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ORIGINAL ARTICLE

NAT2 and *CYP2E1* polymorphisms and antituberculosis drug-induced hepatotoxicity in Peruvian patients

Luis Jaramillo-Valverde[1,2,3] | **Kelly S. Levano**[1] | **David D. Tarazona**[1] | **Silvia Capristano**[1] | **Roberto Zegarra-Chapoñan**[1] | **Cesar Sanchez**[1] | **Velia M. Yufra-Picardo**[4] | **Eduardo Tarazona-Santos**[2,5] | **Cesar Ugarte-Gil**[6,7] | **Heinner Guio**[1,8,9]

[1]Laboratorio de Biotecnología y Biología Molecular, Instituto Nacional de Salud, Lima, Peru

[2]School of Public Health and Administration, Universidad Peruana Cayetano Heredia, Lima, Peru

[3]School of Medicine, Universidad Continental, Huancayo, Peru

[4]Innóvate Peru, Ministerio de la Producción, Lima, Peru

[5]Departamento de Genética, Ecologia e Evolução, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

[6]Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru

[7]School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru

[8]Universidad de Huánuco, Huánuco, Peru

[9]Universidad Científica del Sur, Lima, Peru

Correspondence
Heinner Guio, Laboratorio de Biotecnología y Biología Molecular, Instituto Nacional de Salud, Lima, Perú.
Email: heinnerguio@gmail.com

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Abstract

Background: In Peru, 32,970 people were diagnosed with tuberculosis (TB) in 2019. Although TB treatment is effective, 3.4%–13% is associated with significant adverse drug reactions (ADR), considering drug-induced liver injury (DILI) as the most prevalent. Among the first-line anti-TB drugs, isoniazid (INH) is primarily responsible for the occurrence of DILI. INH is metabolized in the liver by the enzymes N-acetyltransferase-2 (NAT2) and Cytochrome P450 2E1 (CYP2E1). Based on the previous studies, we hypothesized that the interactions between slow CYP2E1 genotype and NAT2 slow acetylators will induce DILI in TB patients.

Methods: In this cross-sectional study, all 377 participants completed their anti-TB treatment, and we genotyped SNPs: rs1041983, rs1801280, rs1799929, rs1799930, rs1208, and rs1799931 for NAT2 and rs3813867 and rs2031920 for CYP2E1.

Results: We found that rapid, intermediate, and slow NAT2 acetylator were 15%, 38%, and 47%, respectively, in the general population. Intermediate NAT2 acetylator is the least prevalent among patients with adverse reactions ($p = 0.024$). We did not confirm our hypothesis, however, we found that the combination of intermediate NAT2 acetylators and CYP2E1 c1/c1 genotype significantly protected (OR = 0.16; $p = 0.049$) against the development of DILI in our population.

Conclusion: We propose that the presence of NAT2 intermediate and CYP2E1 c1/c1 genotype could help in therapeutic drug monitoring, and optimize its therapeutic benefits while minimizing its risk for side effects or toxicity.

KEYWORDS

CYP2E1, hepatotoxicity, NAT2, tuberculosis

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1 | BACKGROUND

Tuberculosis (TB) continues to be the main health problem worldwide. Approximately, 10 million cases and a total of 1.2 million deaths were reported in 2019 ("WHO | Global Tuberculosis Report 2019," 2020). The Region of the Americas accounts for 3% of the total global burden of TB ("WHO | Global Tuberculosis Report 2019," 2020). In Peru, 32,970 people have been diagnosed with TB of which 4.4% corresponds to multidrug-resistant (MDR) tuberculosis ("WHO | Global Tuberculosis Report 2019," 2020).

TB can be treated effectively with first-line anti-TB drugs. However, nearly 5% of patients with drug-susceptible TB have a relapse which may indicate unsuccessful treatment and thus contribute to the development of MDR-TB (Guio et al., 2015). Adverse reactions (ADRs) induced by anti-TB drugs could do both harms and lead to anti-TB treatment failure. In recent years, increases in the rates of ADRs, treatment failures, and MDR-TB have been reported, especially in countries with limited resources (Pasipanodya et al., 2012) and irregularity or noncompliance with treatment (van der Werf et al., 2012).

