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CYP1A1 Variability In Human Populations

Cristina Martínez-Labarga[1], Giuseppina Scano[1], Roberta Lelli[1], Brigitte Peacock[1], Lorenzo Ricci[1], Giuseppina Primativo[1], Irene Contini[1], Gianfranco Biondi[2], Michael H. Crawford[3], Hani S. Hafez[4], Andrea Novelletto[1], Pavao Rudan[5], Gianfranco De Stefano[1]*, Olga Rickards[1]

[1]Dipartimento di Biologia, Università degli Studi di Roma "Tor Vergata", Rome, Italy

[2]Dipartimento di Scienze Ambientali Università dell'Aquila, L'Aquila,Italy

[3]Department of Anthropology, University of Kansas, Lawrence, USA

[4]Zoology Department, Faculty of Science, Suez University, Suez, Egypt

[5]Institute for Anthropological Research, Zagreb and Anthropological Center of the Croatian Academy of Sciences and Arts, Zagreb, Croatia

*Gianfranco De Stefano unfortunately died before the submission of this article. We hope that our work reflects the passion that always characterized his research.

ABSTRACT

The human cytochrome P4501A1 (CYP1A1) enzyme plays an important role in the metabolism of xenobiotics and endogenous substrates. Because polymorphisms within the CYP1A1 gene have been shown to be associated with various cancer risks and with the predicting clinical efficacy of some chemotherapies in different populations, most studies focus on their clinical significance. We, however, were interested in evaluating whether the polymorphisms could be used to distinguish human populations. Four single nucleotide CYP1A1 polymorphisms (rs4646903/ g.75011641; rs1048943/g.75012985; g.75012235; and rs1799814/ g.75012987) were analysed via PCR-RFLP assay in 1,195 individuals of various human groups from all over the world. In order to gain a more complete view of the genetic variability of the CYP1A1 gene, different statistical analyses were performed upon the populations of the present study and upon the limited data gleaned from previously studied populations. The allele and haplotype frequencies vary among populations: the rs4646903 (C) and rs1048943 (G) have been found to be nearly always linked and were found at the highest frequencies in Native Americans, while the variant associated to the position g.75012235 was only detected in certain African populations. Our work clearly indicates that the CYP1A1 polymorphisms differ among populations and that the prediction of genotypes constitutes an important aspect of precision medicine since some variants were associated with certain cancers and rs1048943 show strong association with optimized chemotherapy. Moreover, the CYP1A1 gene plays an important role in the metabolism of xenobiotics and it is likely that its frequencies could be strongly influenced by environmental factors.

Keywords: *P4501A1, nuclear polymorphisms, single-nucleotide polymorphisms (SNPs), restriction fragment length polymorphism (RFLP), human populations*

Introduction

Cytochrome P4501A1 (CYP1A1), one of three members of the CYP1 family, is mainly expressed in extra-hepatic tissues and is considered an essential enzyme in carcinogen metabolism The CYP1A1 gene is located at 15q22–q24, spans 5,810 base pairs, and contains seven exons and six introns[1]. Numerous nucleotide changes in the CYP1A1 human gene have been identified and described,[a] and some of them display inter-population frequency variations, even though only a limited number of populations were examined. More specifically, four point mutations, were analysed, and some were correlated with risk of toxicity or cancer and with the clinical efficacy of some chemotherapies[2–4].

Mutations rs4646903[5] and *m3* at g.75012235[6] are located in the 3'–flanking region downstream of exon 7**,** do not cause amino acid changes**,** and generate an *Msp*I restriction site. Two other mutations are located in exon 7 and are non-synonymous**:** mutation rs1048943 (deter-

[a] https://databases.lovd.nl/shared/genes/CYP1A1

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mined through the loss of a *BsrD*I restriction site) leads to an isoleucine to valine exchange in codon 462[7], while the contiguous rs1799814 (not digested with the *Bsa*I restriction enzyme) causes the substitution of threonine 461 with asparagine[8]. The allele frequency at these four sites varies among different populations; rs4646903 (C) and rs1048943 (G) have been found to be nearly always linked, and *m3* (C) has been detected only in African populations[9]. In this paper we report the allele and haplotype frequency distributions of the four CYP1A1 mutations in several human populations from across the globe.

Material and Methods

One thousand one hundred and ninety five unrelated and apparently healthy subjects of both sexes belonging to various worldwide populations were analysed after they gave the appropriate informed consent. The subjects included 60 people from the north African city of Al Fayyum, middle Egypt, 130 km southwest of Cairo; 177 from Benin, western Africa, belonging to four ethnic groups: 50 Fon, 42 Bariba, 35 Berba, and 50 Dendi; 158 from eastern Africa: 70 Oromo from Asella, city of the Oromia Region, central Ethiopia, and 88 Amhara from Ethiopia. They also included 413 Europeans so subdivided: 100 from central and southern Italy (51 from Molise, 25 from Lazio, 12 from Campania, 8 from Apulia, and 4 from Abruzzo); 100 Croats from different villages of the island of Korčula; 26 individuals belonging to a Croatian community residing in the southern Italian region of Molise; 90 Spaniards from Alcalá de Henares, located 35 km northeast of Madrid; 43 Spaniards sampled in La Vera and Bejar Valleys, Sierra de Gredos, in central Spain; and 54 Serbs sampled near the Studenica monastery, 39 km southwest of Kraljevo, in central Serbia. Additionally, there were 58 Arabs from the city of Dubai, United Arab Emirates (UAE); 68 Asians from Siberia; 142 Ecuadorian Native Americans: 65 Cayapa Indians (Chachi) sampled along the Cayapas river, and 77 Tsachilla (or Colorado Indians); 119 donors from two Ecuadorian communities of African ancestry living in the Esmeraldas province: 73 along Rio Cayapas, and 46 in Viche village.

