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ORIGINAL ARTICLE

Pharmacogenetic variability of tuberculosis biomarkers in native and mestizo Peruvian populations

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Abstract

In Peru, 29 292 people were diagnosed with tuberculosis in 2022. Although tuberculosis treatments are effective, 3.4%–13% are associated with significant adverse drug reactions, with drug-induced liver injury (DILI) considered the most predominant. Among the first-line antituberculosis drugs, isoniazid is the main drug responsible for the appearance of DILI. In liver, isoniazid (INH) is metabolized by N-acetyltransferase-2 (*NAT2*) and cytochrome P450 2E1 (*CYP2E1*). Limited information exists on genetic risk factors associated with the presence of DILI to antituberculosis drugs in Latin America, and even less is known about these factors in the native and mestizo Peruvian population. The aim of this study was to determine the prevalence of *NAT2* and *CYP2E1* genotypes in native and mestizo population. An analytical cross-sectional analysis was performed using genetic data from mestizo population in Lima and native participants from south of Peru. *NAT2* metabolizer was determined as fast, intermediate and slow, and *CYP2E1* genotypes were classified as c1/c1, c1/c2 and c2/c2, from molecular tests and bioinformatic analyses. Of the 472 participants, 36 and 6 *NAT2* haplotypes were identified in the mestizo and native population, respectively. In mestizo population, the most frequent *NAT2**5B and *NAT2**7B haplotypes were associated with DILI risk; while in natives, *NAT2**5G and *NAT2**13A haplotypes were associated with decreased risk of DILI. For *CYP2E1*, c1/c1 and c1/c2 genotypes are the most frequent in natives and mestizos, respectively. The linkage disequilibrium of *NAT2* single nucleotide polymorphisms (SNPs) was estimated, detecting a block between all SNPs natives. In addition, a block between rs1801280 and rs1799929 for *NAT2* was detected in mestizos. Despite the limitations of a secondary study, it was possible to report associations between *NAT2* and *CYP2E* alleles with Peruvian

Abbreviations: CYP2E1, cytochrome P450 2E1; DILI, drug-induced liver injury; HGDP, Human Genome Diversity Project.; INH, isoniazid; MDR-TB, multidrug-resistant tuberculosis; MTB, Mycobacterium tuberculosis; NAT2, N-acetyltransferase-2; NIH, National Institute of Health; SNPs, single nucleotide polymorphisms; TB, tuberculosis; WHO, World Health Organization.

native and mestizo by prevalence ratios. The results of this study will help the development of new therapeutic strategies for a Tuberculosis efficient control between populations.

KEYWORDS
genotype, native and mestizo population, Pharmacogenetic, tuberculosis

1 | BACKGROUND

Worldwide, tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB), is one of the 10 leading causes of death.[1] TB affects anyone at any age but with a greater impact on the economically active population.[2] In 2017, TB caused approximately 1.3 million deaths worldwide. It predominantly affects the poorest social strata in the country's large cities. In Peru, 29 292 people were diagnosed with tuberculosis in 2022.[1]

In Peru, first-line drug treatment had a success rate of 86% according to the World Health Organization (WHO) in 2016.[1] Although TB treatments are effective, 3.4%–13% are associated with significant adverse drug reactions, with drug-induced liver injury (DILI) considered the most predominant.[1] In the human liver, INH is first acetylated by *NAT2* to acetylhydrazine, then oxidized into toxic intermediates by *CYP2E1*.[3] The toxic compounds produced are detoxified by acetylation by *NAT2* and by conjugation reactions catalyzed by GST enzymes. Some risk factors for DILI have already been reported, such as coinfection with HIV, hepatitis B and C, advanced age and female gender.[4,5]

The low concentrations of antibiotics in the blood could be due to an increase in the metabolism of antibiotics due to genetic factors of each person. Thus, there is a classification of metabolizer phenotypes according to the genotype of each person: slow metabolizers and fast metabolizers.[6,7] Genes such as *NAT2*, *CYP2E1* have been evaluated in different populations around the world, including Americans, Africans, Europeans, and Asians.[8–10] A multinational study, that include individuals from Peru, reported that the *NAT2**4*11*12*13*18 genotypes were associated with intermediate and fast metabolizers. However, this study did not provide sufficient evidence to optimize the concentration of the drug and reduce the side effects of isoniazid in the Peruvian populations diagnosed with tuberculosis.[11]

Studies of genetic diversity in populations are important because they identify the unique polymorphisms for each population. The basis of pharmacogenomics is that the genotype obtained in other populations cannot be extrapolated for the choice and dosage of a certain drug. Ancestral admixture genetic analysis of the Peruvian mestizo population from multiple Native American communities in the region[12] reports a distinct population or population that does not allow assumptions from existing pharmacogenomic data.