Drug-induced liver injury (DILI) is one of the most common causes of ADR in high TB burden countries (Wattanapokayakit et al., 2016). In 2013, the General Directorate of Medicines, Supplies and Drugs (DIGEMID) of the Ministry of Health of Peru reported 177 cases of DILI (García-Cortés et al., 2005). The occurrence of DILI affects the continuation of anti-TB treatment, leading to delays in treatment or treatment failure.

Isoniazid (INH), a pro-drug, is one of the main components of TB treatment regimens worldwide. Despite its beneficial effects, severe liver toxicity is associated with INH therapies (Arbex et al., 2010). Metabolism of INH initiates in the liver by the enzyme N-acetyltransferase 2 (NAT2), encoded by the *NAT2* gene (OMIM # 612182), resulting in the acetylation of INH to acetyl-isoniazid (the active form) and isonicotinic acid. There is variation in the acetylation rate of INH which is genetically determined and differs among populations. Individuals may be divided into phenotypic groups according to their acetylation rate as follows: rapid, intermediate, and slow acetylators (McDonagh et al., 2014).

The human NAT2 enzyme is encoded by a highly polymorphic gene, of which 36 alleles have been described (http://louisville.edu/medschool/pharmacology/NAT2.html). Recombinant DNA technology studies, using prokaryotic expression systems, have shown that the alleles NAT2*4, NAT2*12A, NAT2*12B, NAT2*12C, and NAT2*13 encode enzymes with high acetylation activity, while the remaining alleles encode enzymes with low acetylation activity (Hickman et al., 1992). Furthermore, pharmacogenetic studies carried out in different populations have suggested that the alleles NAT2* 5, NAT2*6, and NAT2*7 are responsible for more than 95% of the slow acetylator phenotype (Cascorbi et al., 1995). There is a strong association between polymorphisms in the *NAT2* gene that affect the acetylation rate and thus the individual's phenotypic group, and the risk of DILI in TB patients (Heinrich et al., 2016; Huang, 2014; McDonagh et al., 2014). Additionally, the association between hepatotoxicity and genetic variations in other enzymes associated with INH metabolism have also been reported including in the enzymes cytochrome P450 2E1 (CYP2E1) and glutathione S-transferase (GST; Huang, 2014).

The CYP2E1 (OMIM # 124040) rs2031920 and rs3813867 polymorphisms in the 5′-flanking promoter region of the CYP2E1 gene are reported to affect the transcriptional activity of the CYP2E1 gene (Neafsey et al., 2009). For CYP2E1 rs2031920 and rs3813867 polymorphisms, the three different genotypes are named the homozygous wild-type genotype (c1/c1), heterozygous genotype (c1/c2), and homozygous rare genotype (c2/c2), respectively. Studies have shown that the concomitant presence of slow acetylator *NAT2* and *CYP2E1* c1/c1 genotype may further increase the risk of developing ADR. Evidence from several populations demonstrates that this relationship between developing ADR and the distribution of NAT2 encoding alleles and CYP2E1 genotype differ according to ethnicity (Guaoua et al., 2014).

We have previously reported that the prevalence of NAT2 polymorphisms in Peru is similar to other American populations (Bisso-Machado et al., 2016; Fuselli et al., 2007; Levano et al., 2021). In the mother study, we reported NAT2 and CYP2E1 data in other populations of the American continent and the rest of the world (Levano et al., 2021). Thus, we hypothesized that the interactions between slow CYP2E1 genotype and NAT2 slow acetylators may be associated with DILI, as it has been shown in other populations from the Region.

The aim of this study was to investigate NAT2 functional polymorphisms (NAT2*4, NAT2*5, NAT2*6, NAT2*7, NAT2*11, NAT2*12, and NAT2*13) and CYP2E1 polymorphisms (rs3813867 and rs2031920) and their association with the development of DILI in Peruvian TB patients.

2 | PATIENTS AND METHODS

2.1 | Studied population and participants

Our study includes 377 unrelated individuals, a subgroup of patients diagnosed with pulmonary tuberculosis between 2014 and 2015 recruited from health establishments of the Minister of Health (MINSA) located in Lima and Callao, Perú.