The study protocol was approved by the Ethical Committee of the University of Rome Tor Vergata for each population (Registro sperimentazione N.142/10, 88/11, 89/11, 90/11, 92/11).

Genomic DNA was extracted from whole blood or oral swabs using standard procedures[10]. The four known CYP1A1 mutations were identified by PCR-RFLP analysis under the conditions reported in Table 1. The amplifications and enzymatic digestions were performed according to Cascorbi et al[8] and Martínez-Labarga et al.[11]. In order

TABLE 1

PCR AND RFLP ANALYSIS CONDITIONS

Mutation	Primers	PCR conditions	Restriction enzyme	PCR fragment size (bp)	Restriction fragment length (bp)
rs4646903§	M1F* (3602–3622):	x 35 cycles:	*Msp*I	wt_1: 405	*m1*: 210+195
g.75011641A>G	5' ATACTCACCCTGAACCCCATT 3'	94°C – 30"			
		60°C – 90"			
	P80** (3986–4006):	72°C – 60"			
	5' TAGGAGTCTTGTCTCATGCCT 3'				
rs1048943	M2F** (2304–2328):	94°C – 5',	*BsrD*I	*m2*: 204	wt_2: 149+55
g.75012985T>C	5' CTGTCTCCCTCTGGTTACAGGAAGC 3'	x 35 cycles:			
		94°C – 30"			
	M2R** (2483–2507):	67°C – 45"			
	5' TTCCACCCGTTGCAGCAGGATAGCC 3'	72°C – 60",			
		72°C – 5'			
g.75012235A>G	M3F **(3107–3126):	x 35 cycles:	*Msp*I	wt_3: 339	*m3*: 215+124
	5' GGCTGAGCAATCTGACCCTA 3'	94°C – 30"			
		60°C – 90"			
	M3R* (3426–3446):	72°C – 60"			
	5' TATGCAAGCATGCAAGCTCA 3'				
rs1799814	M2F **(2304–2328):	94°C – 5',	*Bsa*I	m^4: 204	wt_4: 139+65
g.75012987G>T	5' CTGTCTCCCTCTGGTTACAGGAAGC 3'	x 35 cycles:			
		94°C – 30"			
	M2R** (2483–2507):	67°C – 45"			
	5' TTCCACCCGTTGCAGCAGGATAGCC 3'	72°C – 60",			
		72°C – 5'			

* Primers reported in Martínez-Labarga et al.[11]

** Primers reported in Cascorbi et al.[8]

§ The detection of rs4646903 and m3 mutations for the best preserved samples was achieved through the only amplification of 899 bp fragment using the primers M3F and P80, according to Cascorbi et al.[8]

TABLE 2

NOMENCLATURE OF CYTOCHROME P4501A1 (CYP1A1) VARIANTS ANALYSED IN THE PRESENT RESEARCH FROM*

DNA change (cDNA)	Trivial name	Old nomenclature of nucleotide changes	Protein	DNA change (genomic) (hg19)	Variant remark	dbSNP ID
c.1382C>A	m4	2452 C>A	p.(Thr461Asn)	g.75012987G>T	haplotype CYP1A1*4	rs1799814
c.1384A>G	m2	2454 A>G	p.(Ile462Val)	g.75012985T>C	haplotype CYP1A1*2C	rs1048943
c.1384A>G		2454 A>G 3798 T>C	p.(Ile462Val)	g.75012985T>C	haplotype CYP1A1*2B	-
c.2134T>C	m3	3204 T>C	p.(=)	g.75012235A>G	haplotype CYP1A1*3	-
c.*1189T>C	m1	3798 T>C	p.(=)	g.75011641A>G	haplotype CYP1A1*2A	rs4646903

*https://databases.lovd.nl/shared/genes/CYP1A1 and https://www.pharmvar.org/gene/CYP1A1.

to confirm the RFLP results, some samples were sequenced by fluorescent dye labelling on an ABI PRISM 3130 AVANT DNA Sequencer (Life Technologies, Foster City, CA), following the manufacturer's protocols.

CYP1A1 alleles were named following the classification proposed by Cascorbi et al.[8] and the actually recommended nomenclature for the genetic polymorphisms in human P450 genes reported in Table 2.

Allele frequencies were computed by gene counting, and the Hardy-Weinberg equilibrium was then evaluated for each sample with polymorphic results. The allele frequencies were graphically represented through the software SURFER 6 (www.goldensoftware.com) to visualize their geographical cline distribution using the data reported in Supplementary Table 1. The American continent was excluded from this analysis due to the high genetic homogeneity of the Native populations and the expected low variability of colour gradients.

