Pharmacogenetic research activity in Central America and the Caribbean: a systematic review

Aim: The present review was aimed at analyzing the pharmacogenetic scientific activity in Central America and the Caribbean. **Materials & methods:** A literature search for pharmacogenetic studies in each country of the region was conducted on three databases using a list of the most relevant pharmacogenetic biomarkers including 'phenotyping probe drugs' for major drug metabolizing enzymes. The review included 132 papers involving 47 biomarkers and 35,079 subjects (11,129 healthy volunteers and 23,950 patients). **Results:** The country with the most intensive pharmacogenetic research was Costa Rica. The most studied medical therapeutic area was oncology, and the most investigated biomarkers were CYP2D6 and *HLA-A/B*. **Conclusion:** Research activity on pharmacogenetics in Central American and the Caribbean populations is limited or absent. Therefore, strategies to promote effective collaborations, and foster interregional initiatives and research efforts among countries from the region could help for the rational clinical implementation of pharmacogenetics and personalized medicine.

First draft submitted: 24 March 2016; Accepted for publication: 7 July 2016; Published online: 16 September 2016

Keywords: biomarkers • Caribbean region • Central America • pharmacogenetics • pharmacogenomics

The EMA defines pharmacogenetics as “the study of the variability of the expression of individual genes relevant to drug response at cellular, tissue, individual or population level” [1]. One of the aims of this well-established field is to use the genetic information of patients that is believed to potentially influence drug response to optimize drug dose and minimize adverse effects during drug treatment. Although the translation of pharmacogenetics research into clinical practice still faces numerous challenges, several drug regulatory agencies (DRAs) have already included information on promising pharmacogenetic biomarkers in drug labels [2,3].

Most pharmacogenetics studies that substantiate such labeling have been performed in Europe, North America and Asia [4]. How-

ever, little is known about the prevalence of these biomarkers in Central America and the Caribbean, where >80 million people of variable degrees of African, Amerindian and European ancestry live. Some countries, such as Cuba and Puerto Rico, suffered a major influence of European migrants, whereas Mestizos/admixed individuals are more predominant in Guatemala, Nicaragua, El Salvador, Panama, Honduras and Dominican Republic. Afro-descendants are more frequent at Jamaica, Haiti, Curaçao and the surrounding mainland of the Caribbean [5,6]. The reason for studying the prevalence of biomarkers in this region is that it may differ among populations, a fact that is highlighted in drug labels (e.g., for *CYP2C9* and *VKORC1* biomarkers, “lower initial and maintenance doses of warfarin are recommended for Asian

Carolina Céspedes-Garro, María-Eugenia G Naranjo, Fernanda Rodrigues-Soares, Adrián Llerena*, Jorge Duconge, Lazara K Montané-Jaime, Hilda Roblejo, Humberto Fariñas, María de los A Campos, Ronald Ramírez, Víctor Serrano, Carmen I Villagrán & Eva M Peñas-Lledó

*Author for correspondence:
CICAB Clinical Research Centre,
Extremadura University Hospital
& Medical School, Badajoz, Spain
and
RIBEF Ibero-American Network of
Pharmacogenetics & Pharmacogenomics
allarena@unex.es
For full list of author affiliations, please
see page 1723

patients”). Therefore, extrapolating the results from other populations is not always an option.

This study was intended to evaluate the research activity in pharmacogenetics in Central America and the Caribbean by reviewing the biomarkers and therapeutic areas. The ultimate goal was to identify the biomarkers and therapeutic areas that ought to be the focus of future research efforts, as well as to boost pharmacogenetics research in countries with a low scientific activity.

Materials & methods

A literature search was conducted from October 2014 to June 2016 using US National Library of Medicine MEDLINE, Scopus and SciELO databases following a methodology used in previous studies [4,7]. Additionally, the collaboration of the Red Iberoamericana de Farmacogenética y Farmacogenómica or in English as Iberoamerican Network of Pharmacogenetics from the region was required in order to complete the literature search and enrich the review with updated information.

The search terms were ‘country’ and ‘biomarker/probe drug’. Some Caribbean islands are a territory of other countries (for example, Puerto Rico, which is a commonwealth of the USA). However, these islands are treated as individual countries in this review. The 41 countries included in the search were: Guatemala, Belize, Honduras, El Salvador, Nicaragua, Costa Rica, Panama, Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Bonaire, the British Virgin Islands, the Cayman Islands, Cuba, Curaçao, Dominica, the Dominican Republic, Grenada, Guadeloupe, Haiti, Jamaica, Martinique, Montserrat, Puerto Rico, Saba, Saint Barthélemy, Saint Croix, Saint John, Saint Kitts and Nevis, Saint Lucia, Saint Martin, Saint Thomas, Saint Vincent and the Grenadines, Sint Eustatius, Sint Maarten, Trinidad and Tobago, Turks and Caicos Islands, the US Virgin Islands and Water Island.