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The inclusion criteria were patients (i) with daily treatments of isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months, followed by 4 months of treatment of isoniazid and rifampicin, with drug dosages calculated according to body weight; (ii) with normal serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels, no symptoms related to abnormal liver function (i.e., jaundice) prior to anti-TB drug treatment and close monitoring of changes in liver function within 2 months of treatment; and (iii) with and without hepatotoxicity during drug treatment.

Patients with any of the following conditions were excluded from the study: (i) malnutrition; (i) human immunodeficiency virus type 1 (HIV) infection; (iii) alcoholic liver disease or habitual drinking; (iv) hepatitis B or C infection, liver disease, systemic diseases, and/or treatment with drugs other than the anti-TB drugs that can induce hepatotoxicity. All 377 participants (207 males and 170 females) completed their anti-TB treatment.

2.2 | Patient consent statement

This study was approved by the Ethics in Research Committee of the Peruvian National Institute of Health (OI-087-13) and by Universidad Peruana Cayetano Heredia (SIDISI: 102785). Informed consent was obtained from all the participants.

2.3 | Study design and data collection

This was a secondary data analysis, cross-sectional and observational study, with 377 tuberculosis patients, of both genders, aged between 15 and 50 years, which was the age group with the highest tuberculosis prevalence and the economically active one (possibility of infection by transport from one place to another) who lived in the study area (MINSA, 2013).

We have selected a subpopulation with the most prevalent sociodemographic characteristics of the general population. Our study is multicentered to represent better the population studied and to enroll as many DILI cases as possible.

2.3.1 | Data collection sheet

This was designed to make it possible to collect sociodemographic characteristics, as well as clinical results, from medical records, in the studied population. The data collection sheet was accepted by the CIEI-INS. Two nurses, trained by the principal investigator collected the information. The collected clinical records were analyzed by an epidemiologist and a biostatistician.

2.3.2 | Blood samples

After the survey questionnaire. Peripheral blood samples (4 ml) were obtained from all 377 studied patients at baseline.

As this is a secondary analysis of previously collected data (Levano et al., 2021), it was considered pertinent to calculate the statistical power to evaluate the research hypothesis. A power of 98.56% was obtained when comparing the minimum difference of the mean probability of the outcome variable between two categories of the main independent variable (slow genotype and rapid genotype) NAT2, which is the metabolizing enzyme with the most evidence in published scientific studies. A ratio of 0.88 between slow and fast genotypes and a probability of the presence of ADRs with slow and fast metabolizing genotypes of 0.25 and 0.10, respectively, is assumed according to published data in a South American population (Heinrich et al., 2016).

2.4 | Laboratory methods

Genomic DNA was extracted from the peripheral blood of all 377 participants using the genomic DNA extraction kit QIAamp DNA Blood Mini Kit (Qiagen, Germany). The selected genomic DNA regions for the analysis of each gene included the most common reported SNPs (for NAT2: rs1041983, rs1801280, rs1799929, rs1799930, rs1208, and rs1799931; for CYP2E1: rs3813867 and rs2031920). These regions were amplified by PCR using a Platinum Taq DNA polymerase kit (Invitrogen, USA) using the following primers: for NAT2: 5′-GTCACACGAGGAAATCAAATGCT-3 and 5′-CGTGAGGGTAGAGAGGATATCTG-3′; for CYP2 E1: 5′- CCGTGAGCCAGTCGAGTCTA-3′ and 5′-TTCATT CTGTCTTCTAACTGGCAA-3′. PCR-amplified fragments were purified using QIAmp Gel Purification Kit (Qiagen, USA). SNP genotyping on the purified fragments was performed using sanger sequencing (Macrogen, South Korea). Nucleotide substitutions were identified and analyzed using the Geneious version 9.1.5 (Biomatters Ltd., New Zealand).

2.5 | Measures and analysis

The presence of DILI (yes/no) was the outcome. This information was collected from the medical record of each patient and was diagnosed by a medical doctor. The liver

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profile is measured 2 months after starting treatment in all patients with sensitive tuberculosis in Peru (MINSA, 2013). Hepatotoxicity was defined as elevated aminotransferase levels and identified as being three times higher than before initiating TB treatment, with associated symptoms of hepatitis. Symptoms were considered as the occurrence of jaundice, nausea, vomiting, dyspepsia, and asthenia (Ramappa & Aithal, 2013). The reference values adopted were AST—36 UI/ml and ALT—32 UI/ml, according to the manufacturer's instructions (Targa 3000).