Haplotype frequencies were computed twice in order to strengthen the reconstructed haplotypes: first using the software ARLEQUIN v3.5[12] and the maximum-likelihood method, and second using the software PHASE v2.0[13] and a Bayesian method. In order to gain a more complete view of the genetic variability of the CYP1A1 gene, Reynolds et al.'s[14] genetic distances matrix calculated from genotypes of the populations analysed in the present study and those populations, collected from literature, previously tested for all four markers, with ARLEQUIN v3.5 were graphically represented through non-metric Multidimensional Scaling analysis (nm-MDS)[15], using the STATISTICA software package[16] . The partition of genetic variation between and within populations was carried out by assigning the investigated populations to seven groups according to their geographical position; this was accomplished through an Analysis of Molecular Variance (AMOVA)[17] by comparing haplotype frequencies.

Results and Discussion

Allele frequencies for all populations are shown in Table 3. All the populations were in Hardy-Weinberg equilibrium at all SNPs. The combined genotype frequencies at the four markers are reported in Table 4. For all the populations of this study, the haplotype frequencies were calculated and reported in Table 5. Seven new haplotypes, not reported in the official CYP1A1 website[b], were observed, at low frequencies. The frequencies obtained with the maximum-likelihood method are discussed and used in further analyses since the frequencies of some haplotypes were only detected with the Bayesian method. The allele frequencies of the populations analysed in the present research were compared with previously published data.

Concerning the American continent, excluded from the graphic representation, rs4646903 frequencies are very high in the two Native American populations analysed, Cayapa and Tsachilla (80.8% and 68.2%, respectively), as in other Native Americans, in some of which this marker reaches fixation (100%;[18,19]. Likewise, rs1048943 was found to have the highest frequency in the Cayapa and Tsachilla (73.8% and 77.9%); also in this case these results can be compared to those of other Native Americans like the Achè, for instance, who reached fixation also for this marker[18]. These high frequencies support the hypothesis that attributes the loss of genetic variation to the founder effect that occurred during the peopling of the Americas from Asia[20–24]. As regards the variants g.75012235 and rs1799814**,** the Native American populations so far analysed show null or very low frequencies.

For Africa, Asia, and Europe, the single-marker data were graphically represented through the conversion of allele frequencies into contour maps (Figures 1a, 1b, 1c, 1d) to visualize the geographical distribution of each marker. Although Surfer analysis has some limitations, it is a useful method to display the allele distributions. In the complex, it has highlighted a clinal distribution for the four markers. The colour gradient for marker rs4646903 (Figure 1a) shows the deeper intensity of the orange colour in eastern Asia and in western Africa. The Middle Eastern regions present intermediate intensities between those observed in the Asian and in the African populations, while lighter colours characterize Europe and north and eastern Africa. The only exception concerns the Spaniards from Sierra de Gredos, in whom the loss of this allele could have been caused by their geographical isolation, as the sample examined comes from a small mountain community that has been isolated for centuries[25–30]. Moreover,

