for HLA in the pathogenesis of DIH (Spraggs et al., 2011). The study revealed *HLA-DQA1*02:01* association that was replicated in a second cohort. A subsequent study confirmed the findings by identifying an association of *HLA-DRB1*07:01* with lapatinib-induced hepatotoxicity, which is in strong LD

with *HLA-DQA1*02:01* (Schaid et al., 2014). The second and most recent GWAS in 34 cases and 810 controls involving more than a million SNPs identified the association of *HLA-DRB1*07:01* ($p = 7.8 \times 10^{-11}$) with lapatinib-induced hepatotoxicity (Parham et al., 2016).

Lumiracoxib-induced hepatotoxicity

Lumiracoxib is a selective cyclooxygenase-2 inhibitor useful for symptomatic relief of acute pain and osteoarthritis (Bannwarth and Berenbaum, 2007). Concerns over lumiracoxib-induced hepatotoxicity had contributed to the limited clinical application of lumiracoxib in drug markets worldwide (Singer et al., 2010). GWAS to identify risk variants for lumiracoxib-induced hepatotoxicity was performed on 41 cases and 176 treatment tolerants in 682, 386 SNPs (Singer et al., 2010). A number of SNPs in the HLA class II region showed strong evidence of association; the top SNP was rs9270986 ($p = 2.8 \times 10^{-10}$) in *HLA-DRB1*. The findings were replicated in an independent set of 98 cases and 405 controls with the top SNPs rs3129900 ($p = 4.4 \times 10^{-12}$), rs3129934 ($p = 4.9 \times 10^{-11}$), rs313536 ($p = 6.3 \times 10^{-10}$), and rs9270986 ($p = 1.0 \times 10^{-9}$).

Further high-resolution HLA genotyping was performed, and an association with *HLA-DRB1*15:01* ($p = 6.8 \times 10^{-25}$), *DQB1*06:02* ($p = 1.1 \times 10^{-22}$), *DRB5*01:01* ($p = 1.6 \times 10^{-20}$), and *DQA1*01:02* ($p = 1.2 \times 10^{-18}$) was identified. Genotyping for *HLA-DRB1*15:01* allele can serve as means of genetic testing. The results of the study showed the potential to improve the safety profile of lumiracoxib by identifying individuals at high risk for hepatotoxicity. This interesting approach is being considered as a possible means of reintroducing lumiracoxib to the market (Daly, 2012; Stankov et al., 2013).

Platinum-based chemotherapy-induced hepatotoxicity

Platinum-based chemotherapy improves the survival of advanced nonsmall cell lung cancer (NSCLC) patients (Tan et al., 2011); however, DIH in susceptible individuals impedes the success of chemotherapy (Cao et al., 2015). GWAS using 907K SNPs in 334 NSCLC patients, followed by a replication study among 375 NSCLC patients, was performed to identify genetic variants that modify the risk of developing DIH in NSCLC patients receiving platinum-based chemotherapy (Cao et al., 2015). Genome-wide association was identified for rs2838566 in the discovery cohort ($p = 4.9 \times 10^{-5}$), replication cohort ($p = 3.9 \times 10^{-2}$), and the pooled subjects of GWASs and replication cohorts ($p = 2.6 \times 10^{-5}$). The SNP rs2838566 is located in an intergenic region in chromosome 21 with a nearby gene of transient receptor potential cation channel subfamily-M member-2 (*TRPM2*).

The TRPM2 channel protein encoded by the gene is a redox-sensitive Ca^{2+} -permeable channel, which is activated by several secondary messengers and is capable of mediating susceptibility to cell death (Miller, 2006; Perraud et al., 2005). Some studies showed that intracellular oxidants such as hydrogen peroxide and some toxins could modulate Ca^{2+} influx and oxidative toxicity through TRPM2 channel (Hecquet and Malik, 2009; Kaneko et al., 2006). Thus, oxidative stress may play important roles in the mechanisms underlying platinum-based chemotherapy-induced hepatotoxicity (Lu and Cederbaum, 2006). *TRPM2* may affect the susceptibility of hepatotoxicity through the oxidative stress response (Cao

et al., 2015). The findings of the study suggested that genetic variants contribute to the susceptibility of platinum-based chemotherapy-induced hepatotoxicity in NSCLC patients.