NAT2 acetylator genotype, and interest exposure were classified as "slow, intermediate, and rapid," and CYP2E1 genotype was classified as "c1/c1, c1/c2, and c2/c2." The computationally inferred phenotypes using a combination of NAT2 SNPs for the 377 participants were determined using an online software program, NAT2PRED (nat2pred.rit.albany.edu; Kuznetsov et al., 2009; Sabbagh et al., 2009). The other covariates were grouped into (1) demographics (gender and age), (2) alcohol consumption, (3) cholesterol, (4) hemoglobin, (5) glucose, and (6) body mass index (BMI). All the covariables were obtained at the time of the interview from biological samples or in an interview of each patient.

2.5.1 | Statistical analysis

The chi-square test was used, or when necessary, the Fisher exact test to check the statistical significance of differences in the frequency distribution of variables and the Hardy–Weinberg equilibrium. Bivariate logistic regression analysis was performed and the magnitude of the associations was expressed by the odds ratio (OR) as an estimate of relative risk, with a confidence interval of 95% regression. Data analysis was performed using Stata v15 (StataCorp, College Station, TX) considering a statistical significance of $p < 0.05$.

3 | RESULTS

No patient was excluded from the study. This cohort was predominantly male (55%). Sixteen out of 377 participants (4.1%) were diagnosed with DILI, a mild ADR type with symptoms that included nausea and vomiting/gastric pain. Table 1 shows the frequency distribution of both biological and clinical variables.

The prevalence of NAT2 genotypes in the study population was 14.85%, 37.67%, and 47.48% for fast, intermediate, and slow acetylator, respectively. For fast acetylator, we found the NAT2*4/4 genotype (10.88%) to more prevalent, for intermediate acetylator, NAT2*5/4 genotype has 12.73%, and for slow acetylator, NAT2*5/5 genotype has 28.65% of all samples.

In the case of CYP2E1, two polymorphism upstreams (rs2031920 and rs3813867) of the CYP2E1 transcriptional start site appear to be in complete linkage disequilibrium, the prevalence of genotypes was 63.71%, 30.91%, and 5.38% for c1/c1, c1/c2, and c2/c2, respectively.

About 38% of the population showed intermediate NAT2 phenotype, and it was more prevalent in patients without DILI than in patients with DILI ($p = 0.024$; Table 1).

Only 6.25% of the patients with DILI had an NAT2 intermediate genotype. On the other hand, CYP2E1 genotypes were not associated with DILI and the allele frequencies of both groups (with and without adverse reaction) were similar and were in Hardy–Weinberg equilibrium ($p > 0.05$), The chi-square test was used, or when necessary, the Fisher exact test.

Table 2 describes the frequencies of NAT2 acetylator phenotype profile and their respective genotype. Each SNP produced an allele, four were classified phenotypically as rapid acetylators. There was no statistically significant difference between the groups studied. The most frequent genotype observed in rapid acetylation with ADR was NAT2*4/4 (50%). For slow acetylation, the most frequent genotype associated with ADR was NAT2*5/5 (80%). Only one patient with an intermediate phenotype presented DILI. The NAT2 allele frequencies of both group (with and without adverse reaction) presents allelic balance in Hardy–Weinberg equilibrium ($p > 0.05$).

In Table 3, there is no association between allele frequencies and DILI. There is no evidence that the presence of the variant allele of NAT2 could come to constitute an isolated risk or protective factor for developing ADR during TB treatment ($p > 0.05$).

When the effects of combining CYP2E1 genotype and NAT2 acetylator status were examined, it was found that patients who were intermediate NAT2 acetylators and had the CYP2E1 c1/c1 genotype had a significant protection (OR 0.16; 95% CI 0.00–1.25; $p = 0.049$) against developing DILI compared with the most prevalent combination between NAT2 and CYP2e1 genotypes (Table 4).