[b] https://www.pharmvar.org/gene/CYP1A1

TABLE 3

CYP1A1 ALLELE FREQUENCIES WITH STANDARD ERRORS. CR: BAYESIAN 95% CREDIBLE REGIONS

		Allele frequencies			
Populations	N	rs4646903 g.75011641(C)	rs1048943 g.75012985 (G)	g.75012235 (C)	rs1799814 g.75012987 (A)
Egyptians	60	0.092 ± 0.029 *(CR: .052-.157)*	0.042 ± 0.018 *(CR: .018-.094)*	0.042 ± 0.018 *(CR: .018-.094)*	0.225 ± 0.042 *(CR: .160-.308)*
Benin pool	177	0.243 ± 0.023 *(CR: .201-.290)*	0.000 + 0.003 *(CR: .000-.008)*	0.034 ± 0.009 *(CR: .020-.058)*	0.000 + 0.003 *(CR: .000-.008)*
Bariba(Benin)	42	0.250 ± 0.045 *(CR: .170-.353)*	0.000 + 0.012 *(CR: .000-.035)*	0.000 + 0.012 *(CR: .000-.035)*	0.000 + 0.012 *(CR: .000-.035)*
Berba (Benin)	35	0.200 ± 0.048 *(CR: .123-.309)*	0.000 + 0.014 *(CR: .000-.041)*	0.071 ± 0.033 *(CR: .032-.157)*	0.000 + 0.014 *(CR: .000-.041)*
Dendi (Benin)	50	0.270 ± 0.045 *(CR: .193-.365)*	0.000 + 0.010 *(CR: .000-.029)*	0.020 ± 0.016 *(CR: .006-.070)*	0.000 + 0.010 *(CR: .000-.029)*
Fon (Benin)	50	0.240 ± 0.045 *(CR: .167-.333)*	0.000 + 0.010 *(CR: .000-.029)*	0.050 ± 0.024 *(CR: .022-.112)*	0.000 + 0.010 *(CR: .000-.029)*
Amhara (Ethiopia)	88	0.136 ± 0.025 *(CR: .094-.195)*	0.068 ± 0.018 *(CR: .040-.115)*	0.023 ± 0.011 *(CR: .009-.057)*	0.148 ± 0.026 *(CR: .103-.208)*
Oromo (Ethiopia)	70	0.093 ± 0.025 *(CR: .055-.152)*	0.000 + 0.007 *(CR: .000-.021)*	0.007 ± 0.007 *(CR: .002-.039)*	0.121 ± 0.028 *(CR: .077-.186)*
Italians	100	0.105 ± 0.021 *(CR: .070-.155)*	0.040 ± 0.014 *(CR: .021-.077)*	0.000 + 0.005 *(CR: .000-.015)*	0.085 ± 0.022 *(CR: .054-.132)*
Italian Croats	26	0.038 ± 0.026 *(CR: .012-.130)*	0.058 ± 0.035 *(CR: .021-.157)*	0.000 + 0.019 *(CR: .000-.055)*	0.038 ± 0.026 *(CR: .012-.130)*
Croats	100	0.110 ± 0.021 *(CR: .074-.161)*	0.065 ± 0.016 *(CR: .039-.108)*	0.000 + 0.005 *(CR: .000-.015)*	0.045 ± 0.014 *(CR: .024-.083)*
Spaniards	90	0.078 ± 0.020 *(CR: .047-.126)*	0.028 ± 0.012 *(CR: .012-.063)*	0.000 + 0.006 *(CR: .000-.016)*	0.100 ± 0.022 *(CR: .064-.153)*
Sierra de Gredos (Spain)	43	0.000 + 0.012 *(CR: .000-.034)*	0.047 ± 0.024 *(CR: .019-.114)*	0.000 + 0.012 *(CR: .000-.034)*	0.023 ± 0.019 *(CR: .007-.081)*
Serbs	54[a]	0.096 ± 0.029 *(CR: .053-.168)*	0.028 ± 0.016 *(CR: .010-.078)*	0.000 + 0.009 *(CR: .000-.027)*	0.019 ± 0.016 *(CR: .006-.065)*
UAE Arabs	58[b]	0.151 ± 0.036 *(CR: .095-.231)*	0.017± 0.012 *(CR: .005-.060)*	0.010 ± 0.010 *(CR: .003-.056)*	0.043 ± 0.019 *(CR: .019-.097)*
Siberians	68	0.456 ± 0.043 *(CR: .374-.540)*	0.235 ± 0.032 *(CR: .172-.313)*	0.000 + 0.007 *(CR: .000-.022)*	0.015 ± 0.009 *(CR: .005-.052)*
Cayapa Ind. (Ecuador)	65	0.808 ± 0.033 *(CR: .731-.866)*	0.738 ± 0.044 *(CR: .657-.806)*	0.000 + 0.008 *(CR: .000-.023)*	0.000 + 0.008 *(CR: .000-.023)*
TsachillaInd. (Ecuador)	77	0.682 ± 0.038 *(CR: .604-.750)*	0.779 ± 0.031 *(CR: .707-.837)*	0.000 + 0.006 *(CR: .000-.019)*	0.006 ± 0.006 *(CR: .002-.035)*
Rio Cayapas (Ecuador)	73	0.260 ± 0.039 *(CR: .196-.337)*	0.048 ± 0.017 *(CR: .024 -.096)*	0.075 ± 0.024 *(CR: .043-.130)*	0.000 + 0.003 *(CR: .000-.020)*
Viche (Ecuador)	46	0.217 ± 0.044 *(CR: .146-.312)*	0.196 ± 0.040 *(CR: .128-.289)*	0.043 ± 0.021 *(CR: .018-.106)*	0.011 ± 0.009 *(CR: .003-.058)*

the Africans from Benin and the Ecuadorian populations of African origin (Rio Cayapas and Viche) not surprisingly differ statistically from the other African populations: the Amhara, Oromo, and Egyptians. The lower frequencies observed for the latter populations are the result of the heterogeneous genetic structure of Ethiopians and Egyptians, for whom a Eurasian genetic component was attested by previous studies on uniparental and autosomal markers[31–36].

The marker rs1048943 (Figure 1b) presents the deeper intensity of the pink colour in the Middle Eastern and Asian regions. In Africa its presence is observed only in north-eastern populations. In fact, the African populations of the present study were found monomorphic wild-type for this marker with the exception for rs4646903, of the Egyptians (4.2%) and Amhara (6.8%). In the two Ecuadorian communities of African ancestry, the Rio Cayapas and Viche, the resulting frequencies were variable and statistically different, 4.8% and 19.6%, respectively, due to the higher Amerindian contribution to the Viche gene pool than to that of the Rio Cayapas[37–39]. In Europe its frequency slightly increases, reaching a more notice-

