

## ORIGINAL ARTICLE



# SLCO1B1 and ABCG2 genotype-informed phenotypes are related to variation in ramipril exposure

Houwaida Abbes<sup>1,2,3</sup> | Pablo Zubiaur<sup>1</sup> | Paula Soria-Chacartegui<sup>1</sup> |  
 Tamara de la Torre<sup>1</sup> | Gonzalo Villapalos-García<sup>1</sup> | Carmen Candau<sup>1</sup> |  
 Andrea Rodríguez-Lopez<sup>1</sup> | Eva González-Iglesias<sup>1</sup> | Marina Aldama<sup>1</sup> |  
 Marcos Navares-Gomez<sup>1</sup> | Asma Omezzine<sup>2,3</sup> | Dolores Ochoa<sup>1</sup> |  
 Francisco Abad-Santos<sup>1,4</sup>

<sup>1</sup>Clinical Pharmacology Department, Hospital Universitario de La Princesa, Universidad Autónoma de Madrid (UAM), Instituto de Investigación Sanitaria La Princesa (IP), Madrid, Spain

<sup>2</sup>Biochemistry Department, LR12SP11, Sahloul University Hospital, Sousse, Tunisia

<sup>3</sup>Faculty of Pharmacy of Monastir, University of Monastir, Monastir, Tunisia

<sup>4</sup>Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain

## Correspondence

Pablo Zubiaur and Francisco Abad-Santos, Clinical Pharmacology Department, Hospital Universitario de La Princesa, Universidad Autónoma de Madrid (UAM), Instituto de Investigación Sanitaria La Princesa (IP), C/Diego de León, 62, 28006 Madrid, Spain.  
 Email: [pablozubiaurprecioso@gmail.com](mailto:pablozubiaurprecioso@gmail.com) and [francisco.abad@uam.es](mailto:francisco.abad@uam.es)

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## Abstract

Ramipril is an angiotensin-converting enzyme inhibitor used for hypertension and heart failure management. To date, scarce literature is available on pharmacogenetic associations affecting ramipril. The goal of this study was to investigate the effect of 120 genetic variants in 34 pharmacogenes (i.e., genes encoding for enzymes like CYPs or UGTs and transporters like ABC or SLC) on ramipril pharmacokinetic variability and adverse drug reaction (ADR) incidence. Twenty-nine healthy volunteers who had participated in a single-dose bioequivalence clinical trial of two formulations of ramipril were recruited. A univariate and multivariate analysis searching for associations between genetic variants and ramipril pharmacokinetics was performed. SLCO1B1 and ABCG2 genotype-informed phenotypes strongly predicted ramipril exposure. Volunteers with the SLCO1B1 decreased function (DF) phenotype presented around 1.7-fold higher dose/weight-corrected area under the curve (AUC/DW) than volunteers with the normal function (NF) phenotype (univariate  $p$ -value [ $p_{uv}$ ]  $< 0.001$ , multivariate  $p$ -value [ $p_{mv}$ ]  $< 0.001$ ,  $\beta = 0.533$ ,  $R^2 = 0.648$ ). Similarly, volunteers with ABCG2 DF + poor function (PF) phenotypes presented around 1.6-fold higher AUC/DW than those with the NF phenotype ( $p_{uv} = 0.011$ ,  $p_{mv} < 0.001$ ,  $\beta = 0.259$ ,  $R^2 = 0.648$ ). Our results suggest that SLCO1B1 and ABCG2 are important transporters to ramipril pharmacokinetics, and their genetic variation strongly alters its pharmacokinetics. Further studies are required to confirm these associations and their clinical relevance.

## KEYWORDS

ABCG2, pharmacogenetics, pharmacokinetics, ramipril, SLCO1B1

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## 1 | INTRODUCTION

One of the most often used antihypertensive drugs is ramipril, it is a potent and extensively used angiotensin-converting enzyme inhibitors (ACEis).<sup>1,2</sup> It is administered orally once or twice daily to adults with hypertension to achieve a total maximum dose of 10 mg.<sup>3</sup> Oral bioavailability is approximately 50%–60%, and it is absorbed through solute transporters in the small intestine.<sup>4</sup> Its maximum concentration ( $C_{max}$ ) is reached within 1 h after administration ( $T_{max}$ ).<sup>5</sup> Its affinity for plasma proteins is about 73%.<sup>6</sup> As a prodrug, it is rapidly deesterified in the liver to ramiprilat, its active metabolite, after gastrointestinal absorption<sup>6</sup>; the enzymes involved in this process are still unknown. Its elimination half-life ( $T_{1/2}$ ) varies between 2–4 h and ramiprilat between 9–18 h.<sup>5</sup> About 60% of the parent drug and its metabolites, including ramiprilat and glucuronide conjugates, are excreted in the urine and about 40% in the faeces.<sup>5</sup> Ramipril is generally well tolerated; however, mild adverse drug reactions (ADRs) may occur.<sup>6</sup> According to the Spanish ramipril drug label, ADRs are classified into frequent, such as cough, dizziness, fatigue or weakness, and less frequent, such as vertigo, occasionally leading to therapy withdrawal (cough: 1%, dizziness: 0.5%).<sup>3</sup>

The lack of evidence available in the literature on the impact of genetic variation on the response to antihypertensive drugs, such as ramipril, results in the absence of pharmacogenetic guidelines for this family of drugs. However, such information could contribute to explaining the variability in response to treatment; used in a preemptive manner, this information could contribute to providing the patient with precision personalized medicine. Thus, the goal of this study was to investigate the effect of genetic variation on relevant pharmacogenes (i.e., genes encoding for metabolizing enzymes like CYPs, transporters such as ABC or SLC, or other enzymes like COMT or UGT) on ramipril pharmacokinetic variability

and, secondarily, on ADR incidence. To our knowledge, this is the most comprehensive pharmacogenetic study for ramipril performed to date. The present work is part of the La Princesa Multidisciplinary Initiative for the Implementation of Pharmacogenetics (PriME-PGx).<sup>7</sup>