4 | DISCUSSION

The present study is the first to evaluate the association of previously identified pharmacogenomic biomarkers for DILI in a Peruvian population.

Personalized medicine has emerged as a strategy to adjust the dose regimens required to obtain optimal effectiveness in minimizing ADRs or toxicity in front of therapeutic drug monitoring (TDM; Li et al., 2004). To date, TDM for anti-TB drugs is considered routine 2 months

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TABLE 1 Clinical and biological variables of adult patients diagnosed with sensitive pulmonary tuberculosis in Lima during the years 2014–2015

	Total		Adverse reaction (DILI)				
			Yes		No		
Variables	***N***	**%**	***N***	**%**	***N***	**%**	***p* value**
Sex							
Male	207	54.91	10	62.50	197	54.57	
Female	170	45.09	6	37.50	164	45.43	0.533[a]
Age (years)	–	–	24.3[d]	(20.3–30.8)[e]	24.2[d]	(20.9–29.6)[e]	0.995[b]
Alcohol consumption							
No	49	13.00	3	18.75	46	12.74	
Yes	328	87.00	13	81.25	315	87.26	0.346[c]
Cholesterol (mg/dl)	–	–	154.0[d]	(141.2–185.0)[e]	169[d]	(149.0–189.0)[e]	0.214[b]
Hemoglobin (g/dl)	–	–	13.9[d]	(12.2–15.6)[e]	13.6[d]	(12.4–14.9)[e]	0.769[b]
Glucose (mg/dl)	–	–	89.5[d]	(80.0–95.0)[e]	83.1[d]	(77.9–91.1)[e]	0.084[b]
BMI (kg/m^2)	–	–	21.1[d]	(19.7–22.5)[e]	22[d]	(20.3–23.6)[e]	0.182[b]
NAT2 phenotype							
Slow	179	47.48	9	56.25	170	47.09	
Intermediate	142	37.67	1	6.25	141	39.06	**0.024**[c]
Rapid	56	14.85	6	37.50	50	13.85	0.129[a]
CYP2E1 genotype[f]							
c1/c1 (slow)	237	63.71	12	75	225	63.20	
c1/c2 (intermediate)	115	30.91	3	18.75	112	31.46	0.220[c]
c2/c2 (rapid)	20	5.38	1	6.25	19	5.34	0.732[c]

Note: Statistically significant ($p < 0.05$).

Bold value indicates statistically significant

Abbreviations: BMI, body mass index; CYP2E1, cytochrome P450 Family 2 Subfamily E Member 1; NAT2, arylamine N-acetyltransferase.

[a]Chi-square test.

[b]Mann–Whitney test.

[c]Fisher's exact test.

[d]Median.

[e](Q1–Q3).

[f]Missing values.

after starting treatment (MINSA, 2013). Significant functional changes and several polymorphic enzymes involved in drug metabolism have also been identified to an influence on drug systemic concentrations.

The metabolic pathway of INH has been the basis for most of the recent studies seeking to explain the mechanism of ADRs induced by anti-TB drugs. The NAT2 slow acetylator phenotype has been documented as a strong risk factor for the occurrence of such liver damage (Cai et al., 2012; Wang et al., 2011). However, other studies indicate that rapid acetylators would be more vulnerable to liver damage as an ADR induced by anti-TB drugs due to the increased production of hepatotoxins, resulting from the rapid NAT2 enzyme activity (Leiro-Fernandez et al., 2011; Mitchell et al., 1975; Vuilleumier et al., 2006).

According to our results, the age of the patient was not associated with the presence of ADRs, since the patients recruited in the mother study (Levano et al., 2021) belonged to a lower risk age group, 18–50 years. Furthermore, the findings of this study suggest that there are no significant differences in hemoglobin, cholesterol, and BMI levels. However, Yee and colleagues (Yee et al., 2003) reported that continued use of more than one drug, as a result of previous diseases or conditions, can increase the risk of developing ADRs due to drug interactions.

