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“Diversidad genética mundial de NAT2: Una revisión sistemática”

Tesis que presenta:

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DEDICATORIA

A mis padres, por todo su esfuerzo, dedicación, sacrificio, enseñanzas, por su apoyo incondicional a lo largo de toda mi vida, por darme la oportunidad y el empuje para superarme día a día. Por ser los mejores padres que pude haber tenido, es a ellos a quien dedico no solo esta tesis, sino que también todos mis logros actuales y los que están porvenir, porque todo lo que soy, se lo debo a ellos.

RESUMEN

La *N*-acetiltransferasa de arilamina 2 (NAT2) es una enzima altamente polimórfica que participa en el metabolismo de una amplia gama de fármacos y xenobióticos. Variaciones genéticas en NAT2 han sido asociadas con la susceptibilidad a enfermedades complejas. Sin embargo, la intrincada diversidad de NAT2 no ha sido ampliamente descrita, subrepresentando áreas geográficas y poblaciones. Una exhaustiva revisión sistemática (1052 artículos) fue llevada a cabo con estricto control de calidad con la finalidad de ampliar el panorama de diversidad mundial de *NAT2*. Nuestros resultados muestran los patrones de diversidad de 60,888 individuos (122 poblaciones), a partir de los cuales se obtuvieron las frecuencias de los ocho polimorfismos más reportados. Distribuciones similares del alelo ancestral se observaron en los SNPs rs1801279, rs1041983 y rs1799930. Las poblaciones del Este de Asia y las Nativas Americanas presentaron las mayores frecuencias del alelo ancestral en los SNPs rs1801280 (T; rango: 0.60-0.99), rs1799929 (C; rango: 0.91-0.99) y rs1208 (A; rango:0.90-0.98). Los SNPs rs1799931 y rs1495741 mostraron dos panoramas de distribución muy diferentes (poblaciones con altas frecuencias del alelo ancestral (rango:0.55-0.99) y poblaciones con presencia considerable del alelo derivado (rango:0.05-0.79). Por lo que respecta a los estados de acetilación, el fenotipo lento fue el más común (f = 0.44), siendo las poblaciones africanas, europeas y Medio Orientales las que presentaron las mayores frecuencias (rango: 0.48-0.79). El fenotipo rápido se presentó mayoritariamente en las poblaciones del Este de Asia y Nativas Americanas (rango: 0.25-0.53). Nuestros hallazgos expandieron el panorama de diversidad de NAT2 en las poblaciones mundiales y refuerzan los datos reportados por el Proyecto 1000 Genomas, además de representar la diversidad de las poblaciones de África Subsahariana, Norte de África, Medio Oriente y poblaciones subrepresentadas de Asia y Europa.

ABSTRACT

Arylamine N-acetyltransferase 2 (NAT2) is a highly polymorphic enzyme participating in the metabolism of a wide range of drugs and xenobiotics. Despite its clinical relevance, the *NAT2* striking diversity has not been thoroughly examined, under-representing geographic areas and ethnic groups. An exhaustive systematic review (1052 articles) with strict quality control was conducted to broaden the NAT2 diversity landscape. The allele frequencies of eight polymorphisms in 60,888 individuals from 122 populations were obtained. Our findings depicted similar distribution patterns of the ancestral allele in the SNPs rs1801279, rs1041983 and rs1799930. The East Asian and Native American populations presented the highest frequencies of the ancestral allele in the SNPs rs1801280 (T; range: 0.60-0.99), rs1799929 (C; range: 0.91-0.99) and rs1208 (A; range: 0.90-0.98). The SNPs rs1799931 and rs1495741 exhibited two different scenarios: populations with high frequencies of the ancestral allele (range:0.55-0.99) and populations with considerable presence of the derived allele (range:0.05-0.79). Regarding the acetylation status, the slow phenotype was the most common (f = 0.44); the African, European, and Middle Eastern populations presented the highest frequencies (range: 0.48-0.79). The rapid phenotype occurred mainly in East Asians and Native Americans (range: 0.25-0.53). The results reported herein expanded the landscape of NAT2 diversity in global populations, reinforcing those data reported in the 1000 Genomes Project. Furthermore, our findings included the diversity of underrepresented populations such as Sub-Saharan and North Africa, the Middle East, and populations from Asia and Europe.

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1. INTRODUCCIÓN

La *N*-acetiltransferasa de arilamina 2 (NAT2) es una enzima de fase II encargada de metabolizar aminas aromáticas heterocíclicas (HAAs) y algunos fármacos como las sulfonamidas e hidralazina (Sim et al., 2014). Las HAAs han sido categorizadas como carcinógenos de clase 2A con un impacto considerable en las poblaciones humanas (IARC, 1993). Este tipo de carcinógenos no tienen una actividad mutagénica directa, requiriendo de enzimas metabólicas para su activación (Kabir et al., 2010). Así, NAT2 promueve la formación de metabolitos reactivos capaces de formar aductos (*v.gr.:* N-acetoxiésteres) con el ácido desoxirribonucleico (DNA), pudiendo iniciar un proceso mutacional en el que una reparación inadecuada podría conducir a la formación de tumores (Turesky et al., 2009; Rajalakshmi et al., 2015). NAT2 también participa en el metabolismo y la eliminación de fármacos mediante el proceso de acetilación, durante la cual, NAT2 cataliza la transferencia de un grupo acetil coenzima A a fármacos y sustancias químicas que en su estructura posean aminas aromáticas, aminas heterocíclicas o hidrazina (Flockhart and Desta, 2009). Sin embargo, la velocidad con la que esto se lleva a cabo depende del fenotipo de acetilación de cada individuo, el que puede ser rápido, intermedio o lento. Dicho estado de acetilación se determina mediante una prueba de cafeína, en la que se precisa la concentración de sus metabolitos (en µM) en orina: 5-acetilamino-6-formilamino-3-metiluracilo (AFMU) y 1-metilxantina (1X). La relación entre ellos permite distinguir el fenotipo; una relación menor o igual a 0.85 se asocia con el fenotipo lento, mientras que el fenotipo rápido/intermedio presenta una relación mayor a 0.85 (Birch et al., 2018).

Los polimorfismos de un solo nucleótido (SNPs) son cambios en al menos una base de la secuencia de DNA, los que se presentan como mínimo en el 1% de la población (Vignal et al., 2002). A la fecha, se han identificado al menos 43 polimorfismos tipo SNP en la región codificante de *NAT2* (Figura 1). Entre las variaciones más comunes se encuentran los cambios 191G>A (rs1801279), 282C>T (rs1041983), 341 T> C (rs1801280), 481 C>T (rs1799929), 590 G> A (rs1799930), 803 A> G (rs1208) y 857G>A (rs1799931) (Hein & Doll, 2012). La combinación entre éstos siete SNPs y otros más, de las 43 variantes reportadas, determinan el estado de acetilación, siendo el fenotipo rápido el estado ancestral (Sabbagh et al., 2011). Así, el estado de acetilación está determinado por el perfil genético individual. Aquellos individuos portadores de dos alelos de baja actividad son clasificados como acetiladores lentos, mientras que los individuos que portan dos alelos funcionales se consideran acetiladores rápidos; los portadores heterocigotos están relacionados a un fenotipo intermedio (Birch et al., 2018). Dado que estas variantes genéticas causan cambios en la secuencia de aminoácidos, los polimorfismos localizados en *NAT2* adquieren relevancia toxicológica, afectando la actividad de acetilación y consecuentemente la eficiencia de desintoxicación (Liu et al., 2015; Taja-Chayeb et al., 2012). En este sentido, el fenotipo lento, relacionado con la inactivación de aminas biógenas, como la histamina, las que deben ser convertidas en acetil histamina para su eliminación (Zielinska et al., 1997), parece contribuir al desarrollo de alergias y asma (Gawronska-Szklarz *et al.,*2001; Wang *et al.,* 2014) . Este fenotipo también se ha relacionado con el desarrollo de lupus eritematoso, infertilidad masculina y varios tipos de cáncer como el de vejiga y de mama, entre otros (El-Desoky et al., 2005; Nakamura et al., 2007; Santos et al., 2005; Nakamura et al., 2007; Kasajova et al., 2016; Santos et al., 2016; Trang et al., 2018). Por su parte, el fenotipo rápido (comúnmente

representando por la combinación de los fenotipos rápido + intermedio) ha sido relacionado con una mayor concentración de metabolitos reactivos, y con la subsecuente formación de aductos en el DNA, razón por la cual se ha asociado con el desarrollo de cáncer colorrectal y de próstata, entre otros (Huang et al., 2007; Rovito et al., 2005).