TABLE 4

CYP1A1 GENOTYPE (G.75012987-75012985-75012235-75011641) DISTRIBUTION

GENOTYPES				POPULATIONS																			
rs1799814 g.75012987	rs1048943 g.75012985	g.75012235	rs4646903 g.75011641	Egyptians	Benin pool	Bariba	Berba	Dendi	Fon	Amhara	Oromo	Italians	It. Croats	Croats	Spaniards	S. de Gredos	Serbs	UAE Arabs	Siberians	Cayapa Ind.	Tsachilla In.	Rio Cayapas	Viche
C/C	A/A	T/T	T/T	27	99	25	19	27	28	41	41	66	21	69	57	37	41	29	16	2	3	31	19
C/C	A/A	T/T	T/**C**	5	48	13	8	15	12	11	11	11	2	11	10	-	6	9	14	3	-	21	8
C/C	A/**G**	T/T	T/T	2	-	-	-	-	-	1	-	1	1	2	3	4	-	-	4	2	3	-	4
C/C	A/A	T/**C**	T/T	1	10	-	5	2	3	3	1	-	-	-	-	-	-	1	-	-	-	8	1
C/**A**	A/A	T/T	T/T	14	-	-	-	-	-	22	15	13	-	7	17	2	1	4	2	-	-	-	-
C/C	A/A	T/**C**	C/C	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-
C/C	A/A	T/T	C/C	1	18	4	3	6	5	-	-	2	-	-	-	-	-	2	6	2	-	4	-
C/C	G/G	T/T	T/T	1	-	-	-	-	-	1	-	-	1	-	-	-	-	-	-	-	2	-	1
C/C	A/**G**	T/T	C/C	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	9	6	1	-	-
C/C	G/G	T/T	T/**C**	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	1	2	9	-	-
C/C	G/G	T/T	C/C	-	-	-	-	-	-	3	-	-	-	1	-	-	-	-	1	36	35	-	-
C/C	A/**G**	T/T	T/**C**	-	-	-	-	-	-	-	-	4	-	9	2	-	3	2	15	12	23	6	9
C/**A**	A/**G**	T/T	T/**C**	1	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	1	-	-
C/C	A/A	T/**C**	T/**C**	-	2	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	2	1
C/**A**	A/**G**	T/T	T/T	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
A/A	A/A	T/T	T/T	2	-	-	-	-	-	1	-	-	1	1	-	-	-	-	-	-	-	-	-
C/**A**	A/A	C/C	T/T	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
C/**A**	A/A	T/T	T/**C**	3	-	-	-	-	-	2	2	-	-	-	-	-	1	1	-	-	-	-	-
C/C	A/**G**	T/**C**	T/**C**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	2
A/A	A/**G**	T/T	T/T	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
A/A	A/A	T/**C**	T/T	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
C/**A**	A/A	T/T	C/C	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-
Total				60	177	42	35	50	50	88	70	100	26	100	90	43	52	48	68	65	77	73	46

TABLE 5

CYP1A1 HAPLOTYPE FREQUENCIES CALCULATED THROUGH THE MAXIMUM-LIKELIHOOD AND BAYESIAN (IN ITALICS) METHODS

	Haplotype frequencies												
Population	***1** CATT	***2A** CATC	***2B** CGTC	***2C** CGTT	***3** CACT	***4** AATT	**I a** AATC	**II a** CACC	**III a** CGCC	**IV a** AGTC	**V a** AGTT	**VI a** AACT	**VII a** CGCT
Egyptians	0.644±0.047	0.081±0.027	*0.003±0.004*	0.033±0.015	0.017±0.012	0.189±0.039	0.003±0.008			0.008±0.007	0.001±0.002	*0.025±0.000*	
	0.648±0.008	*0.070±0.008*		*0.037±0.004*	*0.017±0.000*	*0.181±0.009*	*0.018±0.009*			*0.007±0.002*			
Benin pool	0.723±0.028	0.243±0.026			0.034±0.011			0.001±0.002					
	0.724±0.002	*0.242±0.002*			*0.033±0.002*								
Bariba	0.750±0.044	0.250±0.044											
	0.750±0.000	*0.250±0.000*											
Berba	0.729±0.049	0.200±0.048			0.071±0.031								
	0.729±0.000	*0.200±0.000*			*0.073±0.000*								
Dendi	0.710±0.045	0.270±0.046			0.020±0.016								
	0.710±0.000	*0.270±0.000*			*0.020±0.000*								
Fon	0.715±0.046	0.235±0.044			0.045±0.019			0.007±0.008					
	0.717±0.008	*0.233±0.008*			*0.043±0.008*								
Amhara	0.676±0.033	0.120±0.026	0.011±0.001	0.023±0.012	0.017±0.010	0.148±0.029	*0.006±0.004*	0.006±0.006					
	0.682±0.004	*0.142±0.004*	*0.011±0.000*	*0.023±0.000*	*0.017±0.000*	*0.114±0.004*		*0.006±0.000*					
Oromo	0.779±0.035	0.093±0.023			0.007±0.007	0.121±0.029	*0.003±0.005*						
	0.782±0.005	*0.090±0.005*			*0.007±0.000*	*0.118±0.005*							
Italians	0.812±0.024	0.076±0.018	0.021±0.010	0.005±0.006		0.072±0.018				0.008±0.007	0.006±0.005		
	0.804±0.005	*0.078±0.006*	*0.025±0.007*	*0.007±0.004*		*0.077±0.004*				*0.001±0.003*	*0.007±0.003*		
It. Croats	0.865±0.042	0.038±0.027		0.058±0.029		0.038±0.026							
	0.865±0.000	*0.038±0.000*		*0.058±0.000*		*0.038±0.000*							
Croats	0.834±0.028	0.056±0.017	0.054±0.016	0.011±0.006		0.045±0.017							
	0.834±0.002	*0.056±0.002*	*0.054±0.002*	*0.011±0.002*		*0.045±0.000*							
Spaniards	0.810±0.032	0.063±0.018	0.010±0.007	0.018±0.009		0.094±0.022	0.006±0.007						
	0.806±0.004	*0.067±0.004*	*0.006±0.004*	*0.022±0.004*		*0.094±0.000*	*0.006±0.000*						
S. de Gredos	0.930±0.024			0.047±0.022		0.023±0.017							
	0.930±0.000			*0.047±0.000*		*0.023±0.000*							
Serbs	0.894±0.030	0.058±0.023	0.029±0.018	*0.005±0.008*		0.010±0.011	0.009±0.009						
	0.883±0.005	*0.069±0.008*	*0.024±0.008*			*0.016±0.005*	*0.003±0.005*						
UAE Arabs	0.772±0.040	0.145±0.034	0.021±0.014	0	0.010±0.009	0.051±0.022	0.0008±0.006						
	0.763±0.010	*0.153±0.010*	*0.010±0.009*	*0.011±0.009*	*0.010±0.000*	*0.049±0.005*	*0.003±0.005*						
Siberians	0.477±0.046	0.272±0.043	0.183±0.038	0.052±0.024		0.015±0.012							
	0.473±0.014	*0.277±0.014*	*0.179±0.014*	*0.056±0.014*		*0.015±0.000*							
Cayapa Ind.	0.159±0.033	0.103±0.029	0.705±0.045	0.034±0.016									
	0.158±0.005	*0.104±0.005*	*0.704±0.005*	*0.034±0.005*									
Tsachilla Ind.	0.207±0.031	0.007±0.007	0.675±0.039	0.105±0.025		0.006±0.008				0.012±0.002			
	0.212±0.004	*0.008±0.004*	*0.662±0.004*	*0.105±0.004*		*0.001±0.002*							
Rio Cayapas	0.666±0.045	0.212±0.035	0.046±0.019	*0.001±0.003*	0.074±0.026			0.0004±0.002	0.002±0.004				0.0002±0.001
	0.664±0.004	*0.213±0.004*	*0.047±0.003*		*0.075±0.002*								
Viche	0.680±0.051	0.100±0.032	0.089±0.035	0.078±0.031	0.015±0.012			0.010±0.012	0.019±0.012		0.011±0.011		0.005±0.007
	0.620±0.019	*0.147±0.019*	*0.052±0.017*	*0.126±0.017*	*0.021±0.008*	*0.006±0.005*		*0.011±0.009*	*0.007±0.007*		*0.005±0.005*		