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

Data were obtained from a bioequivalence trial performed at the Clinical Trials Unit of Hospital Universitario de La Princesa (UECHUP), Madrid (Spain) in 2021 (EUDRA-CT ID:2021-006759-32), approved by the Independent Ethics Committee of the Hospital Universitario de La Princesa and the Spanish Drug Agency. The clinical trial and the pharmacogenetic study were performed in accordance with Spanish legislation, the International Council on Harmonization (ICH) guidelines on Good Clinical Practice<sup>8</sup> and the Revised Declaration of Helsinki.<sup>9</sup> The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies<sup>10</sup> and in accordance with the Equator Network's Strengthening the Reporting of Pharmacogenetic Studies (STROPS) guidelines.<sup>11</sup> The bioequivalence trial comprised 36 healthy volunteers, 29 of whom consented to participate in the present retrospective pharmacogenetic study.

The inclusion criteria were: men or women subjects who gave their written consent to participate in the study, aged from 18 to 55 years old, with no clinically organic or psychiatric conditions, with normal medical records and physical examination, with no significant abnormalities in laboratory tests, with normal vital signs and electrocardiograms (ECGs) and with no allergies to any drug. The exclusion criteria were: subjects with body mass index (BMI) outside the range 18.5–30.0 kg/m<sup>2</sup>,

pregnant or breastfeeding women, smokers or daily users of alcohol and/or acute alcohol intoxication in the last week, having participated in other clinical trials with administration of investigational drugs in the previous 3 months, having donated blood in the month prior to the start of the study, history of difficulty in swallowing and inability to collaborate and respect the instructions during the study.

### 3 | STUDY DESIGN AND PROCEDURES

This bioequivalence clinical trial compared a 5 mg/25 mg ramipril/hydrochlorothiazide test (T) formulation with Delix<sup>®</sup> 5 mg/25 mg tablets as a reference (R) drug (Sanofi-Aventis Deutschland GmbH). It was a phase I, single-dose, randomized, crossover clinical trial with an open-label, replicated design, with 4 sequences and 4 periods and with blinded determination of plasma concentrations. Each volunteer was randomly assigned to either formulation (R or T) with a 7-day washout period between admission days and was required to be hospitalized from at least 10 h before to 12 h after drug administration in all periods and under fasting conditions. They returned to UECHUP for sample extraction and a safety visit after 24 h. The volunteers received each formulation twice.

Blood samples were collected and stored in EDTA K2 tubes (4 ml). The tubes were centrifuged at 4°C for 10 min at 1900 ×g. Once centrifuged, a 0.4-ml plasma aliquot was stored in a −20°C (±5°C) freezer until its shipment to an external bioanalytical lab. The method involved a liquid–liquid extraction procedure with ethyl acetate. Drug plasma levels were determined with a reversed-phase ultra-high-performance liquid chromatography mass spectrometry (UPLC-MS/MS) analytical method validated in accordance with the requirements of the European Medicines Agency (EMA), with a lower limit of quantification (LLOQ) of 200 pg/ml.

#### 3.1 | Pharmacokinetic analysis

All volunteers provided 19 blood samples between the basal dose and 24 h after ramipril intake. The following pharmacokinetic parameters were directly obtained from ramipril plasmatic time-concentration curves:  $C_{\max}$  and  $T_{\max}$ . A non-compartmental analysis was performed using WinNonLin Professional Software (version 8.1, Pharsight Corporation, Palo Alto, California, USA) to determine the remaining pharmacokinetic parameters. According to the linear trapezoid standard rule, the area

under the curve (AUC) between the predose and the dose at the final time point,  $t = 24$  h ( $AUC_{0-24h}$ ), was calculated. The  $AUC_{24h-\infty}$  was calculated by the ratio  $C_{24h}/K_e$ , where  $K_e$  is the constant of elimination of the drug, and the AUC from 0 to infinite was calculated as  $AUC_{0-24h} + AUC_{24h-\infty}$ . Since T was shown to be bioequivalent to R, the mean of each parameter was calculated for each volunteer to control for individual variability.

#### 3.2 | Safety

Ramipril tolerability was addressed through blood, biochemical, urine and serological tests, physical examination and vital sign monitoring, including a 12-lead ECG. Adverse events (AEs) were identified by asking the volunteers a generic question or by spontaneous notification. The algorithm of the Spanish pharmacovigilance system<sup>12</sup> was used to assess causality. Only AEs with a definite, probable or possible link to ramipril use were considered as ADRs and considered for the safety assessment.

#### 3.3 | Genotyping

DNA extraction was carried out from total peripheral blood stored in EDTA-K2 tubes using an automatic DNA extractor (Maxwell<sup>®</sup> RSC instrument, Promega, USA). DNA concentration was measured using a Qubit<sup>®</sup> 3.0 fluorometer (ThermoFisher, USA) and homogenized at 30–70 ng/μl. Genotyping was performed by a QuantStudio 12K Flex qPCR instrument (Applied Biosystems, ThermoFisher, USA) with an OpenArray thermal block and a personalized (Very Important Pharmacogene Open Array, version 3, VIPOA3), which includes the most important variants in clinically important pharmacogenes. The inclusion of genes and variants is based on various criteria: (a) the clinical significance of the gene (i.e., genes associated with drug metabolism, transport and response are covered), (b) the evidence supporting the functional consequence of variants and (c) the frequency of clinically relevant variants in our population (i.e., mainly European, with some African and Latin-American ethnic groups); for this purpose, the information available at the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Pharmvar website, the Pharmacogene Variation Consortium (PharmVar) website and in the Association for Molecular Pathology (AMP) PGx Working Group consensus documents is revised.<sup>13–15</sup> A total of 120 variants in 34 genes were analysed as shown in Table 1. To our knowledge, the enzymes involved in ramipril metabolism are not

TABLE 1 Genotyped alleles and contained variants.