No obstante, estas asociaciones no han sido consistentes entre las poblaciones y, en algunos casos, los hallazgos han sido controversiales. A la luz de esta evidencia, el fenotipo lento de NAT2 parece contribuir al desarrollo de cáncer de mama en mujeres finlandesas, pero no ha mostrado resultados consistentes en mujeres eslovacas, tailandesas y turcas (Kasajova et al., 2016; Kocabaş et al., 2004; Sangrajrang et al., 2010; Sillanpää et al., 2005). Resultados similares se han observado en el cáncer de vejiga, en donde el fenotipo lento se ha relacionado con el desarrollo de esta patología en los egipcios; hallazgo que no han sido consistente en las poblaciones del norte de la India y España (El-Desoky et al., 2005; García-Closas et al., 2005; Mittal et al., 2004). Con respecto al papel de NAT2 en el desarrollo del asma, el fenotipo lento hasido relacionado con el desarrollo de este padecimiento en una población de Polonia, pero no enla población de Turquía (Nacak et al., 2002; Gawronska-Szklarz et al., 2001).

Tales ejemplos resaltan el impacto de la arquitectura genética poblacional en los resultados obtenidos. En este sentido, la diversidad de NAT2 ha mostrado patrones diversos entre las poblaciones mundiales e incluso a nivel inter-étnico (Mortensen et al., 2011). Lo anterior podría apuntar a que, en algunos casos, se podría estar relacionado al padecimiento con el fondo genético de la población, y que posiblemente no haya una contribución de ciertos alelos, genotipos, haplotipos y fenotipos al desarrollo de las diferentes patologías, conduciendo a asociaciones espurias (Greene et al., 2009). La presente revisión sistemática tuvo como objetivo

describir la diversidad de NAT2 en las poblaciones mundiales a nivel fenotípico y genético (alélico y haplotípico). Nuestros hallazgos podrían ser de utilidad en los estudios de índole farmacogenético y toxicogenético, en donde los patrones de frecuencias de algunas poblaciones podrían ser muy particulares. Por otro lado, nuestros resultados resaltan la sub-representación de algunas poblaciones como las africanas, Latinas y de Oceanía. Para el caso particular de México, los estudios son muy escasos, evidenciando la necesidad del estudio de poblaciones tanto Mestizas como Nativas Americanas.

2. REVISIÓN BIBLIOGRÁFICA

Worldwide genetic diversity of NAT2: Systematic Review

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Abstract

Arylamine N-acetyltransferase 2 (NAT2) is a highly polymorphic enzyme participating in the metabolism of a wide range of drugs and xenobiotics. Despite its clinical relevance, the *NAT2* striking diversity has not been thoroughly examined, under-representing geographic areas and ethnic groups. An exhaustive systematic review (1052 articles), with strict quality control, was conducted to broaden the NAT2 diversity landscape. The allele frequencies of eight polymorphisms in 60,888 individuals from 122 populations were obtained. Our findings depicted similar distribution patterns of the ancestral allele in the SNPs rs1801279, rs1041983 and rs1799930. The East Asian and Native American populations presented the highest frequencies of the ancestral allele in the SNPs rs1801280 (T; range: 0.60-0.99), rs1799929 (C; range: 0.91-0.99) and rs1208 (A; range: 0.90-0.98). The SNPs rs1799931 and rs1495741 exhibited two different scenarios: populations with high frequencies of the ancestral allele (range:0.55-0.99) and populations with considerable presence of the derived allele (range:0.05-0.79). Regarding the acetylation status, the slow phenotype was the most common (f = 0.44); the African, European, and Middle Eastern populations presented the highest frequencies (range: 0.48-0.79). The rapid phenotype occurred mainly in East Asians and Native Americans (range: 0.25-0.53). The results reported herein expanded the landscape of NAT2 diversity in global populations, reinforcing those data reported in the 1000 Genomes Project. Furthermore, our findings included the diversity of underrepresented populations such as Sub-Saharan and North Africa, the Middle East, and populations from Asia and Europe.

Keywords: Arylamine N-acetyltransferase 2, Gene polymorphisms, Acetylator phenotype, Diversity

Introduction

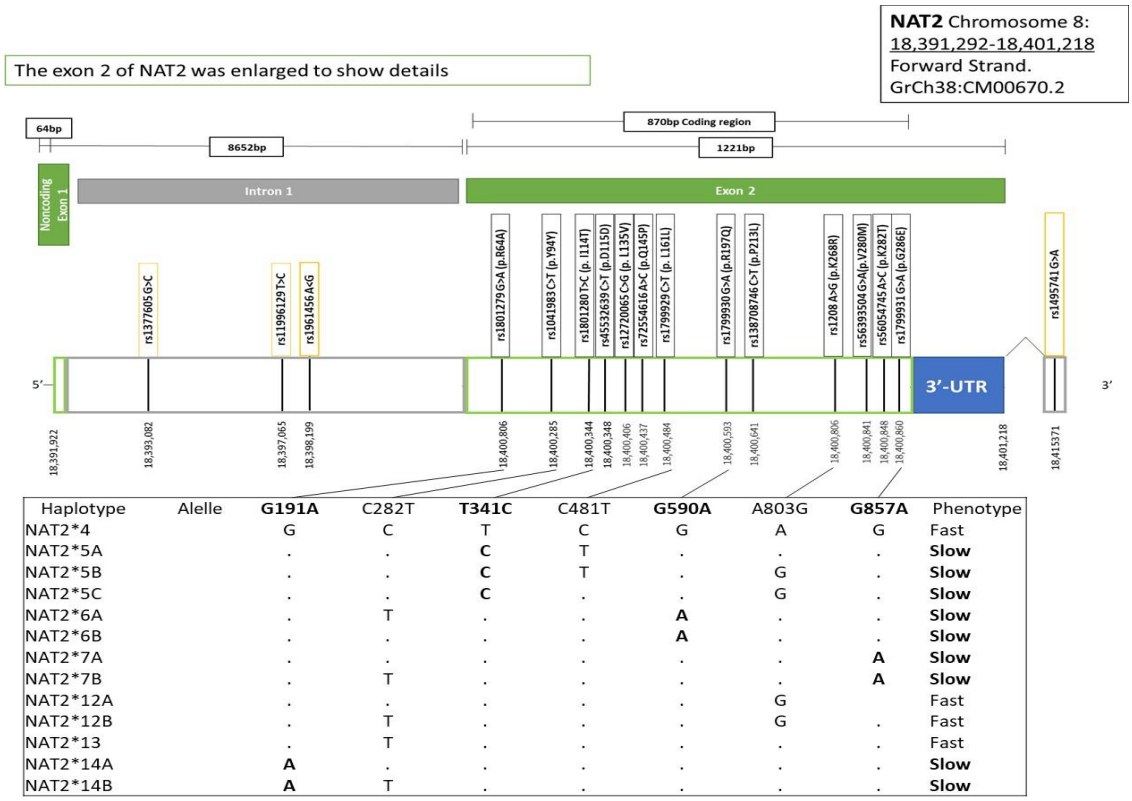
Arylamine N-acetyltransferase 2 (NAT2) is a phase II xenobiotic-metabolising enzyme involved in the metabolism of heterocyclic aromatic amines (HAAs) and drugs such as sulphonamides and hydralazine (Sim *et al*., 2014). HAAs have been categorised as class 2A carcinogens with a remarkable impact on the human populations (IARC, 1993). Of note, most carcinogens do not have a direct mutagenic activity, requiring metabolic enzymes for their activation, thereby adding toxicological relevance to NAT2 and its acetylation phenotypes (Kabir, 2018). NAT2 promotes the HAA activation with the subsequent formation of reactive metabolites capable of forming adducts (i.e., N-acetoxyesters) with the genetic material (Turesky *et al.,* 2009). Such adducts could initiate a mutation process where an improper DNA repair might lead to a tumour formation (Rajalakshmi *et al.,* 2015).

