Genome-wide association study (GWAS) to identify genetic risk factors that increase susceptibility to anti-tuberculosis drug-induced liver injury (ATDILI).

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Background: Anti-tuberculosis drugs (ATD) isoniazid, rifampicin and pyrazinamide are among the most reported causes of drug-induced liver injury (DILI). Previous candidate gene studies, focused on drug metabolising enzyme gene variant association with anti-tuberculosis DILI (ATDILI), have, however, yielded contradictory results.
Aim: To identify genetic risk factors for ATDILI by a genome-wide association study (GWAS).
Methods: Patients who developed ATDILI and ethnically matched controls were enrolled in Bangalore and Vellore, South India. Roussel Uclaf Causality Assessment Method was used for case adjudication. Samples were genotyped with the Illumina Human Core Exome BeadChip, data was phased by SHAPEIT and single nucleotide polymorphisms were imputed by IMPUTE2. We tested for association by logistic or linear regression models and set the genome-wide significance threshold to $5x10^{-8}$. In view of previous reports on association of ATDILI with N-acetyltransferase 2 (NAT2) phenotype, we predicted NAT2 acetylator status using genotypes for NAT*5, *6 and *7 alleles and tested for association by Fisher's Exact test.

Results: We analysed 59 Indian cases (50% male; mean age 40 years) of ATDILI with 220 ethnically matched controls (65% male; mean age 40 years) including 111 patients treated with ATD without DILI and 109 healthy adults. The total DILI cohort was enriched in cases with severe liver injury with 15 (25%) patients developing acute liver failure and/or died; 22 (37%) patients had early onset of DILI (average latency was 45 days). The case-control GWAS did not demonstrate any genome-wide significant association between TBDILI and imputed or genotyped variants. The same negative outcome was obtained when we restricted the analysis to cases with acute liver failure or when we considered the latency as quantitative phenotypes in a case only study design. Regarding NAT2, we found that 40 cases (68%) were slow acetylators compared with 127 controls (58%) but this increased frequency was not

statistically significant (Odds ratio 1.54 (95% CI 0.84-2.84); p=0.18). Only 60% of severe cases were slow acetylators - the group was not more enriched in NAT2 variant alleles than other groups.

Conclusions: Standard GWAS analysis did not identify any high penetrance variants associated with either susceptibility or severity of ATDILI and we did not replicate the previously published NAT2 genetic association. The lack of a positive outcome could be due to the relative low case/control ratio that limits the study power and the complexity of having several culprit drugs involved in the phenotype, with each having individual drug-specific genetic risk factors.

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