Gene	Allele name	Variant/s
<i>ABCB1</i>	Legacy name: C1236T	rs1128503 (T > C)
	Legacy name: C3435T	rs1045642 (T > C)
	Legacy name: G2677 T/A	rs2032582 (T > G/A)
<i>ABCC2</i>	N/A	rs2273697 (G > A)
	N/A	rs3740066 (C > T)
<i>ABCC3</i>	N/A	rs4793665 (C > T)
	N/A	rs9895420 (T > A)
<i>ABCG2</i>	N/A	rs2231142 (C > A)
	N/A	rs2231137 (G > A)
	N/A	rs7699188 (C > T)
<i>CES1</i>	N/A	rs2244613 (C > A)
	N/A	rs71647871 (G > A)
	N/A	rs8192935 (T > C)
<i>COMT</i>	N/A	rs13306278 (C > T)
	N/A	rs4680 (G > A)
	N/A	rs4818 (C > G)
	N/A	rs5993883 (T > G)
<i>CYP1A1</i>	N/A	rs4646903 (T > C)
	N/A	rs1048943 (A > G)
	N/A	rs1799814 (C > A)
<i>CYP1A2</i>	N/A	rs2470890 (T > C)
	N/A	rs2069514 (G > A)
	N/A	rs2069526 (T > G)
	N/A	rs762551 (C > A)
	N/A	rs12720461 (C > T)
	N/A	rs72547516 (A > G)
<i>CYP2A6</i>	N/A	rs28399433 (T > G)
<i>CYP1B1</i>	N/A	rs10012 (C > G)
	N/A	rs1056836 (C > G)
	N/A	rs1800440 (T > C)
<i>CYP2B6</i>	*4	rs2279343 (A > G)
	*5	rs3211371 (C > T)
	*6	rs3745274 (G > T), rs2279343 (A > G)
	*7	rs3745274 (G > T), rs2279343 (A > G), rs3211371 (C > T)
	*9	rs3745274 (G > T)
	*22	rs34223104 (T > C)
<i>CYP2C19</i>	*2	rs4244285 (G > A), rs12769205 (A > G)
	*3	rs4986893 (G > A)
	*4	rs28399504 (A > G)
	*5	rs56337013 (C > T)
	*6	rs72552267 (G > A)
	*7	rs72558186 (T > A)
	*8	rs41291556 (T > C)

TABLE 1 (Continued)

Gene	Allele name	Variant/s
	*9	rs17884712 (G > A)
	*17	rs12248560 (C > T)
	*35	rs12769205 (A > G)
CYP2C8	*2	rs11572103 (A > G)
	*3	rs10509681 (A > G), rs11572080 (G > A)
	*4	rs1058930 (C > G)
CYP2C9	*2	rs1799853 (C > T)
	*3	rs1057910 (A > C)
	*5	rs28371686 (C > G)
	*8	rs7900194 (G > A)
	*11	rs28371685 (C > T)
CYP2D6	*2	rs16947 (C > T), rs1135840 (G > C)
	*3	rs35742686 (T > delT)
	*4	rs3892097 (G > A), (rs1065852 (C > T)), (rs1135840 (G > C))
	*6	rs5030655 (A > delA)
	*7	rs5030867 (T > G)
	*8	rs5030865 (G > A), rs16947 (C > T), rs1135840 (G > C)
	*9	rs5030656 (AAG > delAAG)
	*10	rs1065852, rs1135840 (G > C)
	*12	rs5030862 (G > A), rs16947 (C > T), rs1135840 (G > C)
	*14	rs5030865 (G > A), rs16947 (C > T), rs1135840 (G > C)
	*15	rs774671100 (A > dupA)
	*17	rs28371706 (C > T), rs16947 (C > T), rs1135840 (G > C)
	*19	rs72549353 (AACT>delAACT)
	*29	rs59421388 (G > A), rs1135840 (G > C), rs16947 (C > T)
	*41	rs28371725 (G > A), rs1135840 (G > C), rs16947 (C > T)
	*56	rs72549347 (C > T)
	*59	rs79292917 (G > A)
CYP3A43	N/A	rs61469810 (A > delA)
CYP3A4	*2	rs55785340 (T > C)
	*3	rs4986910 (T > C)
	*4	rs55951658 (A > G)
	*5	rs55901263 (C > G)
	*6	rs4646438 (A > dupA)
	*18	rs28371759 (T > C)
	*20	rs67666821 (T > TT)
	*22	rs35599367 (C > T)
	*36	rs2242480 (G > A)
CYP3A5	*3	rs776746 (A > G)
	*6	rs10264272 (G > A)
	*7	rs41303343 (T > dupT)
NAT2	*5	rs1801280 (T > C)

(Continues)

TABLE 1 (Continued)