NAT2-mediated acetylation is determined from the individual genetic profile; those who carry two low-activity alleles are slow acetylators. By contrast, those individuals bearing two functional alleles are considered fast acetylators; the heterozygous carriers are related to an intermediate phenotype (Birch *et al.,* 2018). Present-days, at least 43 nucleotide changes have been identified in the NAT2 coding region (Fig 1). The most common variations are 191G>A; rs1801279, 282C>T; rs1041983, 341 T> C; rs1801280, 481 C>T; rs1799929, 590 G> A; rs1799930, 803A>G; rs1208, 857G>A; rs1799931 and rs1495741 (Hein & Doll, 2012). Some of these variations cause amino acid changes decreasing the acetylation activity and the detoxification efficiency (Liu *et al*., 2015; Taja-Chayeb *et al*., 2012). The NAT2 low-acetylation phenotype has been related to the inactivation of biogenic amines, such as histamine, converted to acetyl-histamine for elimination, and in turn with allergies and asthma (Zielinska *et al*., 1997). Lupus erythematosus, male

infertility, and bladder and breast neoplasms have also been associated with this phenotype (El-Desoky *et al.,* 2005; Nakamura *et al.,* 2007; Kasajova *et al.,* 2016; Santos *et al.,* 2016; Trang et al., 2018). The fast phenotype has been associated with the overproduction of reactive metabolites, causing DNA adducts, seeming to contribute to colorectal (Huan *et al*., 2007) and prostate cancer development (Huang *et al*., 2007; Rovito *et al*., 2005).

Nonetheless, *NAT2* diversity has shown distinct patterns among worldwide populations (Mortensen *et al*., 2011). Although previous studies have associated the NAT2 acetylation phenotypes with various pathologies, these associations have shown discrepancies among populations, and, in some cases, the findings contradict each other. In light of this evidence, the NAT2 slow phenotype associated with breast cancer in Finnish women has not shown consistent results in Slovak, Thai and Turkish women (Kocabaş *et al*., 2004; Sillanpää *et al*., 2005; Sangrajrang *et al*., 2010; Kasajova *et al*., 2016). Similar results have been observed in bladder cancer, where the slow phenotype has been related to this pathology in the Egyptians, although not in North Indian and Spanish populations (El-Desoky *et al*., 2005; García-Closas *et al*., 2005; Mittal *et al*., 2004). Regarding the NAT2 role to asthma contribution, it has been described in a Poland population, whereas dissimilar results were found in a Turkey study (Nacak et al., 2002; Gawronska-Szklarz *et al.,* 2001).

Such examples highlight the populational genetic architecture's impact on the results obtained, leading to spurious associations (Greene *et al.,* 2009). Given the remarkable diversity presented in *NAT2* and the relevance of considering the genetic background in the association studies, the present systematic review was conducted to describe the *NAT2* genetic diversity in the world populations, which can be used in pharmacogenetic and toxicogenetic approaches.



Haplotype	Alelle	G191A	C282T	T341C	C481T	G590A	A803G	G857A	Phenotype
NAT2*4		G	C	T	C	G	A	G	Fast
NAT2*5A		.	.	**C**	T	.	.	.	**Slow**
NAT2*5B		.	.	**C**	T	.	G	.	**Slow**
NAT2*5C		.	.	**C**	.	.	G	.	**Slow**
NAT2*6A		.	T	.	.	**A**	.	.	**Slow**
NAT2*6B		.	.	.	.	**A**	.	.	**Slow**
NAT2*7A		.	.	.	.	.	.	**A**	**Slow**
NAT2*7B		.	T	.	.	.	.	**A**	**Slow**
NAT2*12A		.	.	.	.	.	G		Fast
NAT2*12B		.	T	.	.	.	G	.	Fast
NAT2*13		.	T	.	.	.	.	.	Fast
NAT2*14A		**A**	.	.	.	.	.	.	**Slow**
NAT2*14B		**A**	T	.	.	.	.	.	**Slow**

Figure 1. Diagram representing the most frequent nucleotide and its acetylator status.

Note: The figure represents the *NAT2* gene structure from beginning to end composed of a non-coding exon (64 base pairs, bp), an intron (8652 bp), a coding exon (1221 bp), and the 3'-untranslated region (3'-UTR). The coding region is found in exon 2 (enlarged), comprised of 870 base pairs. The genetic variants are accompanied by its change at the protein level and its position in agreement with the *Homo sapiens* genome assembly from Genome Reference Consortium Human genome 38. SNP combinations (bold indicate a slow phenotype) result in the haplotypes shown at the bottom of the image.

Materials and methods

Search Strategy

A systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria (PRISMA) was carried out (Moher *et al*., 2009). Our primary outcome was to broaden the *NAT2* genetic and phenotypic landscapes in the human populations.

Articles indexed in PubMed, Embase, Scopus, and Lilacs databases published from October 1992 to October 2020 were included. The search strategy included medical subject headings and the following free text terms: "asthma", "cancer", "neoplasia", "allergy", "hypersensitivity", "ethnic group", "diversity", "N-acetyltransferase 2" and "NAT2" which were combined with "polymorphism, genetic", "polymorphism, single nucleotide", "genetic variation", and "DNA". Aliases for the different genes were also used as a search strategy. Relevant articles selected from the references list of the included items were manually searched to identify additional studies. All studies reviewed were from published data.

Inclusion and exclusion criteria

Inclusion criteria language were restricted to articles published in English and Spanish. Conferences, editorial comments, letters to the editor, meeting summaries, meta-analyses, overlapping publications, reviews, systematic reviews, and thesis were excluded. Those articles where the authors did not publish their genetic data and did not respond to our request were also excluded; e-mails were sent to the authors in three different moments. Further, we exclude those articles where full-text access was not possible to obtain.

The present systematic review included population genetic papers and case-control studies conducted in humans. Those studies without healthy controls and those where the control group presented a Hardy-Weinberg (HW) departure were eliminated. Polymorphism was described as a gene variant present in at least 1% of the population.

Two authors screened all studies retrieved from the research strategy using the title and/or abstract as eligibility criteria. These two authors further participated in data extraction and quality assessment of all the documents independently. Two more authors served asreferees to solve the inconsistencies; the accepted articles were defined as those with at least three positive votes.

Quality evaluation

The quality evaluation of the manuscripts selected was carried out using the quality of genetic association studies test (Q-genie). Q-genie is a tool that evaluates the bias in genetic association studies through eleven questions assessing different parameters on a scale from one to seven (where one is poor and seven is excellent quality) (Sohani *et al*., 2015). Three researchers participated in the quality assessment Q-genie process; disagreements among reviewers were resolved through group discussion. The score obtained from the different questions allowed the exclusion of low-quality studies, increasing the precision of the genetic association studies' conclusions. For the genetic association studies, the score considered acceptable was ≥ 45, whereas for the population genetic studies, some modifications were made; a score ≥ 35 was considered acceptable (Sohani *et al.,* 2015).

Data extraction

The information extracted was: first author's name, publication year, country, ethnicity, gender, study design (case-control or population genetic study), sample size, population age (mean ± SD) and range, genotyping methods, and acetylation phenotype. The single nucleotide polymorphisms (SNPs) within *NAT2*, its location, reference sequence (rs), minor allele frequency (MAF) and the HW expectation were also included (S1 Table).

Different strategies were considered to reduce the possibility of bias within the selected studies. Such strategies included genotyping error rates (> 5% was considered unacceptable), blinded genotyping and the statistical methods to control the risk of false-positive findings. The participants' eligibility criteria, the genetic relationship between them, sex, ethnicity, matching methods between cases and controls, sources of controls (hospital or population), sources of the match (age, residence country and ethnicity), and the sampling process were used also considered.

Statistical Analysis

Genetic diversity

For each study, allele, genotype frequencies, and HW expectations using Weir and Cockerham's *F*-statistics were calculated with Genetix v4.05 (Belkhir *et al.*, 2004). Acetylation's phenotypes frequencies were calculated by direct count. Analysis of molecular variance (AMOVA) was carried out with Arlequin v3.5.2.2 (Excoffier and Lischer, 2010) using 1000 permutations with a significance level of $p < 0.05$.

In those populations in which the authors reported only allelic/genotypic frequencies or minor allele frequency (MAF), these values were used to construct the database that was only used to analyse the genetic contribution without considering the acetylation phenotype. The genotypes were built through random sampling from the database values. The statistical genetic analyses to confirm that the reported frequency values were equal to those obtained were made using Genetix v4.05 (Belkhir *et al.*, 2004).

Comparison with other populations

All data obtained were compared with several populations with similar ancestral and geographic backgrounds. The genetic pools from the 1000 Genomes Project database (http//www.internationalgenome.org) were used for these comparisons. Overall, the genetic pools from Africa, East and South Asia, and Europe were compared with those populations belonging to these geographic regions. The populations belonging to the American Continent were stratified based on their ancestry. Those studies from European-derived populations (i.e., the United States of America and Canada) were compared to the European gene pool and Utah residents with Northern and Western European ancestry from the Human Polymorphism Study Centre collection (CEU). On the other hand, the studies from Latinos and Native American populations were compared with East Asian, European, and other Latino populations from the 1000 Genomes Project database (Gomez *et al.,* 2021).