Thus, in 2018, the technical report by WHO experts underscores an important role in determining metabolization phenotypes during drug administration. For example, for the administration of isoniazid, both in children and adults, the dose is defined as 10–15 mg/kg/day in multidrug-resistant tuberculosis (MDR-TB) regimens (the usual dose is 4–6 mg/kg/day). However, it notes that in North Asia, where the majority of the population has the rapid metabolizer, a dose of 15 mg/kg may be more effective.[13]

There are some studies that report impact of *NAT2* pharmacogenetic variability in pharmacokinetic variability and toxicity differences after isoniazid treatment.[14–16] A previous study concludes that patients with a fast metabolizer should receive 50% more than the standard dose, while patients with a slow genotype should receive half the standard dose.[17] Azuma et al. reported that 78% of the slow metabolizers experienced hepatotoxicity as a consequence of being treated with standard doses of INH, while none of those who received the modified dose reported liver damage.[6] According to the above, the benefit of the modified treatment in the reduction of DILI according to the metabolization of INH was demonstrated.[18]

Although the main mechanisms involved in the development of hepatotoxicity are known, this field has not been significantly explored in Peru, particularly in vulnerable populations. The objective of this study is to estimate the prevalence of metabolizing genotypes in patients during tuberculosis treatment in the mestizo and native Peruvian populations, and to investigate the possible associations of these genotypes with clinical outcomes.

2 | PATIENTS AND METHODS

2.1 | Studied population and participants

Participants of both sexes over 18 years of age belonging to the mestizo populations from Lima and native populations from in Puno, Junín, Cusco and Apurímac. We applied a criterion to optimize individuals to best represent the Native populations: the place of birth of the participant and that of his or her parents and grandparents. Pertinent context for the study, given the high representativeness of the component of native ancestry of the population outside of Lima.

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). Informed consent was obtained from all the participants.

TABLE 1 Frequency of SNPs and NAT2 haplotypes observed in the Peruvian mestizo population.

Nucleotide	282T	341C	481T	590A	803G	857A		
Frequency[a]	0.6550	0.4275	0.5100	0.2600	0.3275	0.2800		
Change AA	Ninguno	I114T	Ninguno	R197Q	K268R	G286E		
Haplotypes	C282T	T341C	C481T	G590A	A803G	G857A	Frequency[b]	Fenotype
NAT2*4	C	T	C	G	A	G	0.1050	FAST
NAT2*5A		C	T				0.0275	SLOW
NAT2*5B		C	T		G		0.1150	SLOW
NAT2*5C		C			G		0.0025	INTERMEDIATE
NAT2*5D		C					0.0125	INTERMEDIATE
NAT2*5E		C		A			0.0025	SLOW
NAT2*5G	T	C	T		G		0.0925	SLOW
NAT2*5J	T	C		A			0.0050	SLOW
NAT2*5KA	T	C				A	0.0175	SLOW
NAT2*5Q		C		A	G		0.0025	SLOW
NAT2*5R	T	C		A	G		0.0025	SLOW
NAT2*5U	T	C	T	A	G		0.0350	SLOW
NAT2*5V	T	C	T				0.0175	INTERMEDIATE
NAT2*5VA	T	C	T			A	0.0375	SLOW
NAT2*6A	T			A			0.0700	SLOW
NAT2*6C	T			A	G		0.0125	SLOW
NAT2*6J	T			A		A	0.0350	SLOW
NAT2*6N	T		T	A			0.0325	SLOW
NAT2* 6R	T		T	A	G		0.0025	SLOW
NAT2*7A						A	0.0050	FAST
NAT2*7B	T					A	0.1250	SLOW
NAT2*7C	T				G	A	0.0100	SLOW
NAT2*7E	T		T			A	0.0250	SLOW
NAT2*7F	T		T		G	A	0.0075	INTERMEDIATE
NAT2*11[a]			T				0.0075	FAST
NAT2*12[a]					G		0.0125	FAST
NAT2*12B	T				G		0.0050	INTERMEDIATE
NAT2*12C			T		G		0.0175	FAST
NAT2*12M	T		T		G		0.0050	INTERMEDIATE
NAT2*13[a]	T						0.0650	FAST
Unknow1		C	T	A	G		0.0050	SLOW
Unknow2	T	C	T	A			0.0425	SLOW
Unknow3			T			A	0.0175	SLOW
Unknow4		C	T	A			0.0100	SLOW
Unknow5	T		T				0.0100	INTERMEDIATE
Unknow6			T	A			0.0025	SLOW

[a]SNPs Frequency.

