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ORIGINAL ARTICLE

Allelic and genotypic frequencies of *NAT2*, *CYP2E1*, and *AADAC* genes in a cohort of Peruvian tuberculosis patients

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Abstract

Background: We determined the frequency of genetic polymorphisms in three anti-TB drug metabolic proteins previously reported: *N*-acetyltransferase 2 (*NAT2*), cytochrome P450 2E1 (*CYP2E1*), and arylacetamide deacetylase (*AADAC*) within a Peruvian population in a cohort of TB patients.

Methods: We genotyped SNPs rs1041983, rs1801280, rs1799929, rs1799930, rs1208, and rs1799931 for *NAT2*; rs3813867 and rs2031920 for *CYP2E1*; and rs1803155 for *AADAC* in 395 participants completed their antituberculosis treatment.

Results: Seventy-four percent of the participants are carriers of slow metabolizer genotypes: *NAT2*5*, *NAT2*6*, and *NAT2*7*, which increase the sensitivity of INH at low doses and increase the risk of drug-induced liver injuries. Sixty-four percent are homozygous for the wild-type *CYP2E1*1A* allele, which could increase the risk of hepatotoxicity. However, 16% had a *NAT2* fast metabolizer phenotype which could increase the risk of acquiring resistance to INH, thereby increasing the risk of multidrug-resistant (MDR) or treatment failure. The frequency of rs1803155 (*AADAC*2* allele) was higher (99.9%) in Peruvians than in European American, African American, Japanese, and Korean populations.

Conclusions: This high prevalence of slow metabolizers for isoniazid in the Peruvian population should be further studied and considered to help individualize drug regimens, especially in countries with a great genetic diversity like Peru. These data will help the Peruvian National Tuberculosis Control Program develop new strategies for therapies.

KEYWORDS

AADAC, *CYP2E1*, *NAT2*, tuberculosis

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1 | BACKGROUND

Tuberculosis (TB) continues to be a leading cause of global morbidity and mortality, with about 10 million cases and a total of 1.2 million deaths reported in 2019 ("WHO | Global Tuberculosis Report 2019," 2020). Even though the current TB regimen is highly effective under optimal conditions, there are still many undefined issues including drug underexposure, high prevalence if drug-related toxicity, selection of resistant strains and variability of response (Motta et al., 2018), which could be explained by the variability in the pharmacokinetics of anti-TB drugs. Mutations or polymorphisms in genes encoding metabolic enzymes, transporters, or carries can lead to this variability in drug pharmacokinetics and pharmacodynamics. The identification of these genetic variations could help select the right anti-TB drug, with the right dosage increasing efficacy and reducing drug-related toxicity and preventing drug resistance (Figueiredo Teixeira et al., 2013; Motta et al., 2018).

To determine if genetic variabilities affecting drug response were present in the Peruvian population, which has a high TB burden with an estimated 32,970 cases in 2019 ("WHO | Global Tuberculosis Report 2019," 2020), including a high prevalence of drug-resistant TB cases, we determined the frequency of genetic polymorphisms in three anti-TB drug metabolic proteins previously reported: *N*-acetyltransferase 2 (*NAT2*) (OMIM # 612182), cytochrome P450 2E1 (*CYP2E1*) (OMIM # 124040), and arylacetamide deacetylase (*AADAC*) (OMIM # 600338) (Guio et al.,). These three proteins participate in the metabolism of the initial phase anti-TB drugs: isoniazid and rifampicin. In the liver, isoniazid is acetylated to its major metabolite, *N*-acetyl-isoniazid by the action of *NAT2*. It is then further deactivated by other enzymes including *CYP2E1* (Bao et al., 2018; Sotsuka et al., 2011). Thus, genetic variations in these two enzymes, leading to alterations in their enzymatic functions can cause variations in isoniazid pharmacokinetics. *AADAC* is one of the few known enzymes responsible for the deacetylation of rifampicin and *AADAC* allele decreased enzyme activity (Lee et al., 2019; Nakajima et al., 2011). Thus, genetic variations in these three enzymes, leading to alterations in their enzymatic functions could cause variations in isoniazid and rifampicin pharmacokinetics. For the present study, we selected previously reported single nucleotide polymorphisms (SNPs) that could alter *NAT2*, *CYP2E1*, and *AADAC* enzyme activity and determine their frequency within a Peruvian population in a cohort of TB patients.