Gene	Allele name	Variant/s
	*6	rs1799930 (G > A)
	*7	rs1799931 (G > A)
<i>SLC19A1</i>	N/A	rs1051266 (T > C)
<i>SLC22A1</i>	N/A	rs72552763 (GAT>delGAT)
	N/A	rs12208357 (C > T)
	N/A	rs34059508 (G > A)
	N/A	rs628031 (A > G)
<i>SLC22A2</i>	N/A	rs316019 (A > C)
<i>SLC28A3</i>	N/A	rs7853758 (G > A)
<i>SLC6A2</i>	N/A	rs12708954 (C > A)
	N/A	rs3785143 (C > T)
<i>SLCO1B1</i>	*3	rs56061388 (T > C)
	*4	rs11045819 (C > A)
	*5	rs4149056 (T > C)
	*6	rs55901008 (T > C)
	*9	rs59502379 (G > C)
	*14	rs2306283 (A > G), rs11045819 (C > A)
	*15	rs2306283(A > G), rs4149056 (T > C)
	*19	rs34671512 (A > C)
	*20	rs34671512 (A > C), rs2306283 (A > G)
	*23	rs373327528 (G > A)
	*31	rs2306283 (A > G), rs59502379 (G > C)
	*37	rs2306283 (A > G)
	*40	rs34671512 (A > C), rs4149056 (T > C)
<i>UGT1A</i>	N/A	rs10929302 (G > A)
<i>UGT1A1</i>	N/A	rs4148323 (G > A)
	N/A	rs887829 (C > T)
	N/A	rs8330 (G > C)
<i>UGT1A3</i>	N/A	rs2008584 (A > G)
<i>UGT1A4</i>	N/A	rs2011425 (T > G)
<i>UGT1A6</i>	N/A	rs10445704 (G > A)
	N/A	rs7592281(G > T)
<i>UGT1A8</i>	N/A	rs1042597 (C > T)
<i>UGT2B10</i>	N/A	rs61750900 (G > T)
<i>UGT2B15</i>	N/A	rs1902023 (A > C)
<i>UGT2B7</i>	N/A	rs7668258 (T > C)

characterized; therefore, variants in genes encoding for CYP, UGT and COMT enzymes were included exploratorily. Similarly, it remains unknown what transporters ramipril is a substrate of; therefore, variants encoding for SLC and ABC transporters were included. The genotype frequency of the genetic variants analysed is included in

Table S1. Hardy–Weinberg equilibrium was met by all variants except for *ABCG2* rs2231137, *CYP3A43* rs61469810 and *NAT2* rs1799930. Due to the low variability derived from the modest sample size, it can be proposed that the observed deviations are caused by mere chance and are not indicative of true deviations from



equilibrium, for example, inbreeding or stratification of the population.

Variants in parentheses may appear in the allele but are not core variants; alleles are defined according to PharmVar rules. The absence of variants in a gene is defaulted to \*1, except for *NAT2*, which is defaulted to \*4. Examples of allele definition: individuals with a C/C genotype for *SLCO1B1* rs56061388 (T > C) and the reference variant in homozygosis in the remaining *SLCO1B1* variants present a *SLCO1B1* \*3/\*3 diplotype. Volunteers with a C/A genotype for *SLCO1B1* rs11045819 (C > A) and the reference variant in homozygosis in the remaining *SLCO1B1* variants present a *SLCO1B1* \*1/\*4 diplotype; individuals with a C/C genotype for *SLCO1B1* rs4149056 (T > C) and an A/G genotype for *SLCO1B1* rs2306283 (A > G) and having the reference variant in homozygosis for the remaining *SLCO1B1* variants have a \*5/\*15 diplotype.

In addition, two *CYP2D6* gene copy number variation (CNV) assays targeting exon 9 (ThermoFisher assay ID: Hs00010001\_cn) and intron 2 (ThermoFisher assay ID: Hs04083572\_cn) were carried out in the same instrument using a 96-well thermal block and a TaqMan™ Copy Number Reference Assay, human RNase P (ThermoFisher catalogue ID: 4403328) as a reference. The analysis was carried out using a CopyCaller™ software. Each sample was run in quadruplicate.<sup>16</sup> This allows the detection of *CYP2D6* gene deletion (\*5), duplication (xN) and some *CYP2D6*-*CYP2D7* and *CYP2D7*-*CYP2D6* hybrids.

### 3.4 | Allele definition and phenotype inference

The PharmVar allele database was used to define *CYP* and *SLCO1B1* star alleles, which is in concordance with CPIC allele definition tables associated with a number of published guidelines (e.g., *CYP2B6* and efavirenz,<sup>17</sup> *CYP2C19*-clopidogrel,<sup>18</sup> *CYP2C9*-anti-inflammatory drugs,<sup>19</sup> *CYP2D6*-tamoxifen,<sup>18</sup> *CYP3A5*-tacrolimus,<sup>20</sup> *SLCO1B1*-statins<sup>19</sup>).<sup>21</sup> The *ABCG2* c.421C > A variant (Q141K, rs2231142) was genotyped and the transporter's genotype-informed phenotype was assigned based on CPIC's statins guideline<sup>19</sup> (Table S2). Thus, individuals carrying an *ABCG2* rs2231142 C/C genotype were classified as normal function (NF); those with an *ABCG2* rs2231142 C/A genotype were classified as decreased function (DF), whereas those with an *ABCG2* rs2231142 A/A genotype were classified as poor function (PF) for this transporter. In accordance with the recommendations of the Dutch Pharmacogenetics Working Group

(DPWG), *CYP3A4* alleles were used to define the pharmacogenetic phenotype<sup>22</sup> (Table S2). For *CYP2C8*, the phenotype was inferred as previously described.<sup>23</sup>

### 3.5 | Statistical analysis

The SPSS software was used to perform statistical analysis (version 23.0, SPSS Inc., Chicago, USA). A Shapiro–Wilk test was used to check the normality of all the variables, and the ones not normally distributed were logarithmically transformed. The same test was used again for log-transformed variables to ensure their normal distribution. Initially, a univariate analysis was carried out, in which the mean of pharmacokinetic parameters or the incidence of ADRs was compared according to sex, biogeographic groups, as reported previously,<sup>24</sup> genotypes and phenotypes. A *p* value lower than 0.05 was considered statistically significant ( $p_{uv}$ ). For pharmacokinetic variables with a normal distribution, parametric tests were used: a *t*-test for variables with two categories and an ANOVA test followed by a Bonferroni post-hoc for variables with more than two categories. For pharmacokinetic variables without a normal distribution, non-parametric tests were used: a Mann–Whitney test for parameters with two categories and a Kruskal–Wallis test for variables with more than two categories. Additionally, to compare the incidence of ADRs according to sex, self-reported ethnicity, genotypes or phenotypes, a Chi<sup>2</sup> test was used. For all these tests, a *p* value lower than 0.05 was considered statistically significant. A subsequent multivariate analysis of the dependent variables was conducted. As independent variables, any variable showing significant associations in the univariate analysis was introduced in the models. For discrete or continuous variables, logistic or linear regression was used, respectively. A *p* value lower than 0.05 was considered statistically significant ( $p_{mv}$ ). The unstandardized  $\beta$  coefficients and the coefficient of determination  $R^2$ , which show the relative contribution of each variable and the overall model fit, are given. The Bonferroni correction for multiple comparisons was applied.