[b]Haplotypes frequency.

2.3 | Study design and data collection

Two mother studies are reported, the first carried out by researchers from the National Institute of Health (NIH) through a cross-sectional study with the objective of describing and determining the frequency of the *NAT2*, *CYP2E1* and *AADAC* genotypes, related to the metabolism of INH and rifampicin (RIF)[19] in the Lima population. The second was carried out by researchers from the Brazilian EPIGEN

Consortium through a cohort study to address the underrepresentation of non-European individuals in studies of human genome diversity, reporting SNPs of clinical importance in the Brazilian and Latin American population.[20]

This study is a secondary analysis of data with an analytical cross-sectional design. Baseline data from both previously described studies were analyzed. The data came from 472 participants of both studies with the objective of seeking the association between the type of Peruvian native or mestizo population and the prevalent *NAT2* metabolizer and *CYP2E1* genotype.

2.3.1 | Data collection sheet

A data collection sheet was developed to collect sociodemographic characteristics and clinical results from medical records in the studied population. The sheet was approved 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

Peripheral blood samples (4 mL) were collected from all 472 study participants at baseline, after completion of the survey questionnaire.

2.4 | Laboratory methods

For the INS original study samples, 200 microliters of peripheral blood were used to extract DNA using the QIAamp DNA Blood Mini Kit (Qiagen). Specific primers for the *NAT2* fragment were designed and *CYP2E1* fragments[19] were PCR amplified using the Taq PCR Master Mix Kit (Qiagen). PCR products were purified using the QIAquick Gel Extraction kit (Qiagen). The purified PCR products were sequenced by a Sanger-type genetic sequencing, using a 96-capillary DNA Analyzer (Applied Biosystems). For multiple alignment analysis, sequences were analyzed using the Autoassembler (Applied Biosystems) and metabolizer and genotype was determined.

In the case of the EPIGEN project, participant's samples were genotyped using the Illumina Omni 2.5 M array. ADMIXTURE analysis was performed on 370 539 SNPs shared by samples from the HapMap Project, the Human Genome Diversity Project (HGDP), and the Epigen-Brazil study population.[20]

2.5 | Measures and analysis

Bioinformatics analysis of NGS data was performed by creating a VCF file with SNPs using the GATK index.[21] The file was then managed with PLINK[22] to recode, rearrange, merge, flip DNA strands, and extract subsets related to pharmacogenetic variants. Haplotype was reconstructed using the platform: Human NAT2 Alleles (Haplotypes).[23] Finally, Haploview was used to analyze and visualize the linkage disequilibrium in the data using the solid spine method.[24]

The association between Peruvian population type and *NAT2* metabolizer and *CYP2E1* genotype was explored using a chi-square test. Prevalence ratios were calculated using Poisson regression models. The association between categorical variables and *NAT2* metabolizer and *CYP2E1* genotypes was also evaluated using a chi-square test. Data analysis was performed using Stata 15. (StataCorp. 2016. Stata Statistical Software: Release 15. College Station), considering a statistical significance of $p < .05$.

3 | RESULTS

After *NAT2* genotyping, it was possible to verify the presence of 6 SNPs previously described in the Peruvian mestizo population and 7 SNPs previously described in the native Peruvian population. We identified 36 haplotypes in the mestizo population and 6 haplotypes

TABLE 2 Frequency of SNPs and NAT2 haplotypes observed in the Peruvian native population.

Nucleotide	190T	191A	282T	341C	481T	590A	803G		
Frequency[a]	0.0000	0.0000	0.8473	0.4167	0.4167	0.0973	0.4167		
Change AA	R64W	R64Q	Ninguno	I114T	Ninguno	R197Q	K268R		
Haplotypes	C190T	G191A	C282T	T341C	C481T	G590A	A803G	Frequency[b]	Fenotype
NAT2*4	C	G	C	T	C	G	A	0.0417	FAST
NAT2*5B				C	T		G	0.1111	SLOW
NAT2*5G			T	C	T		G	0.2500	SLOW
NAT2*5U			T	C	T	A	G	0.0556	SLOW
NAT2*6A			T			A		0.0417	SLOW
NAT2*13A			T					0.5000	FAST

[a]SNPs Frequency.