The 104 biomarkers investigated were extracted from the list proposed by the DRAs US FDA and EMA, and PharmGKB (Table 1) [2–4,8]. Additionally, for the identification of phenotyping studies we searched for commonly used ‘probe drugs’ such

Table 1. Pharmacogenetic biomarkers (n = 104) used for the study based on recommendations from European and American Drug Regulatory Agencies (EMA and US FDA, respectively) and PharmGKB CPIC gene/drug pairs[†].

<i>ABCC4</i>	<i>COQ2</i>	<i>ERBB2</i>	<i>HPRT1</i>	<i>SCN1A</i>
<i>ABCG2</i>	<i>CRHR1</i>	<i>ERCC1</i>	<i>HTR2A</i>	<i>SLC22A1</i>
<i>ADD1</i>	<i>CRHR2</i>	<i>ESR1/PGR</i>	<i>HTR2C</i>	<i>SLC22A2</i>
<i>ADORA2A</i>	<i>CYP1A1</i>	<i>F5</i>	<i>IFNL3</i>	<i>SLC22A6</i>
<i>ADRB1</i>	<i>CYP1A2</i> [‡]	<i>FCGR3A</i>	<i>IL2RA</i>	<i>SLC6A4</i>
<i>ADRB2</i>	<i>CYP2A7P1</i>	<i>FDP5</i>	<i>ITPA</i>	<i>SLCO1B1</i>
<i>ALK</i>	<i>CYP2B6</i>	<i>FIP1L1</i>	<i>c-KIT</i>	<i>SLCO2B1</i>
<i>ANKK1</i>	<i>CYP2C19</i> [‡]	<i>FLOT1</i>	<i>KRAS</i>	<i>SOD2</i>
<i>ATIC</i>	<i>CYP2C8</i>	<i>G6PD</i>	<i>LDLR</i>	<i>SULT1A1</i>
<i>BCR-ABL</i>	<i>CYP2C9</i> [‡]	<i>GGCX</i>	<i>LTC4S</i>	<i>TMEM43</i>
<i>BRAF</i>	<i>CYP2D6</i> [‡]	<i>GNB3</i>	<i>MDR1-ABCB1</i>	<i>TNFRSF8</i>
<i>BTG3</i>	<i>CYP2E1</i>	<i>GRIK4</i>	<i>MRP1-ABCC1</i>	<i>TP53</i>
<i>C11orf65</i>	<i>CYP3A4</i>	<i>GSTA1</i>	<i>MRP2-ABCC2</i>	<i>TPMT</i>
<i>CACNB2</i>	<i>CYP3A5</i>	<i>GSTM1</i>	<i>MS4A1</i>	<i>UGT1A1</i>
<i>CALU</i>	<i>CYP4F2</i>	<i>GSTP1</i>	<i>MTHFR</i>	<i>UGT1A4</i>
<i>CBR3</i>	<i>del (5q)</i>	<i>GSTT1</i>	<i>MTRR</i>	<i>UGT2B15</i>
<i>CCR5</i>	<i>DPYD</i>	<i>HER1</i>	<i>NAT2</i> [‡]	<i>UMPS</i>
<i>CES1</i>	<i>DRD1</i>	<i>HERG1</i>	<i>OATP1B1</i>	<i>VKORC1</i>
<i>CFTR</i>	<i>DRD2</i>	<i>HLA-A</i>	<i>OPRM1</i>	<i>XRCC1</i>
<i>COL22A1</i>	<i>EGFR</i>	<i>HLA-B</i>	<i>PDGFRA</i>	<i>YEATS4</i>
<i>COMT</i>	<i>EPHX1</i>	<i>HMGCR</i>	Philadelphia chromosome	

[†]Data taken from [2,3,8].

[‡]Also referred to as ‘drug metabolizing enzymes’.

Figure 1. Methodology flow chart for the identification of pharmacogenetic studies in the systematic review.

as debrisoquine, sparteine, metoprolol and dextromethorphan (CYP2D6), mephenytoin and omeprazole (CYP2C19), tolbutamide, losartan and diclofenac (CYP2C9), isoniazid (NAT2) and caffeine (CYP1A2).

Articles were selected if the study: involved patients or healthy volunteers (control groups from case–control studies were excluded); from Central America and the Caribbean; analyzed one or more of the selected biomarkers (Table 1) or ‘phenotyping test drugs’; and published between 1975 and 2016.