## 4 | RESULTS

The study's total population comprised 29 healthy volunteers, 15 women (52%) and 14 men (48%). Volunteers mainly self-reported to be Latin-Americans ( $n = 22$ , 76%) and Europeans ( $n = 7$ , 24%). Men displayed a higher weight, height and BMI than women ( $p < 0.001$ ,  $p < 0.001$ ,  $p = 0.022$ , respectively) and similar age (Table 2). However, none of these demographic

TABLE 2 Demographic characteristics of the study population.

			Age		Weight (kg)		Height (m)		BMI (kg/m <sup>2</sup> )	
Variable		N	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Sex	Women	15	35.47	9.32	61.90	8.27	1.62	0.62	23.63	2.38
	Men	14	31.14	7.27	79.41*	9.38	1.74*	0.05	26.06*	3.01
Biogeographic group	Europeans	7	36.43	11.30	66.34	11.38	1.66	0.10	24.03	2.47
	Mixed	22	32.41	7.52	71.63	12.72	1.68	0.09	25.05	3.07
	Total	29	33.38	8.53	70.35	12.42	1.68	0.09	24.81	2.93

Abbreviation: BMI, body mass index.

\* $p < 0.05$  ( $t$ -test).

TABLE 3 Ramipril pharmacokinetic parameters according to sex and ethnicity.

		N	AUC/DW (h*ng*kg/ml*mg)		C <sub>max</sub> /DW (ng*kg/ mg*ml)		T <sub>max</sub> (h)		T <sub>1/2</sub> (h)	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
Sex	Women	15	100.42	44.86	150.09	63.81	0.52	0.17	0.66	0.47
	Men	14	<b><u>116.02</u></b>	53.81	143.83	38.83	0.57	0.19	1.07	1.65
Biogeographic group	Europeans	7	97.45	47.17	149.34	61.24	0.45	0.09	0.55	0.14
	Mixed	22	111.29	50.34	146.35	50.87	0.58	0.20	0.95	1.35
	Total	29	107.95	49.13	147.07	52.40	0.55	0.18	0.85	1.19

Note: No statistical significance in univariate analyses. Underlined  $p < 0.05$  after multivariate analysis (independent variables: sex, SLCO1B1 NF vs. DF, ABCG2 NF vs. DF + PF, UGT1A1 rs2011425 T/T vs. T/G, ABCC3 rs9895420 T/T vs. A/T + A/A, CYP1A2 rs762551 C/C vs. A/C + A/A, SLC22A1 rs628031 A/A vs. G/A + G/G).

Abbreviations: AUC/DW, dose/weight-corrected area under the curve; DF, decreased function; NF, normal function; PF, poor function.

parameters were significantly different according to the self-reported biogeographic group (Table 2).

The mean AUC<sub>∞</sub> and C<sub>max</sub> were  $7.74 \pm 3.42$  h\*ng/ml and  $10.71 \pm 43.85$  ng/ml, respectively. Men showed a mean AUC<sub>∞</sub> of  $7.30 \pm 3.17$  h\*ng/ml and women of  $8.15 \pm 3.70$  h\*ng/ml ( $p = 0.532$ ) and a C<sub>max</sub> of  $9.11 \pm 2.43$  ng/ml and  $12.19 \pm 53.01$  ng/ml, respectively ( $p = 0.061$ ). Men exhibited a higher dose/weight-corrected AUC (AUC/DW) value compared to women even after the Bonferroni correction for multiple comparisons (threshold for significance:  $0.05/7 = 0.007$ ) (unstandardized  $\beta$  coefficient = 0.292,  $R^2 = 0.648$ ,  $p_{mv} < 0.001$ ) (Table 3). The remaining pharmacokinetic parameters were not significantly different according to sex and self-reported biogeographic group.

Healthy volunteers with the SLCO1B1 DF phenotype presented 1.7-fold higher AUC/DW values than volunteers with the NF phenotype ( $p_{uv} < 0.001$ , unstandardized  $\beta$  coefficient = 0.533,  $R^2 = 0.648$ ,  $p_{mv} < 0.001$ ), a 1.5-fold higher C<sub>max</sub>/DW ( $p_{uv} < 0.001$ , unstandardized  $\beta$  coefficient = 0.453,  $R^2 = 0.447$ ,  $p_{mv} < 0.001$ ) and a 2.7-fold higher T<sub>1/2</sub> ( $p_{uv} = 0.016$ ) (Table 4). The AUC/DW and C<sub>max</sub> associations reached the significant

threshold after the Bonferroni correction for multiple comparisons. Furthermore, individuals with ABCG2 DF + PF phenotypes showed 1.6-fold higher AUC/DW compared to those with ABCG2 NF phenotypes ( $p_{uv} = 0.011$ , unstandardized  $\beta$  coefficient = 0.259,  $R^2 = 0.648$ ,  $p_{mv} < 0.001$ ); individuals with DF + PF phenotypes had higher T<sub>1/2</sub> (unstandardized  $\beta$  coefficient = 1.226,  $R^2 = 0.194$ ,  $p_{mv} = 0.028$ ) and T<sub>max</sub> (unstandardized  $\beta$  coefficient = 0.263,  $R^2 = 0.439$ ,  $p_{mv} = 0.002$ ) than NF individuals (Table 4). The AUC/DW and T<sub>max</sub> associations reached the significant threshold after the Bonferroni corrections for multiple comparisons. Additionally, individuals with the UGT1A1 rs2011425 T/G genotype were related to a higher AUC/DW ( $p_{uv} = 0.007$ ) and a higher C<sub>max</sub>/DW ( $p_{uv} = 0.038$ ) compared to volunteers with the T/T genotype (Table 4). Furthermore, participants with ABCC3 rs9895420 A/T + A/A genotypes showed a lower T<sub>max</sub> compared to those with the T/T genotype ( $p_{uv} = 0.050$ ). Similarly, for CYP1A2 rs762551, subjects with the C/C genotype showed lower T<sub>max</sub> than subjects with the A/A and A/C genotypes ( $p_{uv} = 0.034$  and  $p_{uv} = 0.044$ , respectively), and subjects with the