[b]Haplotypes frequency.

in the native population. The frequency of the SNPs, *NAT2* haplotypes and *NAT2* metabolizer phenotypes are described in Tables 1 and 2.

In the case of the mestizo population, the *NAT2**5B and *NAT2**7B haplotypes are the most frequent. The reference allele (i.e., *NAT2*4*) was the most frequent (10.50%) allele in haplotypes with fast phenotype (Table 1). In addition, the SNPs with the highest frequency was rs1041983 (282T) with 40.75% (Table 1). Of the 400 participants, 49.25%, 36.50%, and 14.25% had slow, intermediate, and fast metabolizer phenotypes, respectively (Table 3).

In the case of the native population, the most frequent *NAT2* haplotypes were *NAT25G* and *NAT213A*. Within the haplotypes with fast phenotype, the *NAT2*13A* allele was the most frequent (50%). The SNP with the highest frequency was 282T (0.5833), which was more frequent than the other 6 SNPs. Of the 72 participants, 45.83% and 54.17% had slow and fast metabolizer phenotypes, respectively (Table 2).

After *CYP2E1* genotyping, it was possible to verify the presence of 2 previously described SNPs in mestizo and native Peruvian population. We identified 3 alleles of rs2031920 in the mestizo and native population (Table 4).

The NAT2 and CYP2E1 metabolizer profiles were compared between participants who belonged to the mestizo and native

TABLE 3 Bivariate analysis of genetic characteristics in the native and mestizo Peruvian population.

	Population		
	Native ($n=72$)	Mestiza ($n=400$)	
Variables	***n* (%)**	***n* (%)**	***p***
Gender			.140
Female	36 (55.8)	180 (45.0)	
Male	29 (44.6)	220 (55.0)	
NAT2 metabolizer			<.001
Slow	33 (48.8)	197 (49.3)	
Intermediate	0 (0.0)	146 (36.50)	
Fast	39 (54.2)	57 (14.25)	
NAT2 haplotypes			<.001
NAT2*4	3 (4.2)	42 (10.5)	
NAT2*5B	8 (11.1)	46 (11.5)	
NAT2*5G	18 (25.0)	37 (9.3)	
NAT2*5 U	4 (5.6)	18 (3.8)	
NAT2*6[a]	3 (4.2)	31 (6.6)	
NAT2*13[a]	36 (50.0)	62 (13.1)	
CYP2E1 alleles			<.001
C1/C1	21 (29.2)	254 (63.5)	
C1/C2	33 (45.8)	158 (31.3)	
C2/C2	15 (25.0)	21 (5.2)	

Note: *p* value from statistical test: Chi2.

Abbreviations: *CYP2E1*, cytochrome P450 2E1; *NAT2*, N-acetyltransferase-2.

TABLE 4 Frequencies of genetic variants between the native and mestizo Peruvian population related to antituberculosis treatment.

	Population		
Variables	**Native ($n=72$)**	**Mestizo ($n=400$)**	***p***
282C>T			
CC	11	139	<.001
CT	38	196	
TT	23	65	
G	60	474	<.001
T	84	326	
341T>C			
TT	42	229	.267
TC	28	138	
CC	2	33	
T	112	596	.234
C	32	204	
481C>T			
CC	42	196	.002
CT	28	34	
TT	2	70	
G	112	426	.061
T	32	174	
590G>A			
GG	65	296	.009
GA	6	79	
AA	1	25	
G	136	671	<.001
A	8	129	
803A>G			
AA	42	268	<.001
AG	28	75	
GG	2	57	
A	112	611	.403
G	32	189	
3739G>C			
GG	71	381	.199
GC	0	16	
CC	0	3	
G	142	778	.026
C	0	22	
1053C<T			
CC	21	254	<.001
CT	33	121	
TT	18	21	
C	75	629	<.001
T	69	163	

Note: *p* value from statistical test: Fisher's exact.

TABLE 5 Regression analysis of factors associated with the type of slow metabolizer NAT2.