Results

A total of 1029 publications were drawn from several databases. Of these, 500 duplicates were removed, and 23 publications were manually found. Thus, a total of 552 potential full-text articles were selected for a more detailed evaluation, of which 220 were evaluated with the Q-genie test (Fig 2). One-hundred and sixty full-text publications were accepted to describe the *NAT2* genetic diversity. Of these, 115 came from case-control studies of several pathologies, of which only controls were used (Fig 2; S1 Table).

The genetic diversity found amongst the worldwide populations

The genetic diversity analyses were conducted with 122 populations from 51 countries representing 60,888 individuals. The AMOVA test exhibited a percentage of variation among populations (12.90 %) with a significant percentage within populations (87.10%, p-value $\leq$ 0.0001).

Despite all authors reporting HW equilibrium in their data, our analyses indicated that some populations presented a remarkable departure; these studies were excluded from the rest of the analyses (S1 Table). The frequencies from eight SNPs (rs1801279, rs1041983, rs1801280, rs1799929, rs1799930, rs1208, rs1799931 and rs1495741) and their comparisons with the 1000 genomes project data (http//www.internationalgenome.org) were depicted in the S1 Fig. The SNP with the most genotyped individuals was rs1495741, with a total of 22,571 individuals. Nonetheless, it only represented the diversity of eight countries. Therefore, the SNP rs1799930 representing 18,649 individuals and 46 countries becomes the most studied. On the other hand, rs1801279 was the least studied, with a total of 4733 individuals in 24 countries.

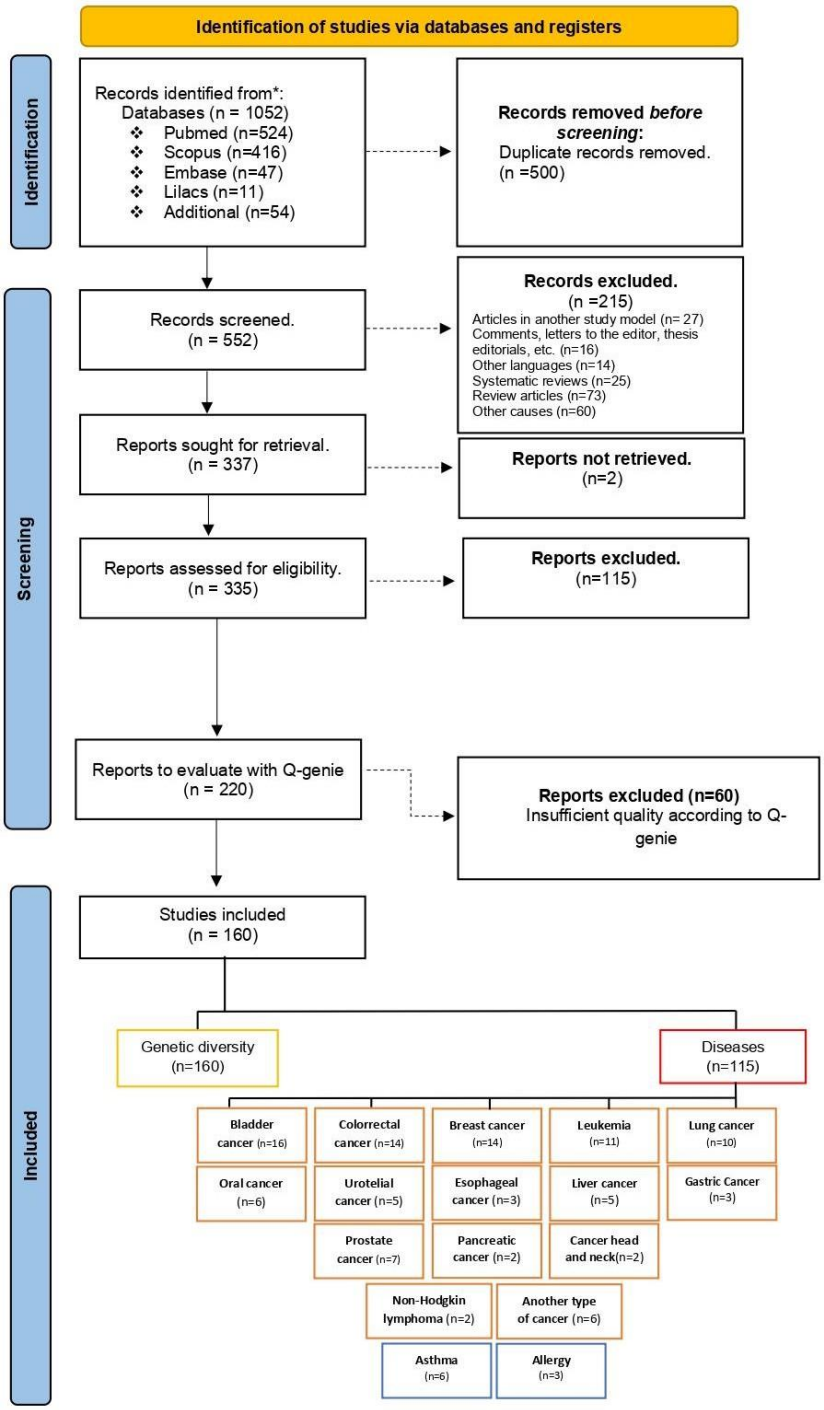


Figure 2. PRISMA diagram detailing the selection of the studies included in the present systematic review.

Note. The numbers in brackets indicate the number of articles.

Similar distribution patterns

The diversity of the SNP rs1801279 was represented by 32 populations obtained from 24 countries (S1A Fig,). Overall, its distribution was fairly homogeneous, being the ancestral allele (G) the most prevalent. By contrast, the derived allele (A) was presented in the African and Brazilian populations (ranges: 0.01-0.19 and 0.02-0.06, respectively). Similar behaviour was found in rs1041983 (S1B Fig), where the ancestral allele (T) was the most prominent (range: 0.26-0.75; standard deviation: 0.084), being the most frequent in Native Americans from Panama (Embera and Ngawbe; range: 0.71-0.75) Of note, some populations from Peru (PER-7) and India (IND-2) showed opposite (S1B Fig).

Regarding rs1799930 (S1E Fig), the distribution of the ancestral allele (G) was highly frequent among the east Asian populations such as Japan and Taiwan, where it was most frequent. Similar patterns were also found in the Native American populations from Panama and Colombia (Chimila, Wayuu and Wiwa).

Highly frequency of the ancestral allele within the East Asians

The frequencies of the SNPs rs1801280, rs1799929 and rs1208 had consistent distribution patterns in East Asia populations. Particularly, the SNP rs1801280 (S1C Fig) presented similar distributions of the ancestral allele (T) in almost all the geographic regions. Populations from the Central and Meridional Asia (i.e., Kyrgyzstan), the southeast Asiatic (i.e., Indonesia and Singapore), and the East Asians presented the highest frequencies of the ancestral allele (range: 0.68-99). Similar trends were observed in the Native Americans from Panama. Yet, the Latinos presented a variable distribution, although the ancestral allele was the most frequent (range:

0.60-0.67). Nonetheless, some exceptions were found in South Africa and in those populations with African-American and Hispanic ancestries where the ancestral allele (range: 0.69-0.78) was the most frequent.

Regarding the distribution of rs1799929, the ancestral allele (C) (S1D Fig) showed distinct patterns in the Africans, and the Middle Eastern characterised by a wide distribution range (range: 0.38-0.63 and 0.46-0.68, respectively) and the presence of populations with a higher prevalence of the derived allele (T) such as Ethiopia (*f*= 0.62) and the United Arab Emirates (*f*= 0.54). While in the European populations, a slight tendency towards high frequencies of the ancestral allele was observed (range: 0.53-0.71). However, the highest frequencies were observed in the Asian region, mainly within the East Asian populations (range: 0.92-0.99). A similar pattern was observed in the Embera and Ngawbe populations; range 0.91-0.98. However, the Colombian Native Americans had different behaviours whit different patterns of the ancestral allele where the lowest frequency was observed in Wiwas (COL-2; 0.65) and the highest in Chimilas (COL-1; 0.83). The admixed Latin American populations showed two tendencies; one was observed in Mexico (range: 0.70-0.72) and the other one in Brazil (range: 0.52-0.71).

For the SNP rs1208 (S1F Fig), the ancestral allele (A) exhibited a widespread distribution in almost all populations, including those from multiethnic studies (range: 0.51-0.80). The populations derived from Europeans, such as Canada and the USA, were in agreement with this distribution. Nevertheless, in populations such as Sudan, Saudi Arabia and Serbia, the derivative allele (G) exhibited a high prevalence (range:0.51-0.58). The Asian populations presented the highest frequencies of the ancestral allele, being the East Asians who exhibited the most

significant distributions (range: 0.95-0.98). A similar pattern was found in the Panamanian Native Americans (range: 0.90-0.98).