A group of the research reported that slow acetylator patients had a higher incidence of hepatitis than intermediate/rapid acetylators (Richardson et al., 2019; Teixeira et al., 2011; Yuliwulandari et al., 2019) and polymorphisms

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TABLE 2 Frequencies of NAT2 genotype with tuberculosis in Lima, Peru

NAT2 genotype		Adverse reaction (DILI)				
		Yes		No		
Rapid acetylator phenotype	***N* = 56**	***N* = 6**	**%**	***N* = 50**	**%**	***p*-value[a]**
NAT2*4/4	41	3	0.5	38	0.8	0.253
NAT2*7/7	5	1	0.2	4	0.1	
NAT2*11/11	8	2	0.3	6	0.1	
NAT2*12/12	2	0	0.0	2	0.0	
Intermediate acetylator phenotype	*N* = 142	*N* = 1	%	*N* = 141	%	
NAT2*5/4	48	0	0.0	48	0.3	0.232
NAT2*6/4	25	1	1.0	24	0.2	
NAT2*7/4	28	0	0.0	28	0.2	
NAT2*11/4	5	0	0.0	5	0.0	
NAT2*12/4	3	0	0.0	3	0.0	
NAT2*13/4	33	0	0.0	33	0.2	
Slow acetylator phenotype	*N* = 179	*N* = 9	%	*N* = 170	%	
NAT2*5/5	108	7	0.8	101	0.6	0.473
NAT2*5/6	14	1	0.1	13	0.1	
NAT2*6/7	54	1	0.1	53	0.3	
NAT2*13/7	3	0	0.0	3	0.0	

Abbreviation: NAT2, Arylamine N-Acetyltransferase.

[a]Fisher's exact test.

this agrees with what we found through the association of intermediate acetylators and the low frequency among patients with liver problems.

Several studies reported that patients with the C1/C1 genotype of the CYP2E1 gene are at higher risk of anti-TB therapy ADRs (Huang et al., 2003; Lee et al., 2010; Vuilleumier et al., 2006; Wang et al., 2010). In our study, we did not find any significant associations between the CYP2E1 genotypes and anti-TB drug-induced ADR as previously reported by Cho et al. (2007). This is in agreement with our result of no association of the CYP2E1 genotype and DILI. The statistically nonsignificant results regarding the CYP2E1 polymorphism and.

hepatotoxicity may be due to the small sample size and low frequency of patients with hepatotoxicity; reevaluation and confirmation are needed in a large-scale population study.

Huang reported an increase in the risk of anti-TB therapy-induced ADR between the C1/C1 genotype and the slow acetylator NAT2 genotype (Huang et al., 2003). In Table 4, we examined the effects of combining CYP2E1 genotype and NAT2 acetylator status, however, we were not able to confirm our hypothesis that the interactions between slow CYP2E1 genotype and NAT2 slow acetylators will induce DILI. However, we have found an interesting result where intermediate NAT2 acetylators and CYP2E1 c1/c1 genotype had significant protection against developing ADR. According to our results, the NAT2 polymorphism associated with the intermediate phenotype and CYP2E1 C1/C1 genotype does not affect therapeutic response and is suspected to be a protective factor for INH-induced hepatotoxicity.

Finally, the present study has the limitations of an observational study with tuberculosis patients attending a routine medical care setting. We analyzed the exposures related to drugs registered by the attending physician. The incidence of anti-TB drug-induced hepatotoxicity is very low (4.2%); however, our study is multicentered to represent better the population studied and to enroll as many DILI cases as possible. Additionally, we did not achieve a sample size with the necessary power to demonstrate a statistically significant association between the NAT2 slow acetylator profile and the development of hepatotoxicity in Peruvian patients undergoing treatment for TB. For this reason, a prospective cohort study in TB patients with or without ADR could confirm our findings. This research highlights the importance of having pharmacogenomic studies and having the identification of polymorphisms associated with the metabolism of the antituberculosis drugs in our Peruvian population related to the influence of ancestry.