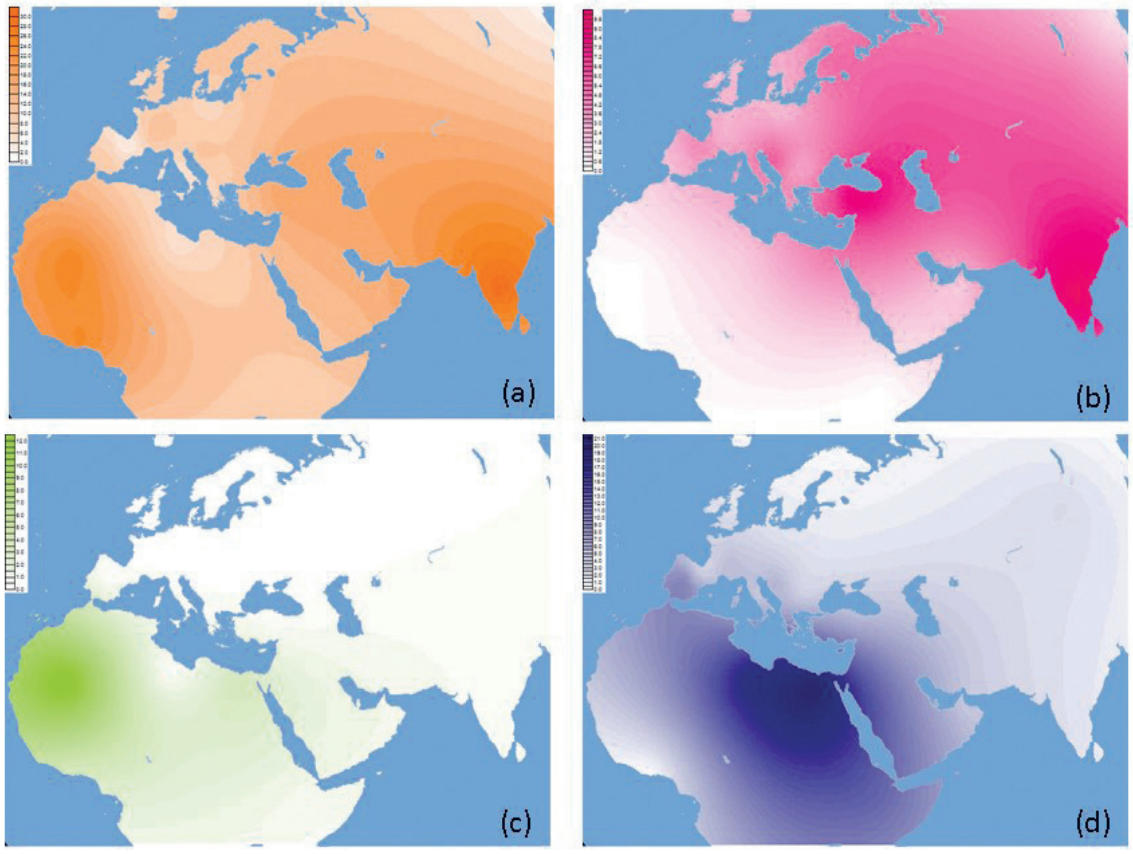

Fig. 1. Geographical distribution of CYP1A1 variants: (a) rs4646903, g.75011641; (b) rs1048943, g.75012985; (c) g.75012235; and (d) rs1799814, g.75012987. The legend at the top and left side of the figure relates the allele frequencies with different color gradations: the deepest color intensity corresponds to the highest allele frequency