2 | PATIENTS AND METHODS

2.1 | Studied populations

Our study includes 395 unrelated individuals diagnosed with pulmonary tuberculosis between 2014 and 2015 recruited from health establishments of the Minister of Health (MINSA) located in Lima and Callao, Peru. The 395 participants (217 males and 178 females) completed their antituberculosis treatment.

2.2 | Genotyping of *NAT2*, *CYP2E1*, and *AADAC*

Genomic DNA was extracted from peripheral blood of all 395 participants using the genomic DNA extraction kit QIAamp DNA Blood Mini Kit (Qiagen). 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; for *AADAC*: rs1803155). These regions were amplified by the PCR using Platinum Taq DNA polymerase kit (Invitrogen, USA) using the following primers: For *NAT2*: 5′-GTCACACGAGGAAATCAAATGCT-3 and 5′-CGTGAGGGTAGAGAGGATATCTG-3′; for *CYP2E1*: 5′-CCGTGAGCCAGTCGAGTCTA-3′ and 5′-TTCATTCTGTCTTCTAACTGGCAA-3′; and for *AADAC*: 5'-TCATTCCTAGCAGAAAGGAGATT-3' and 5′-GCTCACATTTATTCTCTTGCATCG-3′. PCR-amplified fragments were purified using the QIAmp Gel Purification Kit (Qiagen). SNP genotyping on the purified fragments was performed using Sanger sequencing (Macrogen). Nucleotide substitutions were identified and analyzed using the Geneious version 9.1.5 (Biomatters Ltd.).

2.3 | Computational phenotyping for *NAT2*

Predicted phenotypes were determined from genotypes as three types of metabolizers: slow metabolizer (two slow alleles), rapid metabolizer (two rapid alleles), and intermediate metabolizer (one slow and another rapid acetylator allele). The alleles considered rapid were: wild-type *NAT2*∗4, 282C>T (*NAT2*∗13), 481C>T (*NAT2*∗11), and 803A>G (*NAT2*∗12), while the alleles considered slow were: 341T>C (*NAT2*∗5), 590G>A (*NAT2*∗6), 857G>A (*NAT2*∗7), and 191G>A (*NAT2*∗14) (Hein et al., 2000). The computational inferred phenotypes using a combination of *NAT2* SNPs for the 395 participants were determined using an online software program, NAT2PRED (nat2pred.rit.albany.edu) (Kuznetsov et al., 2009; Sabbagh et al., 2009).

2.4 | Statistical analysis

For phenotypic genotypic and allelic frequencies, 95% confidence intervals were calculated. Data analysis was carried out using Stata 15 program (StataCorp. 2016. Stata Statistical Software: Release 15. College Station, TX, USA).