We assessed research activity by country, therapeutic area and biomarker basing on the number of scientific papers published and total number of subjects studied. Subjects were later divided into healthy volunteers and patients. Research activity in each therapeutic area was assessed by counting the number of studies dealing with a disorder related to that area.

Patients studied were later classified by therapeutic area (e.g., oncology) defined according to the classifica-

tion of the CenterWatch [9], with some modifications. For instance, the group classified as ‘genetic diseases’ was removed and instead individual disorders were included in the appropriate therapeutic area (for example, the genetic disorder known as cystic fibrosis was included in the ‘pulmonary/respiratory’ group). Moreover, as in other studies [10], leukemia was included in ‘oncology’ and anticoagulation disorders were classified as ‘cardiovascular’ disorders, whereas ‘neurology’ and ‘psychiatry’ were merged into a single group. Finally, a total of eight therapeutic areas were defined.

One reviewer extracted the data from the original research papers. A second reviewer checked for accuracy. Disagreements were resolved with the aid of a third party.

Results

A nonspecific search strategy in three databases (see ‘Materials & methods’ section) yielded 8301 articles,

and other 25 articles were identified from other sources (Figure 1). A total of 132 studies involving 35,079 subjects – 43 studies with 11,129 healthy volunteers and 89 studies with 23,950 patients – were included. Considering the total population of Central America and the Caribbean, only about $3.96 \times 10^{-4}\%$ of the population has been studied so far. The information about population size and number of studied individuals is presented in Table 2.

Costa Rica was the country with the greatest research output, with 30 published studies and 11,596 recruited individuals, followed by Puerto Rico, with 29 published studies and 8796 subjects recruited (Figure 2). Belize is the only Central American country with no studies of pharmacogenetics. In the Caribbean region, only ten out of 34 countries had conducted pharmacogenetics research.

Oncology was the most frequently studied therapeutic area, with thirty-four studies involving 7635 cancer patients from Guatemala, Nicaragua, Costa Rica, Panama, Cuba, Haiti, the Dominican Republic, Jamaica, Guadeloupe, Martinique and Puerto Rico (Figure 3).

Pharmacogenetic biomarkers reported for both healthy volunteers and patients are shown in Figures 4 & 5, respectively. Forty-seven out of the

104 searched pharmacogenetic biomarkers – including drug-metabolizing enzymes (DMEs) – were studied in countries of the region (Tables 3 & 4). Seventeen studies involving 11,129 healthy volunteers were found; some of them assessed metabolic phenotype frequencies of CYP2D6 in Amerindian populations in Panama (Figure 4). Moreover, eleven studies of five DMEs, which reported only metabolic phenotype frequencies, were included in this review. The most studied pharmacogenetic biomarkers among patients were *HLA-A* and *HLA-B* genes, with twelve reports that involved populations from Barbados, Costa Rica, Cuba, Jamaica, Panama and Puerto Rico. Tables 3 & 4 provide additional information systematically divided into DMEs and transporters, receptors and other biomarkers.

Discussion

To the extent of our knowledge, this is the first study to review the development and current status of pharmacogenetics in Central America and the Caribbean. The country with the greatest research activity in pharmacogenetics was Costa Rica, whereas the medical therapeutic area most frequently studied was oncology. Finally, the most studied pharmacogenetic biomarkers in this region were CYP2D6 and *HLA-A/B* in healthy volunteers and patients, respectively.

Table 2. Population size and number of studied individuals per country.				
Country	Population size		Individuals studied	
	n	%	n	%
Costa Rica	4,919,896	5.6	11,596	39.2
Puerto Rico	3,683,601	4.2	8796	29.8
Panama	3,927,088	4.4	3305	11.2
Cuba†	11,287,014	12.7	3068	10.4
Trinidad and Tobago	1,344,235	1.5	2163	7.3
Jamaica	2,798,837	3.2	1194	4.0
Guadeloupe	468,016	0.5	1261	4.3
Nicaragua†	6,152,176	6.9	553	1.9
Guatemala†	15,789,772	17.8	545	1.8
Haiti†	10,385,782	11.7	327	1.1
Dominican Republic†	10,415,567	11.8	473	1.6
Curaçao	161,836	0.2	162	0.5
El Salvador†	6,364,956	7.2	112	0.4
Martinique	404,705	0.5	254	0.9
Honduras†	8,227,826	9.3	464	1.6
Barbados	286,066	0.3	806	2.7
Total	88,535,000	100.0	35,079	100.0
†Countries that warrant more studied individuals, in regard to their population size compared with the whole region and the proportion of individuals studied in these countries.

Figure 2. Scientific activity in pharmacogenetics in the region. Scientific activity in Central America and the Caribbean considering the (A) number of subjects included and (B) studies published per country.