**TABLE 4** Ramipril pharmacokinetic parameters based on genotypes or phenotypes with significant variability.

			AUC/DW (h*ng*kg/ml*mg)		Cmax/DW (ng*kg/ mg*ml)		T <sub>max</sub> (h)		T <sub>1/2</sub> (h)	
Variable		N	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SLCO1B1 phenotype	NF	15	86.59	22.35	124.08	30.92	0.51	0.14	0.51	0.20
	DF	11	<b>150.67<sup>*#</sup></b>	51.16	<b>191.10<sup>*#</sup></b>	52.59	0.63	0.22	<b>1.39<sup>*</sup></b>	1.84
ABCG2 phenotype	NF	22	94.50	33.92	139.81	41.45	0.49	0.10	0.56	0.25
	DF	5	<b>150.55<sup>†#</sup></b>	80.22	146.70	79.30	<b>0.85<sup>#</sup></b>	0.17	<b>2.24</b>	2.58
	PF	2	<b>149.44<sup>†#</sup></b>	34.37	227.94	37.47	<b>0.44<sup>#</sup></b>	0.03	<b>0.63</b>	0.11
UGT1A1 rs2011425	T/T	23	95.83	35.08	137.02	47.53	0.52	0.15	0.60	0.27
	T/G	6	<b>154.41<sup>**</sup></b>	69.55	<b>185.61<sup>**</sup></b>	56.49	0.66	0.27	1.83	2.48
ABCC3 rs9895420	T/T	23	115.21	52.22	151.07	56.51	0.58	0.19	0.95	1.32
	A/T + A/A	5	75.70	16.87	121.82	21.88	<b>0.43<sup>**</sup></b>	0.05	0.49	0.10
CYP1A2 rs762551	C/C	8	93.19	37.78	142.42	40.56	<b>0.44<sup>\$</sup></b>	0.09	0.49	0.10
	A/C	13	123.34	56.48	154.84	52.82	0.58	0.20	1.19	1.67
	A/A	8	97.71	44.15	139.09	65.93	0.60	0.20	0.68	0.65
SLC22A1 rs628031	A/A	3	150.28	103.89	128.39	24.60	<b>0.80<sup>£</sup></b>	0.23	2.48	3.65
	G/A	11	110.71	45.19	161.26	63.21	0.50	0.17	0.74	0.52
	G/G	15	97.46	36.32	140.40	47.66	0.53	0.15	0.62	0.30

Note: Underlined  $p < 0.05$  after multivariate analysis (independent variables: sex, SLCO1B1 phenotype NF vs. DF, ABCG2 phenotype NF vs. DF + PF, UGT1A1 rs2011425 T/T vs. T/G, ABCC3 rs9895420 T/T vs. A/T + A/A, CYP1A2 rs762551 C/C vs. A/C + A/A, SLC22A1 rs628031 A/A vs. G/A + G/G). Abbreviations: AUC/DW, dose/weight-corrected area under the curve; DF, decreased function; NF, normal function; PF, poor function.

<sup>\*</sup> $p < 0.05$  versus NF phenotype ( $t$ -test).

<sup>†</sup> $p < 0.05$  DF + PF versus NF ( $t$ -test).

<sup>\*\*</sup> $p < 0.05$  versus T/T ( $t$ -test).

<sup>\$</sup> $p < 0.05$  versus A/A and A/C (Mann-Whitney test).

<sup>£</sup> $p < 0.05$  versus G/G and G/A (Mann-Whitney test).

<sup>#</sup> $p < 0.007$  significance after Bonferroni correction for multiple comparisons.

SLC22A1 rs628031 A/A genotype showed higher  $T_{\max}$  compared to subjects with the G/G and G/A genotypes ( $p_{\text{uv}} = 0.040$ ) (Table 4). However, the associations for UGT1A1 rs2011425, ABCC3 rs9895420, CYP1A2 rs762551 and SLC22A1 rs628031 did not reach the significant threshold after Bonferroni correction for multiple comparisons. No further associations were observed. The mean and standard deviation of the pharmacokinetic parameters for the remaining genotypes or phenotypes are shown in Table S3.

#### 4.1 | Safety

No serious ADRs were reported during this study. Only three volunteers suffered ADRs related to the drug intake, including headaches ( $n = 3$ ) and dizziness ( $n = 1$ ). ADR incidence was unrelated to genetic variation or drug exposure.

## 5 | DISCUSSION

Around 65 million adults, or almost one fourth of the population in the United States, suffer with hypertension.<sup>25</sup> In Tunisia, the prevalence of hypertension is around 30.6%<sup>26</sup> and 42.6% in Spain.<sup>27</sup> A continuous rise in blood pressure might destabilize vascular lesions and induce acute coronary events, accelerating the development and progression of atherosclerosis.<sup>28</sup> Each 20/10 mmHg increase in systolic/diastolic blood pressure among people aged 40–90 years doubles the risk of severe coronary events.<sup>29</sup> As a result, rigorous hypertension management is required, and ramipril is a commonly utilized hypertension treatment.<sup>30</sup> To date, scarce literature has been published on potential pharmacogenetic biomarkers related to ramipril treatment effectiveness or safety, which motivated the present work.