Ximelagatran-induced hepatotoxicity

GWAS to evaluate elevated levels of serum alanine aminotransferase (ALAT) during long-term treatment with oral direct thrombin inhibitor, ximelagatran, was conducted (Kindmark et al., 2008). The study involved 74 cases and 130 treatment controls and included both a genome-wide 266,722 tag SNP and large-scale candidate gene analysis. The strongest associations were found in the MHC class II region [rs17426385 close to *HLA-DQA1* ($p = 7.3 \times 10^{-8}$), rs9275141 close to *HLA-DQB1* ($p = 2.0 \times 10^{-7}$), and rs2858869 located in the 5'-flanking region of *HLA-DRB1* ($p = 6.0 \times 10^{-6}$)]. In a replication study, the *HLA-DRB1*07* allele was still statistically significant after Bonferroni correction. The study provided evidence for immune-mediated mechanism in ximelagatran-induced hepatotoxicity.

Multiple drug-induced hepatotoxicity

The largest GWAS that covered 800,769 SNP markers to identify genetic risk factors common to hepatotoxicity resulting from various drugs to elucidate mechanistic pathways underlying DIH has been reported previously (Urban et al., 2012). The hypothesis was that cellular responses to drugs are generally considered to follow similar pathways. Although the GWAS analysis did not find new significant associations with the full cohort, it suggested that risk alleles may be drug specific, rare (minor allele frequency less than 5%), or that DIH may be polygenic (involving many small variants) (Aithal and Grove, 2015). Among the drug-specific tests, the analysis did reveal a significant association of rs17036170 ($p = 1.0 \times 10^{-8}$) in peroxisome proliferator-activated receptor gamma (*PPARG*) with diclofenac-induced hepatotoxicity (30 cases). The gene for *PPARG* is reported to be important for regulating adipogenesis and may have a role in reducing inflammation in certain circumstances (Urban et al., 2012).

Looking Ahead and Future Perspectives

Over the past several decades, a considerable effort has been made to identify genetic factors that predispose to the development of DIH. Recent GWASs have provided insight for genetic variants affecting susceptibility to idiosyncratic DIH. However, usefulness of the data for clinical use or personalized medicine through genetic testing is limited. Various reasons contribute for this. In a context of the limitations of the GWAS of DIH, the possible false-positive results, requirement for large sample sizes, genotyping cost, and insensitivity to rare variants are notable (McCarthy et al., 2008). Accuracy of the finding from GWASs needs to be replicated and confirmed. This is partly due to high prevalence of incidental findings or incidentalome, referring to identifying variants in genes that are unrelated to the patient's primary condition (Brothers et al., 2013; Jamuar et al., 2016).

Another reason for the mixed results of GWASs is that the current biostatistical analysis ignores all prior knowledge about disease pathobiology and often considers only one SNP at a time, thus disregarding their genomic and environmental context. It is interesting to note that while the study of genetic

factors has been scaled up through GWASs and similar broad scope approaches, the study of the environment and the full range of environmental factors that enact on the human host and society, that is, the *environtome*, has not been similarly scaled up. There is a definite need to register and factor in the *environtome* in GWASs as well as the candidate gene studies of the idiosyncratic DIH.

Additional studies on consensus genome-wide expression quantitative trait loci in relation to complex phenotypes might offer new promise in human genetics (Yu et al., 2016). While the GWASs of idiosyncratic DIH warrant further research attention in world populations, we suggest a discursive discovery paradigm whereby the findings from the GWASs fed into candidate gene studies to effectively follow-up on the emerging molecular leads from the GWAS research paradigm.