able colouring in Croatia. Three groups of European origin from Pôrto Alegre[19], Rio de Janiero[40], and Australia[41] resulted in slightly higher frequencies (11.6%, 8%, and 7%, respectively) probably due to genetic contributions from Native populations.

The values of the g.75012235 (C) marker (Figure 1c) confirm its African origin: it is present only in the African and African-derived samples (0.7–7.5%) and in the UAE Arabs with a 1% frequency, due to admixture with different African groups[42].

The deeper intensity of the violet colour related to the marker rs1799814 (Figure 1d) is localized in north-eastern Africa, with frequencies varying between 12.1% and 22.5% in the Ethiopians and Egyptians, highlighting an evident expansion toward the Middle Eastern regions that supports the presence of a migration "corridor" between these two areas. Concerning the European continent, a darker colouring is noticed in the Iberian Peninsula, while Siberians have a low frequency (1.5%).

In the next step, the haplotype frequencies obtained in this study were compared with those available for other populations, supporting what emerged from the analysis of the single polymorphisms. Haplotype *2B (CGTC), defined by the presence of both mutations rs4646903 (C) and rs1048943 (G), had the highest frequency in the Native Americans: 67.5% in the Tsachilla and 70.5% in the Cayapa. This confirms the results obtained considering the single mutations rs4646903 (C) and rs1048943 (G), which both reached the highest values precisely in Native Americans, and in some groups have reached fixation[18–19]. These high frequencies support the hypothesis that attributes the loss of genetic variation to the founder effect that occurred during the peopling of the Americas from Asia. Haplotypes *2A (CATC) and *2C (CGTT), characterized respectively by either the mutation rs4646903 (C) or rs1048943 (G), were found to have quite variable values.

In the Asians and Africans, as well as the populations of African, Middle Eastern, or European ancestry, the haplotype *2B's (CGTC) frequency decreases considerably (in some African and European groups this haplotype was found to be null). This is compensated by an increase of the haplotype *1 (CATT), which presents the wild-type form of all four markers, with values between 47.7% and 93%. Even here the haplotypes *2A (CATC) and *2C (CGTT) showed a considerably variable fluctuation.

Haplotype *3 (CACT) is characterized by the mutation g.75012235 and therefore was detected exclusively in Africans and in groups of African ancestry ranging between 0.7% and 7.4%. The only exception concerns the UAE

sample (1%), due to admixture with different African groups[42].

The presence of the mutation in rs1799814 characterizes the haplotype *4 (AATT). This last haplotype was found to have the highest frequencies in north and eastern Africans (12.1%–18.9%), followed by Europeans (1%–9.4%) and Middle Eastern groups (5.1% and 5.7%). Null frequencies were found in the groups with African ancestry and in the populations from Benin, Japan, and the Cayapa.

The AMOVA was carried out by assigning the investigated populations to seven groups according to their geographical position. The estimates of genetic variation among populations and within populations are 27.69 and 71.62%, respectively, confirming that these four variants present a clear different geographical distribution[8, 9, 11, 43].

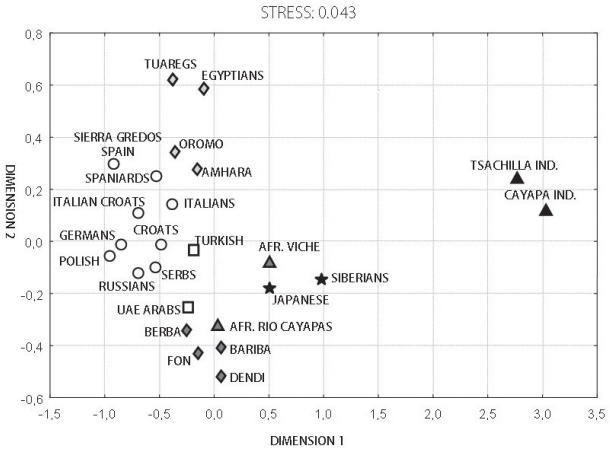

Fig. 2. Non metric Multidimensional scaling (nmMDS) representation of the genetic distances. Symbols refer to geographical location: white circles: Europe; rhombus: Africa, triangle: America (black: Native Americans and grey: populations of African ancestry); star: Asia; and squares: Near Eastern populations. (References.- German: Cascorbi et al.[8]; Polish: Mrozikiewicz et al.[47]; Russian: Gaikovitch et al.[51]; Turkish: Aynacioglu et al. [54]; Japanese: Inoue et al.[59]; Tuareg: Martinez-Labarga et al.[11]).