The average  $AUC_{\infty}$  in this study was  $7.74 \pm 3.42$  h\*ng/ml. This value is lower and not

consistent with what was reported in previous works: at the same dose (5 mg), Ruf et al.<sup>31</sup> reported an  $AUC_{0-4h}$  of  $15.80 \pm 6.34$  h\*ng/ml; moreover, at the dose of 2.5 mg, van Griensven et al.<sup>32</sup> reported an  $AUC_{0-12h}$  of  $10.50 \pm 2.90$  h\*ng/ml, and at the dose of 10 mg, Allegrini et al.<sup>33</sup> reported an  $AUC_{0-168h}$  of  $23.10 \pm 13.30$  h\*ng/ml. The observed  $T_{1/2}$  of ramipril in this work was lower than 1 h; thus, any AUC sampling 7–9 h or more is expected to cover 95% or more of  $AUC_{\infty}$ . This suggests, based on the presented data, that ramipril  $AUC_{\infty}$  could be dose independent. Notably, however, the ramipril formulation was significantly different between studies. In our study, ramipril was co-administered with hydrochlorothiazide, which may reduce ramipril bioavailability. To the best of our knowledge, this is the first work to report the possibility of this interaction. If this interaction is confirmed, the exact mechanism (e.g., a reduced absorption or an accelerated excretion) should be further explored. Nevertheless, differences in ramipril bioavailability might also be caused by other differences in drug formulation and/or by differences in sampling times or in the performance of the studies.

It is widely recognized that sex influences the response to antihypertensive medications.<sup>34</sup> According to Tamargo et al.,<sup>35</sup> because men normally weigh more than women, giving the same dose results in a higher dose/weight in women compared to men, which results in increased drug exposure in women. Here, consistently, men showed an average  $AUC_{\infty}$  of  $7.30 \pm 3.17$  h\*ng/ml and women of  $8.15 \pm 3.70$  h\*ng/ml; these differences were not significant ( $p = 0.532$ ). According to Rydberg et al.,<sup>36</sup> several factors influence the distribution of drugs, including the lean-to-adipose tissue ratio, the volume of circulating plasma, and the abundance of drug-binding plasma proteins. Women are typically exposed to higher levels of water-soluble drugs because they generally have lower body mass and a higher body fat percentage than men (45). Given that ramipril is known to be sparingly soluble in water, this suggests that the drug may be distributed to a greater extent in women, reducing plasma concentration, which could affect the outcomes of ramipril pharmacotherapy (46). This may explain why, when correcting for DW, men had a significantly higher  $AUC/DW$  than women in our study. This is in accordance with the literature that supports that, over time, ACEi effectiveness is diminished in women.<sup>34</sup>

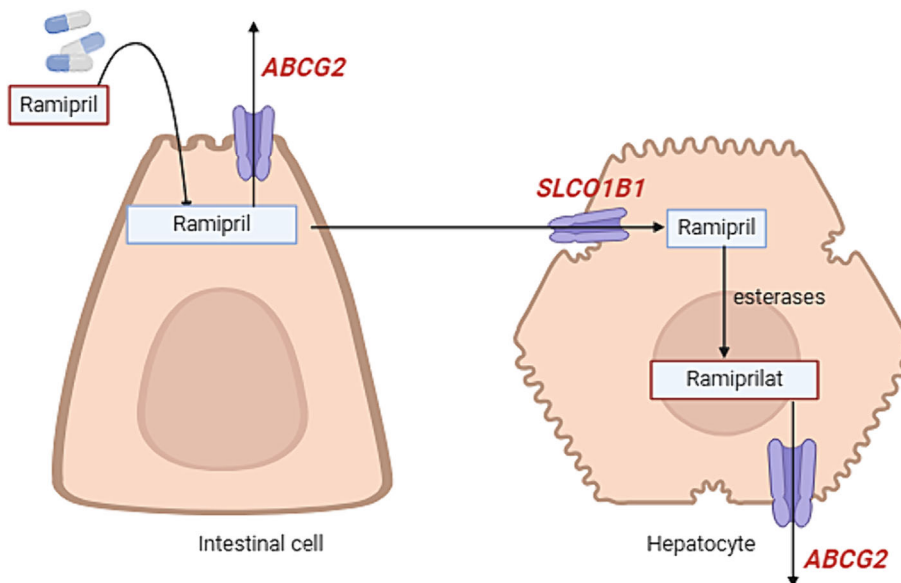
To the best of our knowledge, ramipril is not reported to be a SLCO1B1 substrate. In this study, in contrast, individuals with SLCO1B1 DF presented higher ramipril exposure, almost double that of NF, and higher  $T_{1/2}$ . It is well acknowledged that the SLCO1B1 protein, also

known as organic anion-transporting polypeptide 1B1 (OATP1B1), is mainly located at the sinusoidal membranes of human hepatocytes, where it mediates the influx of their substrates from blood into the hepatocytes.<sup>37</sup> The higher ramipril exposure observed in volunteers with lower OAT1B1 activity suggests that this transporter is involved in its hepatic uptake, as hepatic uptake is needed to transform ramipril into its active metabolite. Based on this and on our data, ramipril is suggested to be a SLCO1B1 substrate.