The need for high-throughput genotyping technologies that allow large numbers of SNPs to be genotyped simultaneously is another limiting factor to perform GWASs in resource-constrained projects and countries. Nevertheless, the current technological advancements and relatively lower prices have made GWASs technically feasible. The future may potentially benefit from the impact of next-generation sequencing technologies capturing both GWAS and CGAS data on genomics, with particular reference to currently available and possible future platforms and bioinformatics.

GWASs for idiosyncratic DIH remain challenging because it is a rare condition, and there are phenotypic variations and ethnic diversity (Kim and Naisbitt, 2016). The sample size limitation is magnified when performing GWASs for idiosyncratic DIH because it requires sufficiently large study subjects to reach a genome-wide significance level. To overcome this limitation, multicenter research networks have been established, namely DILIN—Drug-Induced Liver Injury Network in United States; DILIGEN—a study on the genetics of drug-related liver disease in United Kingdom; EUDRAGENE—in Europe; DILI registry—in Spain; and others (Kim and Naisbitt, 2016). By establishing collaboration and combining cohorts from multiple sites, large-scale GWASs can have higher power to detect and validate the risk variants for DIH.

Another important limitation of GWASs for identifying susceptibility variants for DIH in diverse geographic ancestries could relate to lack of microarrays with good SNP density coverage. The vast majority of GWASs are using arrays designed for European ancestry. However, the SNP coverage of the arrays is low and the tag SNPs are less efficient for non-Europeans, particularly for sub-Saharan African populations (Peprah et al., 2015). Black Africans are the most genetically diverse population characterized by extensive population substructure and less LD among chromosomal loci compared with non-African populations (Teo et al., 2010). This makes the discovery of association signals using the same platforms less efficient in African populations. Therefore, improving the SNP density coverage of genotyping arrays to discover susceptibility variants in African populations is important.

To address the gap in exploring African genomic diversity, Illumina is currently developing an array for GWASs through the Human Heredity and Health in Africa (H3Africa) Initiative, a partnership between NIH, the African Society of Human Genetics, and Wellcome Trust. Availability of cost-effective, African-enriched genotyping arrays and reference

panel for GWASs may promote exploration of variant alleles associated with DIH across populations of African origin in the near future.

So far, the findings from GWASs of idiosyncratic DIH are generally replicated and pointing toward the salient role of GWASs in identifying associations between DIH susceptibility and specific genes, mainly in the HLA region. The observed associations in GWASs on DIH have been successful in demonstrating associations with odds ratios of 2.3 to 80.6 and with reasonable biological plausibility even when the case numbers are small, but further confirmation is still required.

Strong associations between specific HLA alleles with particular drug-related hepatotoxicity have highlighted the central role of the immune system in the pathogenic mechanisms underlying idiosyncratic DIH. Although there have been only a few GWASs conducted for DIH so far, reports of a relatively small number of HLA alleles with overlapping links could provide opportunities to translate into clinical applications. The current international collaborations for further GWASs with better SNP density microarrays may facilitate the development of genetic tests to identify individuals susceptible for developing idiosyncratic DIH.

Acknowledgments

This work was, in part, supported by grants from the Swedish Research Council (grant number: VR 2015-03295) and the NIH/Fogarty International Center Global Infectious Diseases grant D43TW009127. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Disclosure Statement

The authors declare that no conflicting financial interests exist.