Characteristics	Bivariate analysis		
	RP	IC 95%	*p*
Population			
Mestizos	Ref.		
Natives	0.93	0.71–1.22	.602
Gender			
Natives			
Female	Ref.		
Male	0.76	0.43–1.35	.345
Mestizos			
Female	Ref.		
Male	1.08	0.88–1.32	.466
282C>T			
Natives			
CC	Ref.		
CT	0.83	0.53–1.30	.421
TT	0.12	0.03–0.48	.003
Mestizos			
CC	Ref.		
CT	1.91	1.43–2.56	<.001
TT	2.62	1.95–3.52	<.001
341T>C			
Natives			
TT	Ref.		
TC	14.00	4.67–41.98	<.001
CC	14.00	4.67–41.98	<.001
Mestizos			
TT	Ref.		
TC	1.81	1.45–2.25	<.001
CC	2.81	2.33–3.39	<.001
481C>T			
Natives			
CC	Ref.		
CT	14.00	4.67–41.98	<.001
TT	14.00	4.67–41.98	<.001
Mestizo			
CC	Ref.		
CT	1.88	1.47–2.42	<0.001
TT	2.48	1.95–3.16	<.001
590G>A			
Natives			
GG	Ref.		
GA	2.50	1.85–3.37	<.001
AA	2.50	1.85–3.37	<.001
Mestizo			
GG	Ref.		
GA	1.54	1.24–1.91	<.001
AA	2.43	2.12–2.78	<.001
830A>G			
Natives			
AA	Ref.		
AG	14.00	4.67–41.98	<.001
GG	14.00	4.67–41.98	<.001
Mestizos			
AA	Ref.		
AG	1.01	0.76–1.34	<.932
GG	1.68	1.38–2.06	<.001

Note: *p* value from statistical test: Poisson regression.

Peruvian populations. In the case of the mestizo population, the C1/C1 genotype is the most frequent (63%) in native population, the C1/C2 genotype is the most frequent (45.8%). The two populations were not significantly different in terms of the gender variable (*p*: .14). Nevertheless, the *NAT2* and *CYP2E1* profiles were significantly different between the two populations ($p < .001$). This difference was evident in the distribution of haplotypes and alleles. For example, the *NAT25G* haplotype was more frequent in the mestizo population, while the *NAT213A* haplotype was more frequent in the native Peruvian population. Similarly, the *282T SNP was more frequent in the mestizo population, while the *282C SNP was more frequent in the native Peruvian population. These findings suggest that there are genetic differences in the *NAT2* and *CYP2E1* genes between the mestizo and native Peruvian populations.

Comparing the participants from the native and mestizo population, we observed statistically significant differences between the genotypes and allele frequencies of the SNPs *NAT2* 282C>T, 481C>T, 590G>A and the SNP *CYP2E1* 1053 C>T. No significant differences were observed in the other *NAT2* SNPs and the CYP2E1 3739G>C SNP (Table 4).

Overall regression analyses revealed the presence of *NAT2* slow metabolizer type was associated with different exposure factors. Among mestizo participants, non-reference-type genotypes reported a higher prevalence than reference-type genotypes at SNPs 282C>T, 341T>C, 481C>T, 590G>A and this difference was statistically significant ($p > .001$). On the other hand, native participants depicted higher frequencies of non-reference genotypes than reference-type genotypes at the SNPs, 341T>C, 481C>T, 590G>A, and 830A>G, and this difference was statistically significant ($p > .001$). No statistically significant differences were reported between the mestizo and native population and gender with respect to the presence of slow metabolizer *NAT2* (Table 5).

In Poisson-type logistic regression model, the presence of C1/C2 and C2/C2 genotype in *CYP2E1* was associated with different exposure factors (Table 6). Statistically significant differences were

TABLE 6 Regression analysis of associated factors for the non C1/C1 phenotype in CYP2E1.

	Bivariate analysis		
Characteristics	**RP**	**IC 95%**	***p***
Population			
Mestizos	Ref.		
Natives	1.94	1.59–2.36	<.001
Gender			
Natives			
Female	Ref.		
Male	0.93	0.70–1.24	.625
Mestizos			
Female	Ref.		
Male	0.99	0.76–1.29	.950
3739G>C			
Mestizos			
GG	Ref.		
GC	0.85	0.41–1.78	.668
CC	0.91	0.18–4.53	.905
1053C>T			
Natives			
GG	Ref.		
GC	9310.42	6053.42–10615.04	<.001
CC	9310.42	6053.42–10615.04	<.001
Mestizos			
GG	Ref.		
GC	7512.01	6647.54–8495.73	<.001
CC	7512.01	6647.54–8495.73	<.001

Note: *p* value from statistical test: Poisson regression.