Figure 2 reports the two-dimensional plot of the nmMDS analysis of the genetic distance matrix obtained by Reynolds et al.[14] using the individual genotypes. The first dimension distributes the populations into two groups: the Native Americans on the right side and all the other populations on the left, with the Asians and the African Ecuadorians from Viche occupying an intermediate position. Considering the second dimension, the Europeans lie centrally, very close to the north-eastern Africans on the top side. Below are the south Saharan Africans and the groups of African origin more or less associated with Asians. Middle Eastern groups lie centrally between Africans, Asians, and Europeans. As for the Europeans, the Spaniards' results were closer to those of the two north African groups, the Oromo and the Amhara. This could once again indicate an African contribution to the gene pool of the Spanish population. The Serbs and the Croats from Korcula are very close to the Middle Eastern groups, because of admixture in the Balkan populations with these groups, as already reported. The position of the north-eastern Africans in relation to the south Saharans is evidence of their closer relationship with the Europeans. The two Afro-Ecuadorian groups, the Rio Cayapas and Viche, maintain different relationships with the other groups on the plot: the Viche lies closer to the Asians and therefore to the Native Americans while the Rio Cayapas are clearly adjacent to the south Saharans[38]. This denotes a pronounced African influence among the Rio Cayapas. We are therefore not surprised to observe that the Asians and the Viche are the closest group to the Native Americans. Both the Middle Eastern samples stand between the Europeans, Asians, and South Saharans, confirming the contribution of all three groups to the Arab and Turkish genetic pool, especially of the Europeans for the Turkish.

Similar distribution was observed in the two-dimensional plot of the correspondence analysis calculated from allele and haplotype frequencies (data not shown), which accounted for 74.22% of the total variability, which confirms what was deduced in the previous analysis from the genotypes.

In conclusion, this study has provided allele and haplotype frequencies of the four markers of the CYP1A1 gene in populations that have never been analysed before, confirming the importance of these markers. Moreover, the knowledge of genetic variability in CYP450 gene could be the starting point and represents a step towards personalized and optimized palliative chemotherapy[44].

Because the functional role of the genes belonging to the cytochrome P450 subfamily are involved in the detoxification and bioactivation of common environmental pollutants in several species, it is likely that its frequencies could be strongly influenced by environmental factors. However, Voight and colleagues[45] analysed and mapped the recent positive selection in the human genome because it is known that the selective pressure to local environmental conditions occurred during the most recent stages of *Homo sapiens'* evolution. Selection was observed in some electron transport genes of the CYP450 gene cluster on chromosome 1 and in other genes belonging to the same gene family, such as CYP3A5, CYP2E1, and CYP1A2, but not in the CYP1A1 gene.

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Author contributions

Conceived and designed the study: CM-L and OR. Provided financial support: OR. Performed the laboratory analysis: BP, LR, GS and IC. Analyzed the data: CM-L, and GP. Wrote the paper: CM-L, RL, and BP. Provided biological samples: CM-L, GB, MHC, HSH, AN, PR, GFDS, and OR. All the authors edited the manuscript for intellectual content and revised and provided critical comments on the manuscript.

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O. Rickards

Dipartimento di Biologia, Università degli Studi di Roma "Tor Vergata", Via della Ricerca Scientifica n. 1, 00173 Rome, Italy

e-mail: rickards@uniroma2.it

VARIJABILNOST CYP1A1 U LJUDSKIM POPULACIJAMA

S A Ž E T A K

Ljudski enzim citokrom P4501A1 (CYP1A1) igra važnu ulogu u metabolizmu ksenobiotika i endogenih supstrata. Budući da se pokazalo kako su polimorfizmi gena CYP1A1 povezani s različitim rizikom od raka i predviđanjem kliničke učinkovitosti nekih kemoterapija u različitim populacijama, većina studija usredotočuje se na njihov klinički značaj. Ovaj rad, međutim, nastoji procijeniti mogu li se polimorfizmi upotrijebiti za razlikovanje ljudskih populacija. Četiri polimorfizma nukleotida CYP1A1 (rs4646903 / g.75011641; rs1048943 / g.75012985; g.75012235; i rs1799814 / g.75012987) analizirana su pomoću PCR-RFLP testa na 1.195 pripadnika različitih ljudskih grupa iz cijelog svijeta. Kako bi se dobio cjelovitiji prikaz varijabilnosti gena CYP1A1, provedene su različite statističke analize na uzorku iz ovog istraživanja studije i na ograničenom broju podataka dobivenih iz prethodno proučavanih populacija. Učestalost alela i haplotipa varira među populacijama: pokazalo se da su rs4646903 (C) i rs1048943 (G) gotovo uvijek povezani i da imaju najviše frekvencije u američkim indijanskim populacijama, dok je varijanta povezana s položajem g.75012235 otkrivena samo u nekim afričkim populacijama. Rad jasno pokazuje da se polimorfizmi CYP1A1 razlikuju među ljudskim populacijima. Predviđanje genotipova predstavlja važan aspekt precizne medicine budući da su neke varijante povezane s određenim karcinomom a rs1048943 pokazuje jaku povezanost s optimiziranom kemoterapijom. Pored toga, gen CYP1A1 igra važnu ulogu u metabolizmu ksenobiotika i vjerojatno na njegovu učestalost utječu okolišni faktori.