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Conflicts of interest
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Most current article

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Genome-Wide Association Studies of Drug-Induced Liver Injury Make Progress Beyond the *HLA* Region

Dear Editors:

We read the recent pharmacogenomic study by investigators from the Drug-Induced Liver Injury Network (DILIN) and International DILI consortium (iDILIC) with great interest.[1] Their genome-wide association study identified a missense variant (Trp620Arg, rs2476601) in the *PTPN22* gene that was associated with an increased risk for drug-induced liver injury (DILI) caused by various medications. Through the analysis of >2000 DILI cases, the association with the *PTPN22* variant and DILI surpassed genome-wide significance (ie, $P < 5.0 \times 10^{-8}$; odds ratio, 1.4; 95% confidence interval, 1.3–1.6) and was replicated in an independent cohort. This represents a key advance, because this is the first time that a pharmacogenomic variant has been robustly associated with liver injury caused by diverse medication types.

This study underscores the benefits of performing consortia-based pharmacogenomic studies, which have the power to detect signals that can provide biological insights into idiosyncratic adverse drug reactions. However, we would like to note that the authors incorrectly state that their study is the "first confirmed genome-wide association with DILI risk that lies outside the MHC locus." Although the discovery of *PTPN22* is important, a genome-wide association study of interferon-β (IFN-β)–induced liver injury, which was published in July 2018,[2] was the first study to identify a genome-wide significant DILI variant (rs2205986) outside of the MHC region. This novel finding was replicated in an independent cohort and was also associated with peak biochemical liver test results. Notably, rs2205986 is associated with altered expression of an interferon regulatory factor gene, *IRF6*, providing a plausible biological mechanism underlying this signal and illustrating the value of performing analyses restricted to an individual drug in well-phenotyped patients.

The DILIN/iDILIC investigation showed that the risk conferred by *PTPN22* rs2476601 was independent of *HLA* status, even in DILI caused by medications where *HLA* alleles increase risk for this adverse event. In the IFN-β study, extensive *HLA* analyses confirmed the lack of substantial involvement of the MHC locus, further emphasizing the importance of non-*HLA* variants for IFN-β–induced DILI. In line with this, the *PTPN22* variant is also enriched in IFN-β DILI cases compared with disease-matched controls (rs2476601: 1-sided $P = .049$; odds ratio, 1.76; 90% confidence interval, 1.00–3.08; minor allele cases, 14.5% vs controls, 8.9%). In total, 63.1% of IFN-β–induced liver injury cases carry $\geq$1 *IRF6* or *PTPN22* risk variant, compared with only 32.1% of disease-matched controls. The replication observed in the IFN-β DILI genome-wide association study genome-wide association study highlights the robust nature of the DILIN/iDILIC biomarker.

One aspect that still warrants further study is the relationship between *PTPN22* rs2476601 and other traits. For example, as mentioned in the DILI study, the variant is also associated with various autoimmune diseases. The authors performed a subanalysis excluding patients with comorbid autoimmune disease, where rs2476601 remained significantly associated with DILI, but it is uncertain how deeply phenotyped autoimmune diagnoses were captured in this restricted cohort. In addition, the variant has been associated with other liver-related traits such as autoimmune hepatitis,[3] that are not drug induced, the implications of such confounding were not discussed in the study. Further, characterizing DILI with autoimmune features remains an important and relatively unexplored area of research.[4]

As illustrated by the DILIN/iDILIC investigation, large consortia-based studies provide a valuable approach for identifying pharmacogenomic biomarkers, and are becoming increasingly feasible with the decreasing genotyping costs. The *HLA* system is one of the most polymorphic and important genomic regions for many adverse drug reactions and its importance is not restricted to DILI. For example, like DILI, initial progress in identifying

clinically-relevant biomarkers for severe cutaneous adverse reactions was made through identifying key *HLA* alleles for specific medications. However, in the last 5 years, a number of genome-wide significant regions have been identified outside the *HLA* for cutaneous adverse drug reactions through the use of large multi-national studies. These include variants in the *CYP2C9* and *CFH* genes for phenytoin-related cutaneous reactions,[5,6] as well as the *IKZF1* gene and cold medicine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis.[7] In addition to the prognostic usefulness, identifying novel gene associations offers the potential to provide biological insights and inform future drug repurposing studies.

Finally, it is worth noting that *PTPN22* rs2476601 is not found in East Asian individuals and is extremely rare in indigenous African populations, limiting the usefulness of this biomarker in patients of these ancestries. Although the authors should be commended for including cohorts of diverse ancestries in their study, it highlights the need for the inclusion of non-European cohorts in future consortia studies. Diversity in pharmacogenomic studies is especially important to ensure that drug safety and effectiveness can be improved for the global population of patients we all serve.[8]

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More Evidence Needed on the Combination of Diclofenac and Sublingual Nitrates in Preventing Pancreatitis After Endoscopic Retrograde Cholangiopancreatography

Dear Editors:

I read with great interests the article by Tomoda et al[1] evaluating the efficacy of a combination of diclofenac and sublingual nitrates in prevention of postendoscopic retrograde cholangiopancreatography pancreatitis (PEP). The authors declare that prophylaxis with rectal diclofenac and sublingual nitrate significantly decreases the overall incidence of PEP compared with diclofenac suppository alone.[1] PEP is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP), with an incidence of 8.8%–12.4%.[2] Although most PEP cases are mild or moderate, some PEP cases can be fatal with multiple organ failure ensuing. Thus, tremendous endeavors have been made to develop therapy for prevention of PEP. One preliminary randomized controlled trial (RCT) with a small sample size shows superiority of a combination of sublingual nitrate and rectal nonsteroidal anti-inflammatory drugs (NSAIDs) to rectal NSAIDs alone.[3] The RCT with a large sample size of 900 participants conducted by Tomoda et al confirms these conclusion and provides excellent evidences for clinical practice with a combination of NSAIDs and sublingual nitrates in prevention of PEP.[1] Thus, this study conducted by Tomoda et al is important and likely to be included in clinical guidelines. I appreciated the great efforts and excellent work done by the authors. However, I have some concerns to some methods and results provided by this study.

First, in the Methods section of the article, the study stated that, "We estimated that 892 patients (446 per study group) would show at least 80% reduction in the overall incidence of PEP (56.2% in both the groups), from 7.4% (in the diclofenac alone group) to 3.2% (in the combination group), while performing the Fisher's exact test with a 2-sided significance level of 0.05."[1] However, the number of participants for final analysis is 886 with 442 participants in the diclofenac alone group and 444 participants in the combination group, which is less than the estimated sample size. A smaller sample size in this study violates the previous setting protocols of this RCT and might be inadequate to investigate true differences between the 2 therapies for the prevention of a rare complication such as PEP. This accounts for the negative results of subgroup analyses as to PEP severity between the 2 groups. Thus, I recommend increasing the sample size to originally estimated sample size to come to a definite conclusion. Rigorously complying with the protocols is of importance for the validity of the results of a study.

Second, the authors mention that intention-to-treat analysis is used for statistical analysis in the published protocols of this study.[4] However, in the article published in *Gastroenterology*, the authors use modified intention-to-treat analysis