References

- Aithal GP, and Grove JJ. (2015). Genome-wide association studies in drug-induced liver injury: Step change in understanding the pathogenesis. *Semin Liver Dis* 35, 421–431.
- Aithal GP, Watkins PB, Andrade RJ, et al. (2011). Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharmacol Ther* 89, 806–815.
- Andrade RJ, Lucena MI, Alonso A, et al. (2004). HLA class II genotype influences the type of liver injury in drug-induced idiosyncratic liver disease. *Hepatology* 39, 1603–1612.
- Bannwarth B, and Berenbaum F. (2007). Lumiracoxib in the management of osteoarthritis and acute pain. *Expert Opin Pharmacother* 8, 1551–1564.
- Bast BJ, Zhou LJ, Freeman GJ, et al. (1992). The HB-6, CDw75, and CD76 differentiation antigens are unique cell-surface carbohydrate determinants generated by the beta-galactoside alpha 2,6-sialyltransferase. *J Cell Biol* 116, 423–435.
- Brothers KB, Langanke M, and Erdmann P. (2013). Implications of the incidentalome for clinical pharmacogenomics. *Pharmacogenomics* 14, 1353–1362.
- Cao S, Wang C, Ma H, et al. (2015). Genome-wide association study on platinum-induced hepatotoxicity in non-small cell lung cancer patients. *Sci Rep* 5, 11556.
- Chalasani NP, Hayashi PH, Bonkovsky HL, et al. (2014). ACG Clinical Guideline: The diagnosis and management of