Two panoramas of distribution

The ancestral allele (G) of SNP rs1799931 (S1G Fig) had a high prevalence in all populations, mainly in the African and European region (range: 0.94-0.99). The North American Populations (i. e., Canada and USA), the Brazilian, the Middle East and the data from the multiethnic studies showed similar patterns (range: 0.94-0.99). However, some exceptions were observed in the Middle East populations (i.e., Oman, Turkey, and Saudi Arabia), where the derived allele (A) presented a range between 0.09 to 0.17. Similar ranges were found in South Asians (range: 0.05-0.19). By contrast, the East Asians exhibited a more wide distribution (range: 0.09-0.53). Interestingly, the Native American populations from Colombia and Panama presented similar patterns to Latinos with remarkable frequencies of the derived allele (range: 0.12-0.27)

Regarding rs1495741 (S1H Fig), it presented high frequencies of the ancestral allele (G) in Singapore and the East Asian populations (range: 0.55-0.67). On the contrary, Brazilian, European, USA, Pakistani populations and those data from multiethnic studies showed a different behaviour with a higher prevalence of the derived allele (A; range: 0.63-0.79).

Comparison with the 1000 Genomes Project

Overall, the distribution found herein was akin to those reported in the 1000 Genomes Project (http//www.internationalgenome.org). Of note, the present study included data that have been not reported in the mentioned project, such as Sub-Saharan and North Africa, the Middle East region, and the central, eastern and southeastern European countries. In addition,

the data presented herein included Native American ethnic minorities from Colombia and Panama.

Phenotype diversity

The acetylation status of 65,565 individuals, obtained from 200 populations spread over 61 countries (Fig 3), presented different scenarios with remarkable differences between populations and geographic regions. Of these, the slow acetylator status was the most frequent worldwide (f = 0.44), being Africa, the Middle East, and Europe where it was the most frequent (ranges: 0.51-0.72,0.48-0.79, and 0.48-0.60, respectively). Nonetheless, some exceptions were observed in Tunisia, South Africa, France, and Serbia, where the fast-intermediate phenotype was the most prominent (range: 0.65-0.90).

The fast acetylation phenotype was the least frequent (14%), although in East Asian populations and in Native Panamanians, it had a major presence (range: 0.25-0.53 and 0.40-0.53, respectively). It was of particular note that, in the Taiwan (TWN-3) population, the slow phenotype was also highly frequent (f = 0.76).

Although not all the authors reported the intermediate phenotypes, the data evaluated herein suggested a prevalence of 42% globally. The highest frequencies were found in the eastern European populations (range: 0.52-0.54) and within Latinos (range: 0.42-0.68). However, some exceptions were observed in Uzbekistan and Brazil, with a greater tendency to the slow phenotype (f = 0.59 and f = 0.55, respectively). Although the European derived populations followed a trend towards a higher prevalence of the slow phenotype, some particularities were found within the USA populations, which could reflect its cosmopolitan component. Briefly, a

high prevalence of the rapid phenotype (*f* = 0.48) was found in the sample labelled such as USA-16 with Japanese background. The Hispanic populations presented a high frequency of the intermediate phenotype (*f* = 0.46) whereas, the African-Americans presented different patterns. Of these, the population labelled as USA-15 had a similar frequency in the slow and intermediate phenotypes, while the intermediate phenotype exhibited a high frequency in USA-24 (*f* = 0.74).

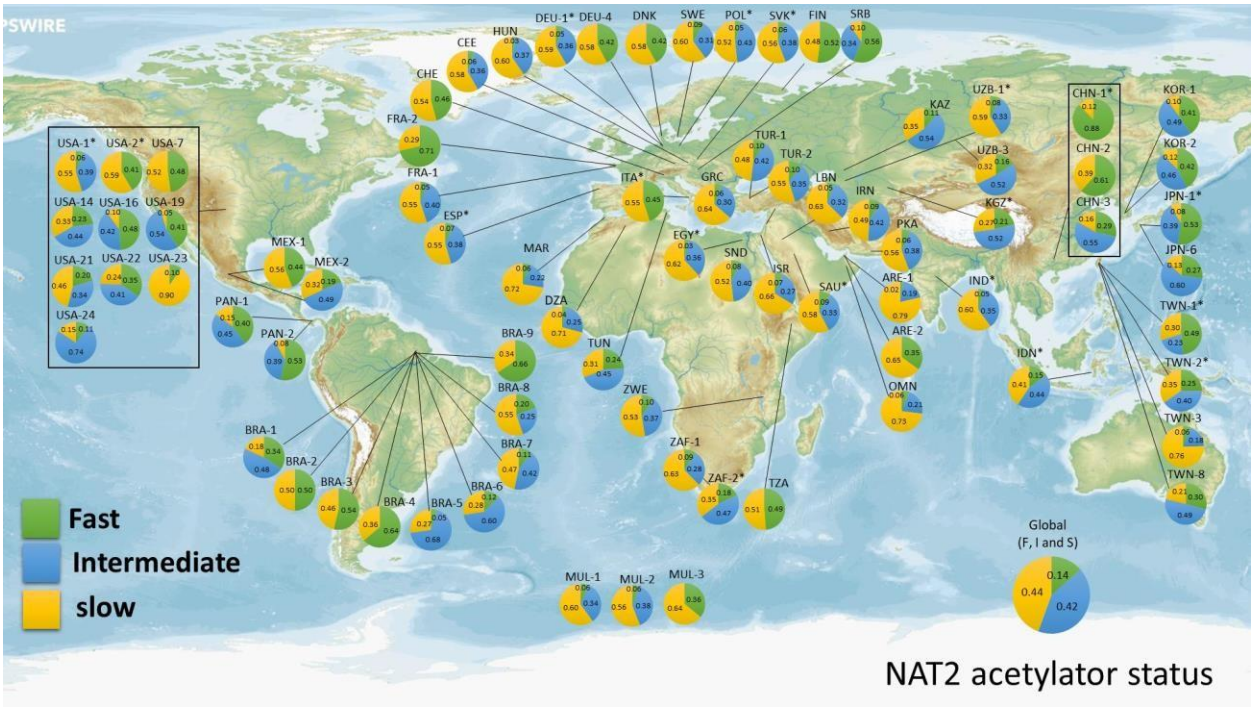


Figure 3. Map of the world depicting the *NAT2* phenotype frequency distributions from the populations analysed herein.

Note. The data were obtained from 130 populations giving a total of 65,565 individuals with the characterised phenotype. The data came from population diversity studies and the controls from genetic association studies. The literature used for its construction with a broad information appears in the SI Table 2 representing the following populations: Algeria (DZA); Bangladesh (BGD); Brazil (BRA); Central and Eastern Europe (CEE); China (CHN); Denmark (DNK); Egypt (EGY); Finland (FIN); Germany (DEU); Greece (GRC); Hungary (HUN); India (IND); Indonesia (IDN); Iran (IRN); Israel (ISR); Italy (ITA); Japan (JPN); Kazakhstan (KAZ); Kyrgyzstan (KGZ); Korea (KOR); Lebanon (LBN); Mexico (MEX); Morocco (MAR); Multi-ethnic (MTE); Netherlands (NLD); Oman (OMN); Pakistan (PKA); Panama (PAN); Poland (POL); Saudi Arabia (SAU); Serbia (SRB); Slovak (SVK); South Africa (ZAF); Spain (ESP); Sweden (SWE); Switzerland (CHE); Taiwan (TWN); Tanzania (TZA); Tunisia (TUN); Turkey (TUR); United Kingdom (GBR); United States of America (USA); Uzbekistan (UZB); Zimbabwe (ZWE). * Indicates that the pie chart was made up of several populations in the same country that had similar frequencies. The map was obtained from http://mapswire.com.

Discussion

The present systematic review explored a more ample and detailed panorama of the global *NAT2* diversity patterns from populational studies and control subjects from case-control studies. Overall, many different scenarios were found, which could affect the recognition and response to drugs and xenobiotics, modifying the susceptibility in developing different pathologies (Orphanides et al., 2003). Therefore, describing the diversity of NAT2 in world populations could give us a broader landscape to understand both the inter and intra-ethnic diversity of populations, a keystone in the pharmacogenomics (Yang et al., 2021). Although our discussion addressed several features where the world populations converge, given the underrepresentation of *NAT2* diversity in Latinos, our discussion was focused on highlight and explain the genetic landscape and heterogeneity of these populations.