3 | RESULTS

In this study, we determined the presence of the six most common SNPs, rs1041983 (282C>T), rs1801280 (341T>C), rs1799929 (481C>T), rs1799930 (590G>A), rs1208 (803A>G), and rs1799931 (857G>A), of the *NAT2* gene in the 395 individuals from Lima and Callao, Peru. No new SNPs were identified, indicating that the *NAT2* gene has no other SNPs in the Peruvian population studied. The allele frequencies of these major *NAT2* SNPs are represented in Table 1. This study found that *NAT2*∗13, C282T, is the most frequent genetic variant (~40% of alleles) among our samples. The allele not harboring any mutation (wild-type *NAT2*∗4) was present in 44 of the 395 samples (~11% of alleles). Table 2 shows the frequencies of *NAT2* genotype obtained from the studied population. The most frequent observed heterozygote was also *NAT2*∗13 C282T (48.6%), followed by *NAT2*∗11 C481T (34.9%) and *NAT2*∗5 T341C (34.7%) among the Peruvian population studied. The lowest frequency of observed heterozygote genotypes was *NAT2*∗12 A803G with a frequency of 18.7%. In homozygote, the *NAT2*∗12 803A>G (31.2%) genotype was the most common one but the lowest homozygote among them was *NAT2*∗6 590G>A (12.5%). The linkage disequilibrium (LD) analysis is shown in Figure 1. The six *NAT2* variants, 282C>T, 341T>C, 481C>T, 590G>A, 803A>G, and 857G>A were applied to Haploview software. The LD for each pair of genetic variants was measured using |D′ | and correlation coefficient (r2 > 0:8). A haplotype block was found in the following SNP positions 341T>C and 481C>T (D′: 0.808 and r^2: 0.437) in Peruvian population samples which is identified as like strong LD. There were no significant differences observed between *NAT2* genotypes with respect to age and gender. The *NAT2* inferred metabolizing status was predicted using the six SNPs analyzed as stated above. As a result, the predicted metabolizing phenotype of fast, intermediate, and slow metabolizers was 14.9%, 38.2%, and 46.8%, respectively (Table 3).

The allelic and genotypic distribution of the rs2031920 (−1053C>T) variant of *CYP2E1* among the studied population is shown in Tables 1 and 2, respectively. The results show an allele frequency of ~21% for the *CYP2E1* variant, and ~79% for the wild-type allele. The observed genotype frequency of the homozygous and heterozygotes were ~7% and ~36%, respectively.

We also analyzed the allele and genotype frequency of the rs1803155 SNP of the *AADAC* gene in the 395 individuals of this study (Tables 1 and 2). According to our results, the *AADAC* genetic variant has an allele frequency of ~99.9%, while the wild-type allele was ~20%. The homozygous and heterozygous genotype distribution were ~85% and ~10%, respectively.

4 | DISCUSSION

Studies in different populations have shown ethnic variabilities in both *NAT2* and *CYP2E1* genotypes and phenotypes. There is still limited information about the genetic variations in the Peruvian population. In the current study, we analyzed *NAT2*, *CYP2E1*, and *AADAC* genotypes and allele frequencies in 395 individuals from Peru. As stated above, *NAT2* and *CYP2E1* are two essential enzymes in the metabolism of INH. Altered *NAT2* and/or *CYP2E1* activities due to polymorphic genotypes can result in (a) the accumulation of toxic substances in the liver, and (b) variations in INH plasma concentrations that can affect the efficacy of the drug.

In the analysis of the *NAT2* gene, the results showed that *NAT2*13* (39.7% of alleles) and *NAT2*7* (35.6% of alleles) were the most frequent genetic variants amount the

TABLE 1 Allele frequencies of *NAT2*, *CYP2E1*, and *AADAC* polymorphisms in a Peruvian population ($n = 395$)

Gene	Allele (Haplotype)	SNP	Position	Substituted amino acid	Allele frequency (95% CI)
NAT2	*NAT2*4*			Wild-type	0.111 (0.089–0.134)
	*NAT2*13*	rs1041983	c.282C>T	Y94Y	0.397 (0.363–0.432)
	*NAT2*5*	rs1801280	c.341T>C	I114T	0.247 (0.216–0.278)
	*NAT2*11*	rs1799929	c.481C>T	L161L	0.329 (0.296–0.363)
	*NAT2*6*	rs1799930	c.590G>A	R197Q	0.138 (0.113–0.163)
	*NAT2*12*	rs1208	c.803A>G	R268K	0.228 (0.198–0.258)
	*NAT2*7*	rs1799931	c.857G>A	G286E	0.356 (0.322–0.390)
CYP2E1	*CYP2E1*1A*			Wild-type	0.79359 (0.765–0.823)
	*CYP2E1*5B*	rs2031920	c.-1053C>T		0.206 (0.177–0.235)
AADAC	*AADAC*1*			Wild-type	0.199 (0.167–0.230)
	*AADAC*2*	rs1803155	c.841G>A	V281I	0.999 (0.967–1.03)