- idiosyncratic drug-induced liver injury. *Am J Gastroenterol* 109, 950–966; quiz 967.
- Chang JC, Liu EH, Lee CN, et al. (2012). UGT1A1 polymorphisms associated with risk of induced liver disorders by anti-tuberculosis medications. *Int J Tuberc Lung Dis* 16, 376–378.
- Chen R, Wang J, Tang S, et al. (2015a). Association of polymorphisms in drug transporter genes (SLCO1B1 and SLC10A1) and anti-tuberculosis drug-induced hepatotoxicity in a Chinese cohort. *Tuberculosis (Edinb)* 95, 68–74.
- Chen R, Zhang Y, Tang S, et al. (2015b). The association between HLA-DQB1 polymorphism and antituberculosis drug-induced liver injury: A case-control study. *J Clin Pharm Ther* 40, 110–115.
- Cho HJ, Koh WJ, Ryu YJ, et al. (2007). Genetic polymorphisms of NAT2 and CYP2E1 associated with antituberculosis drug-induced hepatotoxicity in Korean patients with pulmonary tuberculosis. *Tuberculosis (Edinb)* 87, 551–556.
- Daly AK. (2010a). Drug-induced liver injury: Past, present and future. *Pharmacogenomics* 11, 607–611.
- Daly AK. (2010b). Genome-wide association studies in pharmacogenomics. *Nat Rev Genet* 11, 241–246.
- Daly AK. (2012). Using genome-wide association studies to identify genes important in serious adverse drug reactions. *Annu Rev Pharmacol Toxicol* 52, 21–35.
- Daly AK, Aithal GP, Leathart JB, Swainsbury RA, Dang TS, and Day CP. (2007). Genetic susceptibility to diclofenac-induced hepatotoxicity: Contribution of UGT2B7, CYP2C8, and ABC22 genotypes. *Gastroenterology* 132, 272–281.
- Daly AK, and Day CP. (2001). Candidate gene case-control association studies: Advantages and potential pitfalls. *Br J Clin Pharmacol* 52, 489–499.
- Daly AK, and Day CP. (2009). Genetic association studies in drug-induced liver injury. *Semin Liver Dis* 29, 400–411.
- Daly AK, and Day CP. (2012). Genetic association studies in drug-induced liver injury. *Drug Metab Rev* 44, 116–126.
- Daly AK, Donaldson PT, Bhatnagar P, et al. (2009). HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. *Nat Genet* 41, 816–819.
- Deng R, Yang T, Wang Y, and Tang N. (2012). CYP2E1 RsaI/PstI polymorphism and risk of anti-tuberculosis drug-induced liver injury: A meta-analysis. *Int J Tuberc Lung Dis* 16, 1574–1581.
- Drago A, Giegling I, Schafer M, et al. (2014). Genome-wide association study supports the role of the immunological system and of the neurodevelopmental processes in response to haloperidol treatment. *Pharmacogenet Genomics* 24, 314–319.
- Du H, Chen X, Fang Y, et al. (2013). Slow N-acetyltransferase 2 genotype contributes to anti-tuberculosis drug-induced hepatotoxicity: A meta-analysis. *Mol Biol Rep* 40, 3591–3596.
- Fredriksson L, Wink S, Herpers B, et al. (2014). Drug-induced endoplasmic reticulum and oxidative stress responses independently sensitize toward TNF α -mediated hepatotoxicity. *Toxicol Sci* 140, 144–159.
- Geyer CE, Forster J, Lindquist D, et al. (2006). Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 355, 2733–2743.
- Grove JJ, and Aithal GP. (2015). Human leukocyte antigen genetic risk factors of drug-induced liver toxicology. *Expert Opin Drug Metab Toxicol* 11, 395–409.
- Haas DW, Bartlett JA, Andersen JW, et al. (2006). Pharmacogenetics of nevirapine-associated hepatotoxicity: An Adult AIDS Clinical Trials Group collaboration. *Clin Infect Dis* 43, 783–786.
- Hautekeete ML, Horsmans Y, Van Waeyenberge C, et al. (1999). HLA association of amoxicillin-clavulanate—Induced hepatitis. *Gastroenterology* 117, 1181–1186.
- Hecquet CM, and Malik AB. (2009). Role of H₂O₂-activated TRPM2 calcium channel in oxidant-induced endothelial injury. *Thromb Haemost* 101, 619–625.
- Hirata K, Takagi H, Yamamoto M, et al. (2008). Ticlopidine-induced hepatotoxicity is associated with specific human leukocyte antigen genomic subtypes in Japanese patients: A preliminary case-control study. *Pharmacogenomics J* 8, 29–33.
- Hirschhorn JN, and Daly MJ. (2005). Genome-wide association studies for common diseases and complex traits. *Nat Rev Genet* 6, 95–108.
- Hirschhorn JN, and Gajdos ZK. (2011). Genome-wide association studies: Results from the first few years and potential implications for clinical medicine. *Annu Rev Med* 62, 11–24.
- Hirschhorn JN, Lohmueller K, Byrne E, and Hirschhorn K. (2002). A comprehensive review of genetic association studies. *Genet Med* 4, 45–61.
- Huang YS, Chern HD, Su WJ, et al. (2002). Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. *Hepatology* 35, 883–889.
- Huang YS, Chern HD, Su WJ, et al. (2003). Cytochrome P450 2E1 genotype and the susceptibility to antituberculosis drug-induced hepatitis. *Hepatology* 37, 924–930.
- Huang YS, Su WJ, Huang YH, et al. (2007). Genetic polymorphisms of manganese superoxide dismutase, NAD(P)H: quinone oxidoreductase, glutathione S-transferase M1 and T1, and the susceptibility to drug-induced liver injury. *J Hepatol* 47, 128–134.
- International-HapMap-Consortium. (2005). A haplotype map of the human genome. *Nature* 437, 1299–1320.
- Jamuar SS, Kuan JL, Brett M, et al. (2016). Incidentalome from genomic sequencing: A barrier to personalized medicine? *EBioMedicine* 5, 211–216.
- Kaneko S, Kawakami S, Hara Y, et al. (2006). A critical role of TRPM2 in neuronal cell death by hydrogen peroxide. *J Pharmacol Sci* 101, 66–76.
- Karlsen TH, Melum E, and Franke A. (2010). The utility of genome-wide association studies in hepatology. *Hepatology* 51, 1833–1842.
- Khouri T, Rmeileh AA, Yosha L, Benson AA, Daher S, and Mizrahi M. (2015). Drug induced liver injury: Review with a focus on genetic factors, tissue diagnosis, and treatment options. *J Clin Transl Hepatol* 3, 99–108.
- Kim SH, and Naisbitt DJ. (2016). Update on advances in research on idiosyncratic drug-induced liver injury. *Allergy Asthma Immunol Res* 8, 3–11.
- Kindmark A, Jawaid A, Harbron CG, et al. (2008). Genome-wide pharmacogenetic investigation of a hepatic adverse event without clinical signs of immunopathology suggests an underlying immune pathogenesis. *Pharmacogenomics J* 8, 186–195.
- Lee WM. (2013). Drug-induced acute liver failure. *Clin Liver Dis* 17, 575–586, viii.
- Li C, Long J, Hu X, and Zhou Y. (2013). GSTM1 and GSTT1 genetic polymorphisms and risk of anti-tuberculosis drug-induced hepatotoxicity: An updated meta-analysis. *Eur J Clin Microbiol Infect Dis* 32, 859–868.
- Li LM, Chen L, Deng GH, et al. (2012). SLCO1B1 *15 haplotype is associated with rifampin-induced liver injury. *Mol Med Rep* 6, 75–82.