The genetic landscape of rs1801279, rs1041983 and rs1799930 exhibited similar distributions in the explored populations, consistent with previous studies (Patin et al., 2006; Magalon et al., 2008; Sabbagh et al., 2008, Sabagh et al., 2011; Suarez-Kurtz et al., 2016). These similarities reflected the highly conserved allelic distribution worldwide. Nonetheless, some peculiarities were worth highlighting, such as the remarkable presence of the rs1801279 derived allele in the African populations (range: 0.02-0.19), a possible signature of this ancestry. Some adaptative responses have been related to the diet, which in African populations correspond to a farmer subsistence mode (Elhaik et al 2017). Prior reports have suggested that in this subsistence mode, the derived alleles could be more prevalent, as well as the slow acetylation phenotypes, giving a possible explanation of this feature (Luca et al., 2008; Sabbagh et al., 201 ; Podgorná et al., 2015; Aklillu et al., 2018). A slight presence of this allele was also observed in

Brazilian populations (range: 0.02-0.05). This behaviour could be related to the African slaves brought to Brazil (1550 to 1850; Salzano and Sans, 2014; Souza et al., 2019). A total of 4 million Africans from Guinea, Congo, Angola, Mozambique and Nigeria arrived in this country in that period to work on sugar cane farms, gold mines and coffee plantations (Salzano and Sans, 2014; Souza et al., 2019). The diversity of NAT2 in these African populations has been studied scanty. However, Nigeria and Congo presented one of the highest derived allele frequencies globally (range: 0.08-0.22; Patin et al., 2006; Matimba et al., 2009), which could explain the presence of the derived allele observed in Brazilian populations.

Regarding rs1041983, the highest frequencies of the derivative allele were found in Asian populations (range: 0.25-0.50). Of note that, in the Latino studies, the most prominent frequency was observed within Peruvians (range: 0.25-0.74). Particularly, the population from San Martin (f = 0.74) depicted the highest frequency worldwide. A possible explanation could be associated with the Americas peopling via Beringia (Gomez et al., 2021). Demographic events such as bottlenecks or gene drift could have influenced the high derived allele frequencies observed in this population; genetic drift has more impact on small populations (Gomez et al., 2021). Both Mexican and Peruvian populations presented the leading Native American ancestry in Latin America (Silva-Zolezzi et al., 2009; Sandoval et al., 2013; Santana et al., 2014; Harris et al., 2018). In this light, the inhabitants of San Martin coexist with three Native American groups (Quechua-Laministas, Awajun and Shawi), reinforcing this explanation (Sandoval et al., 2016). In other Native American populations from Colombia, such as Coyaimas and Piapoco-Curipaco, a former study has described the high frequencies of the derivate allele within them (f = 0.50 and f = 0.74, respectively) (Fuselli et al., 2007).

The distribution patterns in rs1799930 within Latinos could mirror the striking demographic histories of each population. The populations with a recent miscegenation process tend to present three ancestries mainly: Native American, European, and African (Santana et al., 2014). The patterns of this last ancestry can vary according to the geographical region. In Mexican populations, Native American (f =0.21) and European ancestry (f =0.41) are usually the most prevalent (Santana et al., 2014). While in Colombian population, the prevalence of an ancestry depends on the region, the Native American ancestry is more common in the southeast (f = 0.65), the European one in the North (f = 0.55), whereas the African ancestry is more prominent in the Pacific Coast (f = 0.63), and in the Caribbean (f = 0.22) (Ossa et al., 2016). On the other hand, the Brazilian population presented a prominent European ancestry; 0.81 and 0.72 in the South and Southeast regions, whereas in the North and Center regions, exhibit the most minor frequencies (f= 0.52 and f= 0.62 respectively) (Souza et al., 2019). The high prevalence of the European background may explain the patterns observed in rs1799930 within Brazilians (range: 0.72-0.86), like those reported in European populations (0.58-0.76) (Garcia-Closas et al., 2005; Sabbagh et al., 2011). The Panamanian Native Americans exhibited similar ancestral allele frequencies, akin to East Asian populations, suggesting a low miscegenation degree.

Regarding rs1799931, its diversity was relatively homogeneous in the African, European, Middle Eastern and North American populations (range: 0.94-0.99), which agreed with other reports (Patin et al., 2006; Magalon et al., 2008; Sabbagh et al., 2008, Sabagh et al., 2011; Suarez-Kurtz et al., 2016). Nevertheless, in Latino populations, considerable heterogeneity was found. The frequencies found in Mexico reflected its miscegenation process, exhibiting an average between those frequencies observed in the European and Native American populations (Santana

et al., 2014; Moreno-Estrada et al., 2014). The Brazilian populations showed trends very similar to those observed in the Europeans, probably linked to the gene flow undergone during the Portuguese conquest and the second-world war (Saloum et al., 2013; Mante et al., 2013; Souza et al., 2019; Pena et al., 2020). The remarkable diversity of these populations highlighted its complex genetic architecture. Nonetheless, the studies, hitherto, have been scanty. Hence, further studies are required to delve into the complete panorama of these populations.

In the present systematic review, we include the SNP rs1495741, which emerges as an excellent candidate to replace the panel of 7-SNPs to predict the acetylation phenotype of NAT2 (García-Closas et al., 2011). Although this SNP allows depicted am exciting panorama, there are few studies currently focused on this SNP (we reported twelve), so more studies are required to portray the true diversity of this SNP.

The Colombian and Panamanian Native American populations exhibited a very particular behaviour regarding rs1801280, rs1799929, rs1799930, and rs1208, showing high ancestral allele frequencies. Similar distributions have been reported in the East Asian populations (Patin et al., 2006; Sabagh et al., 2011; Suarez-Kurtz et al., 2016). The particular diversity observed in Native American populations could be related to its ancestral connection with the East Asians, and the demographic events underwent by these populations such as bottlenecks and founder effects (Bortolini et al., 2003; Halderson and Bolnick et al., 2008; Hunley and Healy et al., 2011; Regueiro et al., 2013). In turn, NAT2 data could reinforce the Americas peopling via Beringia (Tamm et al., 2007; Biso-Machado et al., 2016; Moreno-Mayar et al., 2018; Gomez et al., 2021).

Except for the SNP rs1799931, the East Asian populations (China, Japan, Korea and Taiwan) explored in the present study exhibited high frequencies of the ancestral allele (Patin et al., 2006; Sabagh et al., 2011; McDonagh et al., 2014; Suarez-Kurtz et al., 2016). These prevalences suggest that this region could mainly characterized as fast acetylator phenotype which agrees with the results found in the phenotypes section (Fig 3) (Hein & Doll, 2012).

Acetylator status in East Asia and an overview of phenotypic diversity

Regarding the state of acetylation, each geographic region and even some populations presented particular patterns. The highest prevalence of the rapid phenotype was observed in East Asia and Native American populations (range: 0.25-0.53). Similar findings have been reported by other authors (Lin et al., 1994; Fuselli et al., 2006; Sabagh et al., 2008; Mortensen et al., 2011). In this setting, prior studies have emphasized the role of the subsistence mode in the prevalence of the acetylation phenotype of populations (Luca et al., 2008; Sabbagh et al., 2011). The slow phenotype has been associated with farming populations, while the fast phenotype with hunter-gatherers; this last one seems to be beneficial in the presence of a diet rich in folate (Luca et al., 2008; Sabbagh et al., 2011; Podgorná et al., 2015; Aklillu et al., 2018). In East Asia, despite having a diet based on rice (one of the poorest sources of folate), this is offset by the consumption of fish and soybean sources highly rich in folate that could restore folate levels, both key ingredients in East Asian cuisine (Sonoda et al., 2004; Choi et al., 2008; Mo et al., 2013). Nonetheless, further studies are needed to clarify this scenario. However, some controversies were observed in the Paiwan people from Taiwan, where a high frequency of the slow phenotype (f = 75.5) was observed. This acetylator status could be related to its ancestry; Austronesian speakers (Trejaut et al., 2005). Prior studies in a New Guinea population belonging to the region

comprised by the Austronesian speakers has reported high frequencies of the slow phenotype (*f* = 0.50) reinforcing our findings (Trejaut et al., 2005; Mortensen et al., 2015). Diet may also be playing a relevant role since the habitual consumption of millet in Paiwan populations has been described, related to a high source of folate (Chen et al., 1974).