TABLE 2 Genotype frequency of *NAT2*, *CYP2E1*, and *AADAC* genes in a Peruvian population ($n = 395$)

Gene	Allele	Wild-type frequency (proportion, 95% CI)	Heterozygote frequency (proportion, 95% CI)	Homozygote frequency (proportion, 95% CI)
NAT2	NAT2*13 (C282T)	C/C: 142 (0.359, 0.312–0.407)	C/T: 192 (0.486, 0.437–0.535)	T/T: 61 (0.154, 0.119–0.190)
	NAT2*5 (T341C)	T/T: 229 (0.580, 0.531–0.628)	T/C: 137 (0.347, 0.300–0.394)	C/C: 29 (0.073, 0.048–0.099)
	NAT2*11 (C481T)	C/C: 196 (0.496, 0.447–0.546)	C/T: 138 (0.349, 0.302–0.396)	T/T: 61 (0.154, 0.119–0.190)
	NAT2*6 (G590A)	G/G: 303 (0.767, 0.725–0.809)	G/A: 75 (0.190, 0.151–0.229)	A/A: 17 (0.043, 0.023–0.063)
	NAT2*12 (A803G)	A/A: 268 (0.678, 0.632–0.725)	A/G: 74 (0.187, 0.149–0.226)	G/G: 53 (0.134, 0.101–0.168)
	NAT2*7 (G857A)	G/G: 210 (0.532, 0.482–0.581)	G/A: 89 (0.225, 0.184–0.267)	A/A: 96 (0.243, 0.201–0.285)
CYP2E1	*CYP2E1*5B(C−1053T)	C/C: 250 (0.641, 0.594–0.688)	C/T: 119 (0.359, 0.312–0.406)	T/T: 21 (0.076, 0.032–0.076)
AADAC	*AADAC*2 (G841A)	G/G: 19 (0.048, 0.027–0.069)	G/A: 41 (0.104, 0.074–0.134)	A/A: 335 (0.848, 0.813–0.883)

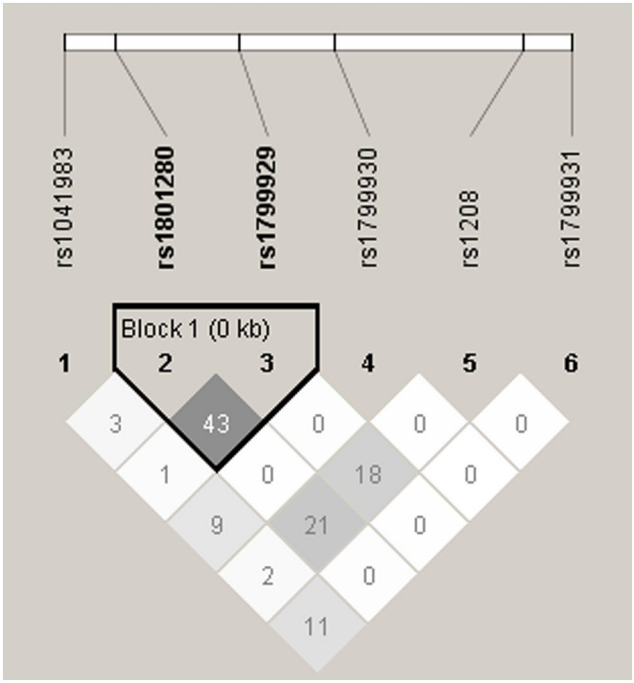

FIGURE 1 Linkage disequilibrium for *NAT2* metabolizer-associated SNPs in Peruvian population studied

TABLE 4 Distribution of *NAT2* alleles among the Peruvian population studied compared with various human population