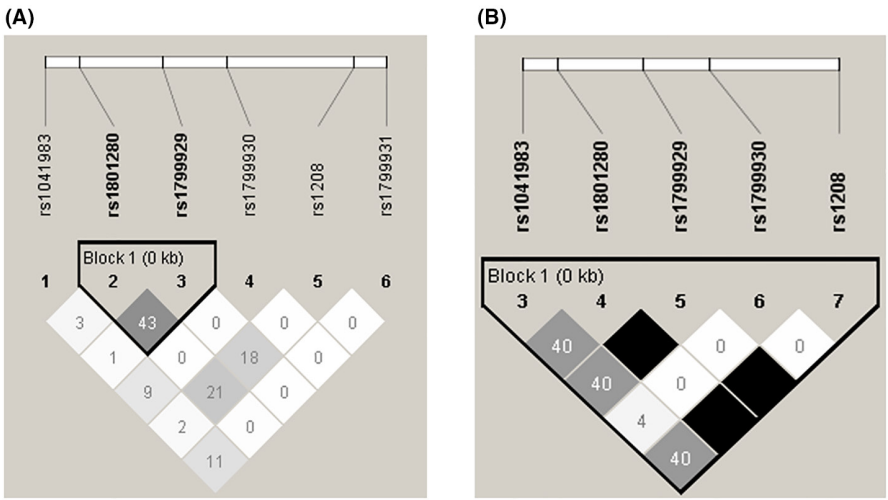

FIGURE 1 Linkage disequilibrium for SNPs associated with metabolizer *NAT2*. (A) Mestizo population (B) Native population. For the mestizo population, a block of 140 bp of genomic distance between SNPs rs1801280 and rs1799929 was detected. For the native population, a block of 520 bp of genomic distance was detected between the SNPs rs1041983, rs1801280, rs1799929, rs1899930 and rs1208.

reported between the native and mestizo population (RP = 1.94, $p > .001$). Within the mestizo and native participants, the non-reference genotypes reported a higher prevalence than the reference genotypes in the SNP 1053C>T and this difference was statistically significant ($p > .001$). No statistically significant differences were reported between gender and SNP 3739G>C with respect to the presence of slow metabolizer *CYP2E1*.

Since they presented more than one variant in the genotyping, the linkage disequilibrium of the *NAT2* SNPs was estimated. For the mestizo population, a block of 140 bp of genomic distance between

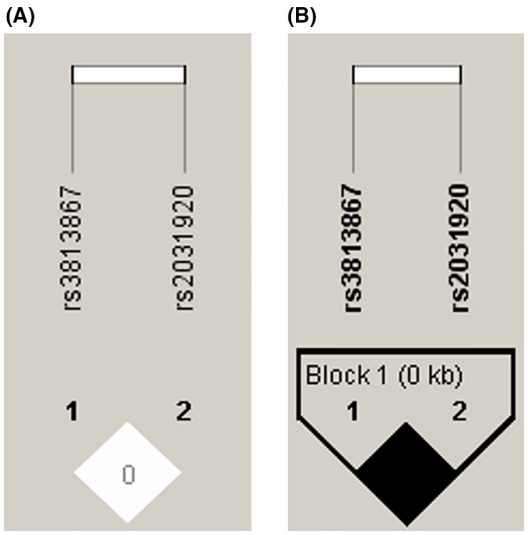

FIGURE 2 Linkage disequilibrium for SNPs associated with metabolizer *CYP2E1*. (A) Mestizo population (B) Native population for the mestizo population, a block was not detected between SNPs rs3813867 and rs2031920 by the solid spine method. For the native population, a block of 240 bp of genomic distance was detected between the SNPs rs3813867 and rs2031920.

SNPs rs1801280 and rs1799929 was detected (Figure 1A). For the native population, a block of 520 bp of genomic distance was detected between the SNPs rs1041983, rs1801280, rs1799929, rs1899930 and rs1208 (Figure 1B).

Linkage disequilibrium of *CYP2E1* SNPs was also estimated. For the mestizo population, a block was not detected between SNPs rs1801280 and rs1799929 by the solid spine method (Figure 2A). For the native population, a block of 240 bp of genomic distance was detected between the SNPs rs1801280 and rs1799929 (Figure 2B).