- Lu Y, and Cederbaum AI. (2006). Cisplatin-induced hepatotoxicity is enhanced by elevated expression of cytochrome P450 2E1. *Toxicol Sci* 89, 515–523.
- Lucena MI, Andrade RJ, Martinez C, et al. (2008). Glutathione S-transferase m1 and t1 null genotypes increase susceptibility to idiosyncratic drug-induced liver injury. *Hepatology* 48, 588–596.
- Lucena MI, Molokhia M, Shen Y, et al. (2011). Susceptibility to amoxicillin-clavulanate-induced liver injury is influenced by multiple HLA class I and II alleles. *Gastroenterology* 141, 338–347.
- Mallal S, Nolan D, Witt C, et al. (2002). Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* 359, 727–732.
- Manolio TA. (2013). Bringing genome-wide association findings into clinical use. *Nat Rev Genet* 14, 549–558.
- McCarthy MI, Abecasis GR, Cardon LR, et al. (2008). Genome-wide association studies for complex traits: Consensus, uncertainty and challenges. *Nat Rev Genet* 9, 356–369.
- Miller BA. (2006). The role of TRP channels in oxidative stress-induced cell death. *J Membr Biol* 209, 31–41.
- Motsinger-Reif AA, Jorgenson E, Relling MV, et al. (2013). Genome-wide association studies in pharmacogenomics: Successes and lessons. *Pharmacogenet Genomics* 23, 383–394.
- Mugusi S, Ngaimisi E, Janabi M, et al. (2012). Liver enzyme abnormalities and associated risk factors in HIV patients on efavirenz-based HAART with or without tuberculosis co-infection in Tanzania. *PLoS One* 7, e40180.
- Nanashima K, Mawatari T, Tahara N, et al. (2012). Genetic variants in antioxidant pathway: Risk factors for hepatotoxicity in tuberculosis patients. *Tuberculosis (Edinb)* 92, 253–259.
- O'Donohue J, Oien KA, Donaldson P, et al. (2000). Co-amoxiclav jaundice: Clinical and histological features and HLA class II association. *Gut* 47, 717–720.
- Ohno M, Yamaguchi I, Yamamoto I, et al. (2000). Slow N-acetyltransferase 2 genotype affects the incidence of isoniazid and rifampicin-induced hepatotoxicity. *Int J Tuberc Lung Dis* 4, 256–261.
- Ostrov DA, Grant BJ, Pompeu YA, et al. (2012). Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire. *Proc Natl Acad Sci U S A* 109, 9959–9964.
- Parham LR, Briley LP, Li L, et al. (2016). Comprehensive genome-wide evaluation of lapatinib-induced liver injury yields a single genetic signal centered on known risk allele HLA-DRB1*07:01. *Pharmacogenomics J* 16, 180–185.
- Pearson T, and Manolio T. (2008). How to interpret a genome-wide association study. *JAMA* 299, 1335–1344.
- Peprah E, Xu H, Tekola-Ayele F, and Royal CD. (2015). Genome-wide association studies in Africans and African Americans: Expanding the framework of the genomics of human traits and disease. *Public Health Genomics* 18, 40–51.
- Perraud AL, Takanishi CL, Shen B, et al. (2005). Accumulation of free ADP-ribose from mitochondria mediates oxidative stress-induced gating of TRPM2 cation channels. *J Biol Chem* 280, 6138–6148.
- Petros Z, Lee MM, Takahashi A, et al. (2016). Genome-wide association and replication study of anti-tuberculosis drugs-induced liver toxicity. *BMC Genomics* 17, 755.
- Phillips E, Bartlett JA, Sanne I, et al. (2013). Associations between HLA-DRB1*0102, HLA-B*5801, and hepatotoxicity during initiation of nevirapine-containing regimens in South Africa. *J Acquir Immune Defic Syndr* 62, e55–e57.
- Pirih N, and Kunej T. (2017). Toward a taxonomy for multi-omics science? Terminology development for whole genome study approaches by omics technology and hierarchy. *OMICS* 21, 1–17.