To our knowledge, ramipril is not reported to be an ABCG2 substrate either. However, volunteers in this study with ABCG2 PF and DF phenotypes presented an approximately 50% higher AUC than NF. ABCG2, also known as breast cancer resistance protein (BCRP), is an efflux transporter widely expressed in the proximal tubules of the kidneys, the liver and the intestines.<sup>38</sup> It serves as a tissue barrier by increasing the excretion of its substrates into the bile and urine as well as reducing the absorption of those substrates from the gastrointestinal tract and circulation.<sup>39</sup> Ramipril and ramiprilat are known to be excreted in the bile. Accordingly, ramipril may be excreted from the liver via ABCG2. The association between ABCG2 variation and the pharmacokinetics of multiple drugs has been largely studied.<sup>38</sup> For instance, ABCG2 genotyping predicts rosuvastatin-induced musculoskeletal ADRs.<sup>19,40</sup> Consistently, ramipril could also be excreted less in individuals with ABCG2 DF and PF phenotypes, resulting in higher systematic exposure.<sup>41</sup> However, ABCG2 is also involved in absorption, excreting drugs from intestinal cells to the intestinal lumen. Thus, lower transporter activity might result in lower ramipril efflux and, therefore, higher plasmatic exposure. Thus, the ABCG2 intestinal role might also explain the differences observed in ramipril pharmacokinetics.<sup>42</sup>

Surprisingly, SLCO1B1 and ABCG2 are key transporters for rosuvastatin pharmacokinetics,<sup>43</sup> but these are structurally unrelated molecules.<sup>19</sup> However, when evaluating some of their physical–chemical properties, some similarities can be observed: rosuvastatin has a molecular weight of 481.54 g/mol and a predicted logP of 1.5–1.9, while ramipril has a molecular weight of 416.51 g/mol and a predicted logP of 0.9–1.5. Furthermore, their strongest acidic pKa is similar, with values of 4.0 and 3.8, respectively. The fact that both molecules partially share some physical–chemical properties and the results obtained in this research argue in favour of the implication of both SLCO1B1 and ABCG2 in ramipril pharmacokinetics. However, further study is needed since this pair of transporters might be involved in the pharmacokinetics of more drugs independently of their

**FIGURE 1** Schematic representation of the hypothetical role of ABCG2 and SLCO1B1 in ramipril pharmacokinetics.



physicochemical properties. A schematic representation of our hypothesis on ramipril pharmacokinetics is shown in Figure 1.

Further *in vitro* research is required to confirm the SLCO1B1/ABCG2-ramipril interaction, and additional *in vivo* research is required to confirm the clinical relevance of their genotype-informed phenotypes.

Even though they are novel, the remaining associations observed in this study should be considered with caution, as the variants were in genes with a lower level of structural and functional validation. These affect *UGT1A1*, *CYP1A2*, *SLC22A1* and *ABCC3* associations, which should be further explored to reach any conclusion as they could be spurious or of a lower magnitude.

Although our safety analysis revealed no significant AEs associated with ramipril exposure across different genotype-informed phenotypes, it is important to interpret these findings cautiously due to the relatively small sample size included in our study and to the administration of a single dose of the drug to healthy volunteers. However, this methodology was useful in previous studies conducted in our clinical trials unit with modest sample sizes, where CYP2B6 PMs showed higher efavirenz exposure and higher nightmare incidence.<sup>44</sup>

## 5.1 | Limitations

The major limitation of this work was the limited sample size of the population, which may affect the statistical power, and several pharmacogenetic biomarkers may be excluded due to their rare frequency. Furthermore, the

administration of a single dose of ramipril prevented us from researching the drug's efficiency or long-term safety. However, the power of this study was that it is the first one to elaborate on the relationship between such pharmacogenetic biomarkers and ramipril efficacy/safety.

## 6 | CONCLUSIONS

SLCO1B1 and ABCG2 genotype-informed phenotypes strongly predicted ramipril exposure. This suggests that SLCO1B1/ABCG2 are important transporters for ramipril pharmacokinetics. To the best of our knowledge, this is the first comprehensive pharmacogenetic study of ramipril and the first to suggest these gene–drug interactions. Further research is required to confirm the interactions between *SLCO1B1* and *ABCG2* variation and ramipril pharmacokinetics and their clinical relevance.

## AUTHOR CONTRIBUTIONS

**Conceptualization:** Houwaida Abbès, Pablo Zubiaur and Francisco Abad-Santos. **Methodology:** Houwaida Abbès and Pablo Zubiaur. **Software:** Houwaida Abbès, Paula Soria-Chacartegui and Pablo Zubiaur. **Validation:** Pablo Zubiaur and Francisco Abad-Santos. **Formal analysis:** Houwaida Abbès and Pablo Zubiaur. **Investigation:** Houwaida Abbès, Pablo Zubiaur, Paula Soria-Chacartegui, Tamara de la Torre, Gonzalo Villapalos-García, Carmen Candau, Andrea Rodríguez-Lopez, Eva González-Iglesias, Marina Aldama, Marcos Navares-Gomez, Asma Omezzine, Dolores Ochoa and Francisco Abad-Santos. **Resources:** Dolores Ochoa and Francisco Abad-Santos.

**Data curation:** Houwaida Abbes and Pablo Zubiaur. **Writing—original draft preparation:** Houwaida Abbes and Pablo Zubiaur. **Writing—review and editing:** Houwaida Abbes, Pablo Zubiaur, Paula Soria-Chacartegui, Andrea Rodríguez-Lopez, Eva González-Iglesias, Asma Omezzine and Francisco Abad-Santos. **Visualization:** Houwaida Abbes, Pablo Zubiaur and Francisco Abad-Santos. **Supervision:** Pablo Zubiaur and Francisco Abad-Santos. **Project administration:** Pablo Zubiaur and Francisco Abad-Santos. **Funding acquisition:** Francisco Abad-Santos. All authors have read and agreed to the published version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

F. Abad-Santos and D. Ochoa have been consultants or investigators in clinical trials sponsored by the following pharmaceutical companies: Abbott, Alter, Aptatargets, Chemo, Cinfa, FAES, Farmalider, Ferrer, GlaxoSmithKline, Galenicum, Gilead, Italfarmaco, Janssen-Cilag, Kern, Moderna, MSD, Normon, Novartis, Servier, Silver Pharma, Teva and Zambon. The remaining authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

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

## ORCID

Houwaida Abbes  <https://orcid.org/0009-0005-8059-7349>

Francisco Abad-Santos  <https://orcid.org/0000-0002-6519-8885>

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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