The slow phenotype had the highest prevalence in African, European and Middle Eastern populations; other authors have described similar patterns (Bell et al., 1993; Dandara et al., 2003; Garcia-Closas et al., 2005; Sabbagh et al., 2008; Jarrar et al., 2010; Touré et al., 2012; Mthiyane et al., 2020). These high prevalences could be a feature associated with selective pressure in populations (Podgorná et al., 2015; Elhaik et al., 2017). In this setting, subsistence mode could play an essential role in the prevalence of the slow phenotype, suggesting that populations with a subsistence mode linked to agriculture will have lower folate intakes, whereas a slow phenotype is more favourable (Luca et al. al., 2008; Sabbagh et al., 2011).

The intermediate phenotype presented a high frequency at a global level (*f* = 0.42), especially in Eastern European and Latino populations. This high frequency could be explained under the phenomenon of the heterozygous advantage, in which the heterozygous genotype confers a higher relative fitness than the homozygous genotype (Hedrick, 2012). However, studies should be done to test this hypothesis.

Our study gives a comprehensive overview of the distribution of allelic and phenotypic frequencies, essential in the development of personalized medicine and in the toxicogenetic associated with NAT2, which play a critical role in these areas. Furthermore, variations in NAT2 have been associated with diseases such as cancer, asthma, and allergies (Gawronska-Szklarz et

al., 2001; El-Desoky et al., 2005; Wang et al., 2014; Kasajova et al., 2016). Therefore, knowledge of the diversity of NAT2 worldwide becomes essential to understand the susceptibility of populations to the development of certain pathologies. Likewise, the present study includes, for the first time, a diversity pattern of ethnic minorities such as populations from the Middle East, Sub-Saharan Africa, North Africa, and countries in Central, Eastern, and Southeast Europe. Present-days, the European and European-derived populations have been the most studied; 96% of the studies were done in European populations, and in the last years, the Asian populations have been represented in 20% (Bustamante et al., 2011; Popejoy and Fullerton, 2016). Thus, our study opens the door to reiterate the importance of conducting more diversity studies in underrepresented populations, especially in those that are highly diverse and heterogeneous, such as Latino and African populations.

As in other studies, some weaknesses were presented, mainly associated with the lack of data in some populations and the reconstruction of genotypes and haplotypes. In terms of phenotypic diversity, not all authors report the three phenotypes of NAT2 restricting the representation of this data.

Conclusions

This systematic review provided a detailed description of allelic and phenotypic diversity from a global perspective. In addition, our results highlighted the lack of data in geographical regions such as Latin America, sub-Saharan Africa, the Middle East, and Oceania, reinforcing the necessity to include ethnic minorities.

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3. DISCUSIÓN Y CONCLUSIONES

La presente revisión sistemática exploró un panorama más amplio y detallado de los patrones de diversidad NAT2 globales de estudios poblacionales e individuos obtenidos (controles) de estudios de casos y controles. En general, se encontraron muchos escenarios diferentes, que podrían afectar el reconocimiento y respuesta a fármacos y xenobióticos, modificando la susceptibilidad en el desarrollo de diferentes patologías (Orphanides et al., 2003). Por lo tanto, describir la diversidad de NAT2 en las poblaciones mundiales podría brindarnos un panorama más amplio para comprender la diversidad inter e intraétnica de las poblaciones, una piedra angular en la farmacogenómica (Yang et al., 2021). Aunque nuestra discusión abordó varias características donde convergen las poblaciones mundiales, dada la subrepresentación de la diversidad NAT2 en las poblaciones Latinas, nuestra discusión se centró en resaltar y explicar el panorama genético y la heterogeneidad de estas poblaciones.

El paisaje genético de rs1801279, rs1041983 y rs1799930 exhibió distribuciones similares en las poblaciones estudiadas, estuvieron en concordancia con estudios previos (Patin et al., 2006; Magalon et al., 2008; Sabbagh et al., 2008, Sabagh et al., 2011; Suarez-Kurtz et al., 2016). Estas similitudes reflejan la distribución alélica altamente conservada en todo el mundo. No obstante, cabe destacar algunas peculiaridades, como la notable presencia del alelo derivado de rs1801279 en las poblaciones africanas (rango: 0.02-0.19), una posible firma de esta ascendencia. Algunas respuestas adaptativas se han relacionado con la dieta, que en las poblaciones africanas corresponden a un modo de subsistencia del agricultor (Elhaik et al 2017).Reportes anteriores han sugerido que, en este modo de subsistencia, los alelos derivados podrían ser más prevalentes,

así como los fenotipos de acetilación lenta, dando una posible explicación de esta característica (Luca et al., 2008; Sabbagh et al., 201; Podgorná et al., 2015; Aklillu et al., 2018). También se observó una ligera presencia de este alelo en poblaciones brasileñas (rango: 0.02-0.05). Este comportamiento podría estar relacionado con los esclavos africanos traídos a Brasil (1550 a 1850; Salzano y Sans, 2014; Souza et al., 2019). Un total de 4 millones de africanos provenientes de Guinea, Congo, Angola, Mozambique y Nigeria llegaron a este país en ese período para trabajar en fincas de caña de azúcar, minas de oro y plantaciones de café (Salzano y Sans, 2014; Souza et al., 2019). La diversidad de NAT2 en estas poblaciones africanas ha sido escasamente estudiada. Sin embargo, Nigeria y Congo presentaron una de las frecuencias alélicas derivadas más altas a nivel mundial (rango: 0.08-0.22; Patin et al., 2006; Matimba et al., 2009), lo que podríaexplicar la presencia del alelo derivado observado en poblaciones brasileñas.

Con respecto a rs1041983, las frecuencias más altas del alelo derivado se encontraron en poblaciones asiáticas (rango: 0.25-0.50). Cabe destacar que, en los estudios en poblaciones latinas, la frecuencia más prominente se observó dentro de los peruanos (rango: 0.25-0.74). En particular, la población de San Martín (f = 0,74) presentó la frecuencia más alta a nivel mundial. Una posible explicación podría estar asociada con el poblamiento de las Américas a través de Beringia (Gomez et al., 2021). Los eventos demográficos como los cuellos de botella o la deriva genética podrían haber influido en las altas frecuencias alélicas derivadas observadas en esta población; la deriva genética tiene más impacto en poblaciones pequeñas (Gomez et al., 2021). Tanto la población mexicana como la peruana presentan niveles altos de la ascendencia Nativo Americana en las poblaciones de América Latina (Silva-Zolezzi et al., 2009; Sandoval et al., 2013; Santana et al., 2014; Harris et al., 2018). En este sentido, los habitantes de San Martín conviven

con tres grupos de nativos americanos (Quechua-Laministas, Awajun y Shawi), lo que refuerza esta explicación (Sandoval et al., 2016). En otras poblaciones Nativas Americanas de Colombia, como Coyaimas y Piapoco-Curipaco, se ha descrito altas frecuencias del alelo derivado (f = 0.50 y f = 0.74, respectivamente) (Fuselli et al., 2007), sugiriendo que esta alta frecuencias del alelo derivado puede deberse a su carga genética.

Los patrones de distribución en rs1799930 dentro de las poblaciones latinas podrían reflejar las sorprendentes historias demográficas de cada población. Las poblaciones con un proceso de mestizaje reciente tienden a presentar tres ancestros principalmente: Nativa americana, europea y africana (Santana et al., 2014). Los patrones de esta última ascendencia pueden variar según la región geográfica. En las poblaciones mexicanas, la ancestría Nativa americana (f = 0.21)y la ascendencia europea (f = 0.41) suelen ser los más prevalentes (Santana et al., 2014). Mientrasque en la población colombiana, la prevalencia de una ascendencia depende de la región, ya que se ha observado que la ascendencia Nativa Americana es más común en el sureste (f = 0,65), la europea en el norte (f = 0,55), mientras que la ascendencia africana es más prominente en la Costa del Pacífico (f = 0,63) y en el Caribe (f = 0,22) (Ossa et al., 2016). Por otro lado, las poblaciones brasileñas presentan una ascendencia europea prominente; 0.81 y 0.72 en las regiones Sur y Sudeste, mientras que en las regiones Norte y Centro, exhiben frecuencias más bajas (f = 0.52 y f = 0.62 respectivamente) (Souza et al., 2019). La alta prevalencia de la ancestría europea puede explicar los patrones observados en rs1799930 en los brasileños (rango: 0,72-0,86), como los reportados en poblaciones europeas (0,58-0,76) (García-Closas et al., 2005; Sabbagh et al., 2011). Los Nativos Americanos panameños exhibieron frecuencias del alelo ancestral elevadas, similares a las poblaciones dedel Este de Asia, lo que sugiere un bajo grado

de mestizaje.