- Possuelo LG, Castelan JA, de Brito TC, et al. (2008). Association of slow N-acetyltransferase 2 profile and anti-TB drug-induced hepatotoxicity in patients from Southern Brazil. *Eur J Clin Pharmacol* 64, 673–681.
- Reuben A, Koch DG, and Lee WM; Acute Liver Failure Study Group. (2010). Drug-induced acute liver failure: Results of a U.S. multicenter, prospective study. *Hepatology* 52, 2065–2076.
- Roy B, Chowdhury A, Kundu S, et al. (2001). Increased risk of antituberculosis drug-induced hepatotoxicity in individuals with glutathione S-transferase M1 'null' mutation. *J Gastroenterol Hepatol* 16, 1033–1037.
- Russmann S, Jetter A, and Kullak-Ublick GA. (2010). Pharmacogenetics of drug-induced liver injury. *Hepatology* 52, 748–761.
- Schaid DJ, Spraggs CF, McDonnell SK, et al. (2014). Prospective validation of HLA-DRB1*07:01 allele carriage as a predictive risk factor for lapatinib-induced liver injury. *J Clin Oncol* 32, 2296–2303.
- Sharma SK, Balamurugan A, Saha PK, Pandey RM, and Mehra NK. (2002). Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antituberculosis treatment. *Am J Respir Crit Care Med* 166, 916–919.
- Singer JB, Lewitzky S, Leroy E, et al. (2010). A genome-wide study identifies HLA alleles associated with lumiracoxib-related liver injury. *Nat Genet* 42, 711–714.
- Spraggs CF, Budde LR, Briley LP, et al. (2011). HLA-DQA1*02:01 is a major risk factor for lapatinib-induced hepatotoxicity in women with advanced breast cancer. *J Clin Oncol* 29, 667–673.
- Stankov K, Sabo A, and Mikov M. (2013). Pharmacogenetic biomarkers as tools for pharmacoepidemiology of severe adverse drug reactions. *Drug Dev Res* 74, 1–14.
- Stephens C, Lopez-Nevot MA, Ruiz-Cabello F, et al. (2013). HLA alleles influence the clinical signature of amoxicillin-clavulanate hepatotoxicity. *PLoS One* 8, e68111.
- Stevens JL, and Baker TK. (2009). The future of drug safety testing: Expanding the view and narrowing the focus. *Drug Discov Today* 14, 162–167.
- Stoyanov E, Ludwig G, Mizrahi L, et al. (2015). Chronic liver inflammation modifies DNA methylation at the precancerous stage of murine hepatocarcinogenesis. *Oncotarget* 6, 11047–11060.
- Taylor A, Faulkner L, Naisbitt DJ, and Park BK. (2015). The chemical, genetic and immunological basis of idiosyncratic drug-induced liver injury. *Hum Exp Toxicol* 34, 1310–1317.
- Tan XL, Moyer AM, Fridley BL, et al. (2011). Genetic variation predicting cisplatin cytotoxicity associated with overall survival in lung cancer patients receiving platinum-based chemotherapy. *Clin Cancer Res* 17, 5801–5811.
- Teo Y, Small K, and Kwiatkowski D. (2010). Methodological challenges of genome-wide association analysis in Africa. *Nat Rev Genet* 11, 149–160.
- Urban TJ, Daly AK, and Aithal GP. (2014). Genetic basis of drug-induced liver injury: Present and future. *Semin Liver Dis* 34, 123–133.
- Urban TJ, Shen Y, Stolz A, et al. (2012). Limited contribution of common genetic variants to risk for liver injury due to a variety of drugs. *Pharmacogenet Genomics* 22, 784–795.
- Vuilleumier N, Rossier MF, Chiappe A, et al. (2006). CYP2E1 genotype and isoniazid-induced hepatotoxicity in patients treated for latent tuberculosis. *Eur J Clin Pharmacol* 62, 423–429.
- Wang WYS, Barratt BJ, Clayton DG, and Todd JA. (2005). Genome-wide association studies: Theoretical and practical concerns. *Nat Rev Genet* 6, 109–118.
- Yimer G, Amogne W, Habtewold A, et al. (2012). High plasma efavirenz level and CYP2B6*6 are associated with efavirenz-

