Genetic Polymorphisms Implicated in Nonalcoholic Liver Disease or Selected Other Disorders Have No Influence on Drug-Induced Liver Injury

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With the application of genetic testing to contemporary medical diagnostics and practice, it has become apparent that the phenotypes of many disorders are modulated by host genetic factors. The aim of the current study was to determine whether selected single nucleotide polymorphisms (SNPs) unrelated to the human leukocyte antigen region or other immune pathways, including those associated with nonalcoholic fatty liver disease (NAFLD), may influence development, severity, or outcomes of drug-induced liver injury (DILI). Thirteen variants previously associated with NAFLD and/or selected other liver diseases were tested in 832 Caucasian DILI cases and 10,397 Caucasian population controls. DILI cases were attributed to multiple agents (177 individual drugs), with 56 cases due to herbal/dietary supplement products. Allele frequencies were imputed from recent genome-wide association studies and compared to those for European control samples from the Gnomad database. Significance was tested by linear regression or logistic regression, depending on the nature of the trait. Any variant that passed the Bonferroni threshold of \( P < 0.0004 \) was considered a significant association. None of the variants proved to be significantly associated with DILI as phenotype nor with any of the selected severity traits. Among the variants studied, rs1421085, found in the fat mass and obesity associated (FTO) gene, showed a marginal protective effect (odds ratio, 0.8; 95% confidence interval, 0.77–0.95; \( P = 0.005 \)). None of the genetic polymorphisms tested were significantly associated with the risk of development, severity, or outcome of DILI. Conclusion: SNPs implicated in common liver diseases, such as NAFLD, do not play a substantial role in DILI pathogenesis across agents. It remains possible that these variants could be involved with DILI due to single agents, but this will require the evaluation of larger numbers of bona fide cases. (Hepatology Communications 2019;3:1032-1035).

With the application of genetic testing to contemporary medical diagnostics and practice, it has become apparent that the phenotypes of many disorders are modulated by host genetic factors. For example, the susceptibility to and progression of nonalcoholic fatty liver disease (NAFLD) have been associated with the p. I148M variant in the patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene and the p. E167K variant of transmembrane 6 super family 2 (TM6SF2). In
contrast, susceptibility to idiosyncratic drug-induced liver injury (DILI), a rare form of liver disease, has been associated primarily with genes that influence innate or adaptive immune responses.\(^3,\)\(^4\)

The aim of the current study was to determine whether selected single nucleotide polymorphisms (SNPs) unrelated to the human leukocyte antigen region or other immune pathways, including those associated with NAFLD, may influence development, severity, or outcomes of DILI.

Materials and Methods

Thirteen variants previously associated with NAFLD and/or selected other liver diseases were tested in 832 Caucasian DILI cases and 10,397 Caucasian population controls (Table 1).\(^5\) DILI cases were attributed to multiple agents (177 individual drugs), with 56 cases due to herbal/dietary supplement products. All cases had DILI Network (DILIN) causality scores equal to or higher than probable (judged 51%-100% likely due to a drug). None of the subjects from DILIN had been enrolled as acute cases (within 14 days of onset). Eight variants were imputed from the most recent genome-wide association study,\(^5\) and four additional variants were directly genotyped only in DILI cases, except for the hydroxysteroid dehydrogenase 17B13 (HSD17B13) splice variant, which was typed only in a subset of the DILI cases (n = 384). For the latter variants, the allele frequencies for European (non-Finnish) control samples in the Gnomad database were used (https://gnomad.broadinstitute.org/).

The DILI cases were also categorized by severity and chronic DILI. Chronic DILI was defined as evidence of ongoing liver injury 6 months after DILI onset, as described.\(^3,\)\(^5\) The significance was tested by linear regression or logistic regression, depending on the nature of the trait. For genotyped variants and binary traits, associations were compared to European control samples listed in the Gnomad database and by Fisher’s exact test.

Any variant that passed the Bonferroni threshold of \( P < 0.0004 \)\(^{0.05} \)\(^{13} \) was considered a significant association. Follow-up analyses were done for the most strongly associated variants by testing in an independent Caucasian cohort of 974 DILI cases from the International DILI Consortium\(^5\) and in African
None of the variants proved to be significantly associated with DILI as phenotype (Table 1) nor with any of the selected severity traits (Supporting Table S1). Among the variants studied, rs1421085, found in the fat mass and obesity associated (FTO) gene, showed a marginal protective effect (odds ratio, 0.8; 95% confidence interval, 0.77-0.95; P = 0.005, with similar trends also in Hispanic and African-American cohorts), but Caucasian replication cases showed a higher frequency of the variants (Supporting Table S1).

Discussion

None of the genetic polymorphisms tested were significantly associated with the risk of development, severity, or outcome of DILI. These data suggest that...
SNPs implicated in common liver diseases, such as NAFLD, do not play a substantial role in DILI pathogenesis across agents. However, it remains possible that these variants could be involved with DILI risk or outcome due to a single drug, but this will require the evaluation of larger numbers of bona fide cases due to specific drugs. In addition, rare variants may play a role in DILI pathogenesis, but additional studies using whole exome or genome testing are required.

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Supporting Information

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