Population	Peru (current study)	Brazil (2016)	Mexico (2012)	Spain (2011)
*NAT2*4 (Wild-type)	0.111	0.258	0.306	0.186
*NAT2*13 (C282T)	0.099	0.008	0.008	—
*NAT2*5 (T341C)	0.420	0.446	0.312	0.417
*NAT2*11 (C481T)	0.035	—	—	—
*NAT2*6 (G590A)	0.099	0.150	0.174	0.292
*NAT2*12 (A803G)	0.013	0.023	0.048	—
*NAT2*7 (G857A)	0.223	0.096	0.140	0.106

alleles was *NAT2*5* (Table 4). It is established that the frequency of *NAT2*5* in European populations is ~50%, in African populations is ~33% to 42% and in Asian populations is ~5% (Borlak & Reamon-Buettner, 2006; Cascorbi et al., 1995; Sekine et al., 2001; Tiis et al., 2020). According to our results, the allele frequency of *NAT2*5* is ~25%. The other two slow metabolizer alleles are *NAT2*6* and *NAT2*7*. The *NAT2*6* is common in all populations mentioned above with a frequency of ~30%. Conversely, the frequency of *NAT2*7*

Gene	Metabolizing phenotype[a] proportion (95% CI)		
NAT2	Fast	Intermediate	Slow
	0.149 (0.114–0.185)	0.382 (0.334–0.430)	0.468 (0.419–0.518)

TABLE 3 Predicted metabolizing phenotype for *NAT2* in a Peruvian population ($n = 395$)

[a]The metabolizing phenotype was determined using the online software http://nat2pred.rit.albany.edu/.

population studied. *NAT2*13* is a silent mutation, Y94Y, that does not alter the metabolizer phenotype, whereas *NAT2*7* results in an amino acid substitution, G286E, that leads to a significant decrease in the enzyme's activity (Lakkakula et al., 2014; Vatsis et al., 1991). The distribution of the *NAT2* polymorphisms in the population studied were similar to other American populations in that one of the most frequent is low in European populations (~2%) and African populations (~3% to 6%). In Asian populations, the frequency of *NAT2*7* is ~10% to 12% (Tiis et al., 2020). Diverging from these reports, in our studied population the allele frequency of *NAT2*6* is ~14% and of *NAT2*7* is ~36%. As stated above, reduced *NAT2* activity, which is observed in *NAT2*7* variants, can lead to adverse drug reactions due to increased

accumulation of toxic metabolites. Additionally, our study revealed that the genotype frequency (predicted phenotype) of slow metabolizers is ~47%. The relationship of *NAT2* polymorphisms with INH-induced hepatotoxicity in TB patients among different populations were studied (Azuma et al., 2013; Borlak & Reamon-Buettner, 2006; Cascorbi et al., 1995; Ganachari et al., 2010; Huerta-García et al., 2020; Sekine et al., 2001; Tiis et al., 2020; Zahra et al., 2020), but the previously published studies have demonstrated inconsistent results. Therefore, analysis of the slow genotypes should become part of the dosage regimen of INH in TB patients undergoing anti-TB treatment to prevent drug-induced liver injuries (Azuma et al., 2013; Ganachari et al., 2010; Huerta-García et al., 2020; Zahra et al., 2020).

After *NAT2* acetylates INH converting it to acetyl-INH, it can enter the *CYP2E1* pathway, which couples with the glutathione-*S*-transferase (GST) metabolic pathway to facilitate the elimination of toxic metabolites (Guio, Levano, Sánchez, et al., ; Singla et al., 2014; Teixeira et al., 2011). Studies have shown that individuals with the *CYP2E1* wild-type allele (c1/c1 genotype) have a higher *CYP2E1* activity that those with *CYP2E1*5B* allele (c1/c2 or c2/c2 genotype). Thus, these individuals can generate more hepatotoxins and therefore increase the risk of drug-induced liver injuries (Huang et al., 2003; Singla et al., 2014; Vuilleumier et al., 2006). In our studied population, the allele frequency of the *CYP2E1*5B* is ~79%, which increases the risk of hepatotoxicity specially in patients with a slow metabolizer phenotype for *NAT2* (Guaoua et al., 2014; Singla et al., 2014).