- based HAART-induced liver injury in the treatment of naive HIV patients from Ethiopia: A prospective cohort study. *Pharmacogenomics J* 12, 499–506.
- Yimer G, Ueda N, Habtewold A, et al. (2011). Pharmacogenetic & pharmacokinetic biomarker for efavirenz based ARV and rifampicin based anti-TB drug induced liver injury in TB-HIV infected patients. *PLoS One* 6, e27810.
- Yoon S, Molloy MJ, Wu MP, Cowan DB, and Gussoni E. (2007). C6ORF32 is upregulated during muscle cell differentiation and induces the formation of cellular filopodia. *Dev Biol* 301, 70–81.
- Yu CH, Pal LR, and Moulton J. (2016). Consensus genome-wide expression quantitative trait loci and their relationship with human complex trait disease. *OMICS* 20, 400–414.
- Yuan L, and Kaplowitz N. (2013). Mechanisms of drug-induced liver injury. *Clin Liver Dis* 17, 507–518.

Address correspondence to:

Eleni Aklillu, PhD
Division of Clinical Pharmacology
Department of Laboratory Medicine
Karolinska University Hospital
Karolinska Institutet
Stockholm SE-141 86
Sweden

E-mail: eleni.aklillu@ki.se

Abbreviations Used

- ABCB1* = ATP-binding cassette subfamily-B member-1
- AC = amoxicillin–clavulanate
- AGBL4* = ATP/GTP-binding protein-like 4
- CGASs = candidate gene association studies
- CYP2B6 = cytochrome P450 2B6
- DIH = drug-induced hepatotoxicity
- FAM65B = family with sequence similarity-65 member-B
- GSTM1 = glutathione S-transferases M1
- GWASs = genome-wide association studies
- HER2 = human epidermal growth factor receptor-2
- HLA = human leukocyte antigen
- LD = linkage disequilibrium
- MHC = major histocompatibility complex
- NSCLC = nonsmall cell lung cancer
- Nrf2* = nuclear factor erythroid 2-related factor 2
- SLCO1B1 = solute carrier organic anion transporter family member-1B1
- SNPs = single-nucleotide polymorphisms
- ST6GAL1* = ST6 β -galactosamide α -2, 6-sialyltransferase-1
- SOD2 = superoxide dismutase 2
- UGT2B7 = UDP-glucuronosyltransferase 2B7
- UGT1A1* = uridine diphosphate glucuronosyltransferase 1A1