Respecto al rs1799931, su diversidad fue relativamente homogénea en las poblaciones de África, Europa, Medio Oriente y Norteamérica (rango: 0,94-0,99), lo que coincidió con otros informes (Patin et al., 2006; Magalon et al., 2008; Sabbagh et al., 2011). Sin embargo, en las poblaciones Latinas se encontró una heterogeneidad considerable. Las frecuencias encontradas en México reflejaron su proceso de mestizaje, exhibiendo un promedio entre las frecuencias observadas en las poblaciones europeas y Nativas Americanas (Santana et al., 2014; Moreno-Estrada et al., 2014). Por su parte, las poblaciones brasileñas mostraron tendencias muy similares a las observadas en las poblaciones europeas, probablemente ligadas al flujo genético experimentado durante la conquista portuguesa y la segunda guerra mundial (Saloum et al., 2013; Mante et al.,2013; Souza et al., 2019; Pena et al., 2020). La notable diversidad de estas poblaciones destacó su compleja arquitectura genética. No obstante, los estudios, hasta ahora, han sido escasos. De ahí que sean necesarios más estudios para profundizar en el panorama completo de estas poblaciones.

En la presente revisión sistemática, incluimos el SNP rs1495741, que surge como un excelente candidato para reemplazar el panel de 7-SNPs para predecir el fenotipo de acetilación de NAT2 (García-Closas et al., 2011). Aunque este SNP permite representar un panorama apasionante, existen pocos estudios actualmente enfocados en este SNP (reportamos doce), por lo que se requieren más estudios para retratar la verdadera diversidad ligada a este SNP.

Las poblaciones de Nativos Americanos colombianos y panameños exhibieron un comportamiento muy particular con respecto a rs1801280, rs1799929, rs1799930 y rs1208, mostrando altas frecuencias del alelo ancestral. Se han informado distribuciones similares en las

poblaciones del Este de Asia (Patin et al., 2006; Sabagh et al., 2011; Suarez-Kurtz et al., 2016). La diversidad particular observada en las poblaciones de Nativos Americanos podría estar relacionada con su conexión ancestral con el Este de Asia, y los eventos demográficos que sufrieron estas poblaciones, como cuellos de botella y efectos fundadores (Bortolini et al., 2003; Halderson y Bolnick et al., 2008; Hunley y Healy et al., 2011; Regueiro et al., 2013). Así mismo, los datos de NAT2 podrían reforzar el poblamiento de América a través de Beringia (Tamm et al., 2007; Biso-Machado et al., 2016; Moreno-Mayar et al., 2018; Gomez et al., 2021).

A excepción del SNP rs1799931, las poblaciones del Este de Asia (China, Japón, Corea y Taiwán) exploradas en el presente estudio exhibieron altas frecuencias del alelo ancestral (Patin et al., 2006; Sabagh et al., 2011; McDonagh et al., 2014; Suarez-Kurtz et al., 2016). Estas prevalencias sugieren que esta región podría caracterizarse principalmente como fenotipo acetilador rápido, lo que concuerda con los resultados encontrados en la sección de fenotipos (Fig 3) (Hein & Doll, 2012).

El estado de acetilador en Asia oriental y una descripción general de la diversidad fenotípica

Con respecto al estado de acetilación, cada región geográfica e incluso algunas poblaciones presentaron patrones particulares. La prevalencia más alta del fenotipo rápido se observó en laspoblaciones del Este de Asia y en Nativos Americanos (rango: 0,25-0,53). Otros autores han informado hallazgos similares (Lin et al., 1994; Fuselli et al., 2006; Sabagh et al., 2008; Mortensen et al., 2011). En este contexto, estudios previos han enfatizado el papel del modo de subsistencia en la prevalencia del fenotipo de acetilación en las poblaciones (Luca et al., 2008; Sabbagh et al., 2011). El fenotipo lento se ha asociado con poblaciones agrícolas, mientras que el fenotipo rápido con cazadores-recolectores; este último parece ser beneficioso en presencia de

una dieta rica en folato (Luca et al., 2008; Sabbagh et al., 2011; Podgorná et al., 2015; Aklillu et al., 2018). En el Este de Asia, a pesar de tener una dieta basada en arroz (una de las fuentes más pobres de folato), esto se compensa con el consumo de pescado y fuentes de soja altamente ricas en folato que podrían restaurar los niveles de folato, ambos ingredientes clave en la cocina de Asia Oriental (Sonoda et al., 2004; Choi et al., 2008; Mo et al., 2013). No obstante, se necesitan más estudios para aclarar este escenario.

Sin embargo, se observaron algunas controversias en el pueblo Paiwan de Taiwán, donde se observó una alta frecuencia del fenotipo lento (f = 75,5). Este estado de acetilación podría estar relacionado con su ascendencia; Hablantes austronesios (Trejaut et al., 2005). Estudios previos en una población de Nueva Guinea perteneciente a la región compuesta por hablantes de austronesio han reportado altas frecuencias del fenotipo lento (f = 0.50) reforzando nuestros hallazgos (Trejaut et al., 2005; Mortensen et al., 2015). La dieta también puede estar jugando un papel relevante ya que se ha descrito el consumo habitual de mijo en las poblaciones de Paiwan, relacionado con una alta fuente de folato (Chen et al., 1974).

El fenotipo lento tuvo la mayor prevalencia en las poblaciones africanas, europeas y del Medio Oriente; otros autores han descrito patrones similares (Bell et al., 1993; Dandara et al., 2003; Garcia-Closas et al., 2005; Sabbagh et al., 2008; Jarrar et al., 2010; Touré et al., 2012; Mthiyane et al., 2020). Estas altas prevalencias podrían ser una característica asociada con la presión selectiva en las poblaciones (Podgorná et al., 2015; Elhaik et al., 2017). En este contexto, el modo de subsistencia podría jugar un papel esencial en la prevalencia del fenotipo lento, lo que sugiere que las poblaciones con un modo de subsistencia vinculado a la agricultura tendrán

menores ingestas de folato, donde un fenotipo lento es más favorable (Luca et al., 2008; Sabbagh et al., 2011).

El fenotipo intermedio presentó una alta frecuencia a nivel global (f = 0,42), especialmente en las poblaciones de Europa del Este y poblaciones Latinas. Esta alta frecuencia podría explicarse bajo el fenómeno de la ventaja heterocigótica, en el que el genotipo heterocigoto confiere una mayor aptitud relativa que el genotipo homocigoto (Hedrick, 2012). Sin embargo, se deben realizar estudios para probar esta hipótesis.

Nuestro estudio ofrece un panorama completo de la distribución de frecuencias alélicas y fenotípicas, esenciales en el desarrollo de la medicina personalizada y en la toxicogenética asociada a NAT2, que juegan un papel crítico en estas áreas. Además, las variaciones en NAT2 se han asociado con enfermedades como el cáncer, el asma y las alergias (Gawronska-Szklarz et al., 2001; El-Desoky et al., 2005; Wang et al., 2014; Kasajova et al., 2016). Por tanto, el conocimiento de la diversidad de NAT2 a nivel mundial se vuelve fundamental para comprender la susceptibilidad de las poblaciones al desarrollo de determinadas patologías. Asimismo, el presente estudio incluye, por primera vez, un patrón de diversidad de minorías étnicas como poblaciones de Oriente Medio, África Subsahariana, África del Norte y países de Europa central, oriental y del Sudeste. En la actualidad, las poblaciones europeas y derivadas de Europa han sido las más estudiadas; El 96% de los estudios se realizaron en poblaciones Europeas, y en los últimos años, las poblaciones Asiáticas han empezado a ser representadas en un 20% (Bustamante et al., 2011; Popejoy y Fullerton, 2016). Así, nuestro estudio abre la puerta a reiterar la importancia de realizar más estudios de diversidad en poblaciones subrepresentadas, especialmente en aquellas que son muy diversas y heterogéneas, como las poblaciones latinas y africanas.

Al igual que en otros estudios, se presentaron algunas debilidades, principalmente asociadas a la falta de datos en algunas poblaciones y la reconstrucción de genotipos y haplotipos. En términos de diversidad fenotípica, no todos los autores informan que los tres fenotipos de NAT2 restringen la representación de estos datos.

Esta revisión sistemática proporcionó una descripción detallada de la diversidad alélica y fenotípica desde una perspectiva global. Además, nuestros resultados destacaron la falta de datos en regiones geográficas como América Latina, África subsahariana, Medio Oriente y Oceanía, lo que refuerza la necesidad de incluir a las minorías étnicas.

El jurado designado por el Departamento de Toxicología del Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional aprueba la tesis:

“Diversidad genética mundial de NAT2: Una revisión sistemática”

Que presenta el LBG. Jorge Enrique Gutierrez Virgen para su examen final de Maestro en Ciencias en la Especialidad de Toxicología, el día 08 de diciembre del año 2021.

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