An important enzyme in the metabolism of RIF is *AADAC* catalyzing its deacetylation to 25-deacetyl-RIF (Nakajima et al., 2011; Png et al., 2012; Thomas et al., 2020). Polymorphic variations affecting this enzyme's activity can also result in the accumulation of toxic substances and variations in RIF plasma concentrations that can affect the efficacy of this drug. In this study, we analyzed the nonsynonymous SNP rs1803155 (*AADAC**2 allele), which leads to a change in amino acid (V281I) in the coding region (Shimizu et al., 2012). An allele frequency of ~60% for *AADAC*2* has been reported in European American, African American, Japanese, and Korean populations. In our studied population, the allele frequency of *AADAC*2* is ~99.9%. A limitation in this study is the number of SNPs analyzed in each gene, especially in *AADAC*. The analysis of additional genetic variations in *AADAC* can provide additional information in the metabolism of RIF. For example, the allele *AADAC**3 (g.13651G>A/g.14008T>C), not analyzed in the current study, has shown a reduced metabolizing activity for RIF (Shimizu et al., 2012). Additionally, studies have reported genetic polymorphisms in other RIF metabolizing enzymes, including carboxylesterase 1(CES1) (OMIM # 114835) and carboxylesterase 2 (CES2) (OMIM # 605278) (Sloan et al., 2017), as well as in drug transporters and /or their transcriptional regulators, including SLCO1B1 (OMIM # 604843) (Yang et al., 2019) and ABCB1 (OMIM # 171050) (Pontual et al., 2017).

Countries have begun clinical trials focused on personalization of tuberculosis treatment to reduce the consequences for patients in treatment (Huerta-García et al., 2020; Yoo et al., 2020). In countries like Peru, where high rates of tuberculosis are recorded and therefore more people in treatment, the pharmacogenomics of individuals becomes a crucial tool for an optimum tuberculosis treatment. This review highlights the importance of having pharmacogenomic studies and having the identification of polymorphisms associated to the metabolism of the antituberculosis drugs in our Peruvian population. Future studies should evaluate adverse effects such as hepatotoxicity and treatment failure.

5 | CONCLUSION

In conclusion, our study showed the distribution of *NAT2*, *CYP2E1*, and *AADAC* genetic polymorphisms in a Peruvian population diagnosed with tuberculosis. This is a preliminary study to help understand the genetic basis of metabolizing polymorphisms in our population, and thus contribute to the use of this and future data in determining the safe INH and RIF dose in slow and fast metabolizers and thus minimizing adverse drug reactions. According to our results, ~74% of the participants are carriers of slow metabolizer genotypes: *NAT2*5*, *NAT2*6*, and *NAT2*7*, which increase the sensitivity of INH at low doses and increase the risk of drug-induced liver injuries. Additionally, ~64% are homozygous for the wild-type *CYP2E1**1A allele, which could increase the risk of hepatotoxicity. This high prevalence of slow metabolizers for isoniazid in the Peruvian population should be further studied and considered to help individualize drug regimens, especially in countries with a great genetic diversity like Peru. However, 16% had a *NAT2* fast metabolizer phenotype which could increase the risk of acquiring resistance to INH, thereby increasing the risk of multidrug-resistant (MDR) or treatment failure. The frequency of rs1803155 (*AADAC**2 allele) was higher (99.9%) in Peruvians than in European American, African American, Japanese, and Korean populations. These data will help the Peruvian National Tuberculosis Control Program develop new strategies for therapies, and in addition, these data are of worldwide interest to identify the distribution of genotypes and allelic frequencies related to the enzymes that participate in the metabolism of antituberculosis drugs.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

Study design: LK, TD, SC, VLT, SL, MTA, SA, RC, and GH. Performed the experiments: LK, JVL, TD, CS, and SCR. Analyzed the data: LK, JVL, TD, VLT, and ZCR. Contributed materials/analysis tools: SC, SL, MTA, SA, RC, and GH. All authors have read and approved the final manuscript.

ETHICAL APPROVAL

Our study was approved by the Ethics in Research Committee of the Peruvian National Institute of Health (INS), and written informed consent was obtained from all the participants.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study could be obtained from the authors upon reasonable requirements.

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