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TABLE 3 Association of NAT2 alleles with adverse reaction (DILI) in adult patients diagnosed with sensitive pulmonary tuberculosis in Lima during the years 2014–2015

		Adverse reaction (DILI)				Total				
		Yes		No						
	Phenotype	*N*	%	*N*	%	*N*	%	OR	CI (95%)	*p* value
NAT2 alleles										
NAT2*11	Rapid									
CC		8	4.1	188	95.9	196	49.6	1		
(CT + TT)		8	4.0	191	96.0	199	50.4	0.98	0.3–3.1	0.975
NAT2*12	Rapid									
AA		11	4.1	257	95.9	268	67.8	1		
(AG + GG)		5	3.9	122	96.1	127	32.2	0.96	0.3–3.1	0.937
NAT2*13	Rapid									
CC		9	6.3	133	93.7	142	35.9	1		
(CT + TT)		7	2.8	246	97.2	253	64.1	0.42	0.1–1.3	0.084
NAT2*5	Slow									
TT		9	3.9	220	96.1	229	58.0	1		
(TC + CC)		7	4.2	159	95.8	166	42.0	1.08	0.3–3.3	0.887
NAT2*6	Slow									
GG		12	4.0	291	96.0	303	76.7	1		
(GA + AA)		4	4.3	88	95.7	92	23.3	1.1	0.3–3.8	0.869
NAT2*7	Slow									
GG		11	5.2	199	94.8	210	53.2	1		
(GA + AA)		5	2.7	180	97.3	185	46.8	0.5	0.1–1.6	0.202

Note: Statistically significant ($p < 0.05$).

Logistic regression.

Abbreviations: CI (95%), confidence interval; NAT2, Arylamine N-Acetyltransferase; OR, Odds ratio.

TABLE 4 Combined effects of N-acetyltransferase 2 (NAT2) acetylator status and cytochrome P450 2E1 (CYP2E1) genotype

			Adverse reaction (DILI)			
NAT2 acetylator status	CYP2E1 genotype	*n*	Yes	No	OR (CI)	*p* value
Slow	C1/C1	107	7	100	Reference	
	C1/C2 or C2/C2	57	2	55	0.52 (0.51–2.87)	0.417
Intermediate	C1/C1	93	1	92	0.16 (0.00–1.25)	**0.049**
	C1/C2 or C2/C2	49	0	49	–	–
Rapid	C1/C1	36	4	32	1.79 (0.36–7.54)	0.374
	C1/C2 or C2/C2	18	1	17	0.84 (0.02–7.27)	0.874

Note: Exact confidence levels were not possible with zero count cells.

$p < 0.05$ indicates that the 95% confidence interval (CI) of the odds ratio (OR) did not include.

Odds ratios were estimated using a logistic regression model.

5 | CONCLUSION

We found that 38% of the population had intermediate NAT2 acetylator phenotype and that it was more prevalent in patients without DILI than patients with DILI. The combination of intermediate NAT2 acetylators and CYP2E1 c1/c1 genotype had significant protection against developing DILI compared with the most prevalent combination in our population (slow NAT2 acetylator and CYP2E1 c1/c1 genotype). This phenotype does not affect

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therapeutic response and is suspected to be a protective factor for INH-induced hepatotoxicity in Peruvian patients.

We believe that future tuberculosis treatment could personalize drug doses according to the polymorphism profiles of patients. Further studies with the Peruvian population and larger sample sizes are required to confirm our findings.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Study design: LJ-V, CU-G, HG. Performed the experiments: LJ-V. Analyzed the data: LJV, KSL, DDT, SC, RZ-C, CS, VY-P, ET-S, CU-G, HG. All authors have read and approved the final manuscript.

ETHICAL COMPLIANCE

Our study was approved by the Ethics in Research Committee of the Peruvian National Institute of Health and Ethics Committee of the Universidad Peruana Cayetano Heredia. Written informed consent was obtained from all the participants.

ORCID

Luis Jaramillo-Valverde https://orcid.org/0000-0001-5093-6067
Kelly S. Levano https://orcid.org/0000-0001-6519-6305
David D. Tarazona https://orcid.org/0000-0002-9273-0590
Silvia Capristano https://orcid.org/0000-0002-8119-0621
Roberto Zegarra-Chapoñan https://orcid.org/0000-0002-0471-9413
Cesar Sanchez https://orcid.org/0000-0001-7300-0085
Eduardo Tarazona-Santos https://orcid.org/0000-0003-3508-3160
Cesar Ugarte-Gil https://orcid.org/0000-0002-2833-9087
Heinner Guio https://orcid.org/0000-0003-0078-1188

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