4 | DISCUSSION

We investigated the prevalence of NAT2 and CYP2E1 genotypes in 72 native and 400 mestizo participants from Peru. The results showed similar prevalence of the NAT2 slow metabolizer phenotype in the native population (48.8%) than in the mestizo population (49.3%). On the other hand, the prevalence of the CYP2E1 C1/C1 phenotype was high in the mestizo population (63.5%) than in the native population (29.2%).

The higher prevalence of the CYP2E1 C1/C2 or C2/C2 phenotype in the native population is likely due to the high incidence rates of tuberculosis, childhood malnutrition, and intestinal parasite infection, together with the precarious living conditions that are commonly observed in native populations in southern Peru. Peruvian natives are considered as distinct populations from other populations in Peru and in other parts of the world, not only due to ethnic, environmental and cultural aspects but also in terms of genetic diversity.[12]

Currently, it is recognized that genetic polymorphisms influence the metabolism of drugs used in the treatment of tuberculosis and are a risk factor for hepatotoxicity.[25] The relationship between an individual metabolization profile, based on SNPs of the *NAT2* gene, and the efficacy or toxicity of isoniazid in the body has already been established. Ohno et al.[26] demonstrated that people with a slow metabolizer profile are at increased risk of developing isoniazid-induced hepatotoxicity.[27] Other studies have suggested that lowering the standard dose in patients with a slow *NAT2* metabolizer profile could reduce adverse reactions during tuberculosis treatment.[28,29] On the other hand, some authors have proposed that increasing the standard dose in patients with a rapid NAT2 metabolizer profile may contribute to an optimal drug level that would result in more effective treatment.[17,30]

Among the SNPs already described within the *NAT2* coding region, the six most frequent SNPs in the world were identified in our sample: 341T>C, 590G>A and 857G>A related to the slow metabolizer profile, while that 282C>T, 481 C>T and 803 A>G do not alter the metabolizer phenotype.[31] The SNPs 341T>C and 481C>T were those observed within those that reported the highest frequency in the Peruvian native and mestizo population and are also found in high frequencies among Europeans. Thus, when we compared native and mestizo participants, we found a higher frequency of these two SNPs in mixed race participants. We also observed a difference in the 282C>T variant between the two groups of participants, with higher frequencies in the natives.

According to our findings, it is revealed that there is a difference in the metabolization profiles in the *NAT2* gene in the Peruvian population, which reveals the importance of considering pharmacogenetic schemes in therapy against diseases such as tuberculosis.[6,16]

According to Watanabe et al.,[32] the -1053C>T polymorphism of the CYP2E1 gene is located in a transcription regulation region, linked to gene expression. Studies that have evaluated the association of these polymorphisms with hepatotoxicity induced by antituberculosis drugs have shown contradictory results. Lee et al.[33] verified that the presence of the C1/C1 genotype would be a risk factor for developing isoniazid-induced hepatotoxicity, while other studies have reported conflicting results.[3] Our results showed an association between the type of population and the no C1/C1 T phenotype for *CYP2E1*.

Our findings suggest that there are differences in the NAT2 and CYP2E1 genotypes between the native and mestizo populations in Peru that is correlated with clinical reports about toxicity and treatment failure in Peruvian populations.[34–36] These differences could have implications for the risk of hepatotoxicity associated with the use of antituberculosis drugs. Further studies are needed to confirm our findings and to investigate the clinical implications of these genetic differences.

5 | CONCLUSION

Although our study results provide valuable insights into the frequency of metabolizing genotypes for anti-TB drugs in Peru, particularly among native populations, a deeper understanding of the

factors associated with these genotypes is needed. Longitudinal studies including large samples have revealed that genetic polymorphisms play an important role in drug metabolism. Despite the limitations of a secondary study, our findings suggest that the type of Peruvian native and mestizo population is associated with the metabolizing profile and *NAT2* and *CYP2E* alleles, as reported by prevalence ratio.

AUTHOR CONTRIBUTIONS

Study design: LJ-V. Performed the experiments: LJ-V, Analyzed the data: LJ-V, KSL, DDT, SC, CS, JAP, ET-S, HG. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, LJ-V, upon reasonable request.

ETHICAL COMPLIANCE

Our study was approved by the Ethics in Research Committee of the Peruvian National Institute of Health. Written informed consent was obtained from all the participant.

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