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CLINICAL LIVER

Association of Liver Injury From Specific Drugs, or Groups of Drugs, With Polymorphisms in HLA and Other Genes in a Genome-Wide Association Study

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BACKGROUND & AIMS: We performed a genome-wide association study (GWAS) to identify genetic risk factors for drug-induced liver injury (DILI) from licensed drugs without previously reported genetic risk factors. **METHODS:** We performed a GWAS of 862 persons with DILI and 10,588 population-matched controls. The first set of cases was recruited before May 2009 in Europe (n = 137) and the United States (n = 274). The second set of cases were identified from May 2009 through May 2013 from international collaborative studies performed in Europe, the United States, and South America. For the GWAS, we included only cases with patients of European ancestry associated with a particular drug (but not flucloxacillin or amoxicillin-clavulanate). We used DNA samples from all subjects to analyze HLA genes and single nucleotide polymorphisms. After the discovery analysis was concluded, we validated our findings using data from 283 European patients with diagnosis of DILI associated with various drugs. **RESULTS:** We associated DILI with rs114577328 (a proxy for A*33:01 a HLA class I allele; odds ratio [OR], 2.7; 95% confidence interval

[CI], 1.9−3.8; $P = 2.4 \times 10^{-8}$) and with rs72631567 on chromosome 2 (OR, 2.0; 95% CI, 1.6−2.5; $P = 9.7 \times 10^{-9}$). The association with A*33:01 was mediated by large effects for terbinafine-, fenofibrate-, and ticlopidine-related DILI. The variant on chromosome 2 was associated with DILI from a variety of drugs. Further phenotypic analysis indicated that the association between DILI and A*33:01 was significant genome wide for cholestatic and mixed DILI, but not for hepatocellular DILI; the polymorphism on chromosome 2 was associated with cholestatic and mixed DILI as well as hepatocellular DILI. We identified an association between rs28521457 (within the lipopolysaccharide-responsive vesicle trafficking, beach and anchor containing gene) and only hepatocellular DILI (OR, 2.1; 95% CI, 1.6−2.7; $P = 4.8 \times 10^{-9}$). We did not associate any specific drug classes with genetic polymorphisms, except for statin-associated DILI, which was associated with rs116561224 on chromosome 18 (OR, 5.4; 95% CI, 3.0−9.5; $P = 7.1 \times 10^{-9}$). We validated the association between A*33:01 terbinafine- and sertraline-induced DILI. We could not validate the association between DILI and rs72631567, rs28521457, or rs116561224. **CONCLUSIONS:** In a GWAS of persons of European descent with DILI, we associated HLA-A*33:01 with DILI due to terbinafine and possibly fenofibrate and ticlopidine. We identified polymorphisms that appear to be associated with DILI from statins, as well as 2 non−drug-specific risk factors.

Keywords: Medication; Liver Damage; Side Effect; Anti-Fungal Agent.

Hepatotoxicity is the second most common cause of drug attrition during development, and post-marketing withdrawal,[1] and idiosyncratic drug-induced liver injury (DILI) accounts for 11%−17% of cases of acute liver failure in the United States and Europe.[2,3] The typical incidence of DILI varies from approximately 1% with the anti-tumor necrosis factor agents[4] to 0.04% with some widely used antimicrobials such as amoxicillin-clavulanate.[5] During the past 15 years, increasing progress on identifying genetic risk factors for DILI has been made. In particular, associations with HLA class I and II alleles have been reported for DILI caused by a range of drugs, though a particular HLA genotype does not appear to be relevant to all forms of idiosyncratic DILI.[6]

Previously, a genome-wide association study (GWAS) involving cohorts of DILI cases related to one particular drug only resulted in identification of 1 or more drug-specific HLA risk alleles.[7–11] A large study involving 783 DILI cases due to a range of different drugs also resulted in a genome-wide significant HLA signal, but this association was abolished once 296 cases of DILI due to flucloxacillin and amoxicillin-clavulanate were excluded.[12] This partly reflects the fact that amoxicillin-clavulanate is a very common cause of DILI worldwide and flucloxacillin is an equally common cause in a number of Northern European countries.[13] Therefore, DNA collections from DILI cases will generally be highly enriched in cases relating to these 2 drugs, making detection of associations related to other compounds more difficult.

We have expanded our previous study of DILI caused by a range of different drugs,[12] and after excluding cases relating to amoxicillin-clavulanate and flucloxacillin, we have more than doubled the number of cases, with additions from Europe, Australia, South America, and the United States. We now report that HLA-A*33:01 is associated with risk of DILI, particularly due to terbinafine, fenofibrate, and ticlopidine, and especially with a cholestatic or mixed phenotype. We have also found novel non−major histocompatibility complex (MHC)-related signals apparently shared across a range of different drugs; an intronic single nucleotide polymorphism (SNP) in the lipopolysaccharide-responsive vesicle trafficking, beach and anchor containing (LRBA) gene is associated with hepatocellular DILI and an intergenic SNP on chromosome 2, rs72631567, with DILI generally. An additional drug-specific genome-wide significant signal that could not be confirmed is also reported.

Materials and Methods

Drug-Induced Livery Injury Discovery Cohort

The cases in the study were from 2 separate recruitment phases. Phase 1 consists of 411 cases included in a previous study (from the Drug-Induced Liver Injury Network [DILIN], DILIGEN, and Eudragene)[12] and phase 2 more recently recruited cases (n = 451) of which a small subset was included in a recent report.[14]

Phase 1 cases. These cases included 411 DILI cases not due to amoxicillin-clavulanate or flucloxacillin, with a defined casual drug and with causality score greater than possible (Roussel Uclaf Causality Assessment Method score ≥3) recruited in Europe (n = 137) or the United States (n = 274) before 2009. Clinical characteristics of these cases and methods used for genotyping have been described in detail previously.[12] Additional exome chip analysis (Illumina Infinium HumanCoreExome BeadChip) was performed on 150 of these 411 cases at the Broad Institute, Boston, MA.

Phase 2 case recruitment: International Drug-Induced Liver Injury Consortium. The International Drug-Induced Liver Injury Consortium (iDILIC) cases were recruited between May 2009 and May 2013 as part of an international collaborative study involving recruitment centers in the United Kingdom (Newcastle, Nottingham, Liverpool, London, Dundee), Sweden (Uppsala and Gothenburg), Spain (Malaga and Barcelona), France (Montpellier), The Netherlands (Utrecht), Germany (Kiel), Australia (Brisbane), Switzerland (Zurich), Finland (Helsinki), Argentina (Rosario), Uruguay (Montevideo), and Chile (Santiago). All participants provided

*Authors share co-first authorship; §Authors share co-senior authorship.

Abbreviations used in this paper: AF, allele frequency; CM, cholestatic-mixed; DILI, drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network; GWAS, genome-wide association study; HC, hepatocellular; iDILIC, International Drug-Induced Liver Injury Consortium; LRBA, lipopolysaccharide-responsive vesicle trafficking, beach and anchor containing; MHC, major histocompatibility complex; OR, odd ratio; SNP, single nucleotide polymorphism.

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