In contrast with the increasing body of scientific literature describing pharmacogenetic biomarkers in other populations worldwide [142], it is evident that research of pharmacogenetics in Central American and the Caribbean populations is limited or absent. Bearing in mind the studied countries, Cuba, Nicaragua, Guatemala, Haiti, Dominican Republic, El Salvador and Honduras warrant a higher number of individuals to be studied, since the proportion of individuals studied in these countries is lower than that of their population size compared with the whole region (Central America and the Caribbean) (Table 2). For instance, Guatemala involved 17.8% out of the whole population size from Central America and the Caribbean region, but only 1.8% out of the studied individuals was from this country. Further, it is important to note that more studies, involving a higher amount of individuals, are needed in Central America and the Caribbean region, given that only 0.039% out of individuals living in this region has been studied.

The first study of pharmacogenetics conducted in Central America and the Caribbean was performed in 1975, with the description of *G6PD* polymorphisms in healthy volunteers from Cuba [51]. This study was followed by other reports including healthy volunteers

that were focused on metabolic phenotype frequencies of DMEs in Amerindian populations from Panama in the 1980's [20,31–34,72,73]. Later, research efforts were focused also in patients, including the description of novel mutations of the *LDLR* gene in Cuban [112] and Costa Rican [113] families with hypercholesterolemia, the immunologic profile of *HLA-A* [94] in Panamanian patients with renal transplantation and the genetic polymorphism of the *MTHFR* gene and its influence as a risk factor for stroke in Jamaicans with sickle cell disease [61].

Most recently, the growing interest in incorporating pharmacogenetics into clinical practice in order to make drug therapies safer and more effective has fostered the study of relevant pharmacogenetic biomarkers in different populations worldwide. This has been boosted by the introduction of relevant biomarkers in drug labels by major DRAs. Three Central American and Caribbean countries – Costa Rica, Puerto Rico and Cuba – have shown significant interest in this area of research, as evidenced by the considerable number of articles published in peer-reviewed journals. However, this does not occur in several Central American countries – particularly Honduras and Belize – and in most Caribbean countries, where research in the field of pharmacogenetics is very limited or absent.

Figure 3. Number of studies conducted in Central America and the Caribbean clustered by medical therapeutic area.

From 2001 to date, population studies represent most of the published scientific literature on pharmacogenetics in Central America and the Caribbean. It is noteworthy that most of the studies conducted in the region are not primarily focused on pharmacogenetic phenotype analyses, but rather on genetic epidemiology or population genetics. We can only speculate on the reasons for the scarcity of research in these regions: affordability: evidently, the level of financial resources is much higher in first world countries; accessibility: the availability of adequate facilities and equipment staffed by competent technical personnel are key for conducting pharmacogenetics research but are usually lacking in the developing world; research priorities in the country: researchers in these regions seem to focus more on research topics that are considered ‘more relevant’ to the country’s needs. For example, in countries where extreme poverty is sizable, pharmacogenetics research may not be considered a priority by the relevant authorities and, as a result, funding for scientific research in this area is not provided. Indeed, the US NLM MEDLINE lists 80 articles published in 2014 by researchers from Honduras. However, the majority of the articles focus on infectious and zoonotic diseases and nutrition and social issues; lack of research proposals and initiatives that attract financial support from international and regional agencies for pharmacogenetics research;

lack of interest in this field of research since although pharmacogenetics is included in drug labels, so far it has not been translated into clinical practice; exclusion of pharmacogenetics studies that did not involve biomarkers listed by the DRAs.

The most frequently investigated therapeutic area was oncology, mainly due to the scientific contribution of Costa Rica with nine out of the 34 cancer studies found. Cardiovascular ranked second with Puerto Rico [25–27,62–64] and Costa Rica [11,15,16,50,60,65,113] as the main contributors. Neurology/psychiatry placed third with a greater contribution of the Caribbean islands of Curaçao [85,86,110], Martinique [87], Jamaica [56,61], Cuba [82] and Puerto Rico [35,36,66,95] (Figure 3). These results are in agreement with the global trend of scientific research in these areas [10].

It is noteworthy that some well-known pharmacogenetic biomarkers related to infectious diseases or drug therapies to treat such conditions are not significantly over-represented in the countries of this region despite the high prevalence, morbi-mortality and incidence of infectious diseases and HIV–AIDS in these developing countries [143].

A limitation of this review is that not all scientific research studies conducted in Latin America are reported in scientific journals due to a lack of tradition or to a linguistic burden [144]. Furthermore, this

systematic review did not assess potential publication bias.

Concerning biomarkers, the studies that included healthy volunteers predominantly targeted the highly polymorphic *CYP2D6* gene [10]. This may be a result of the worldwide trend to study *CYP2D6* and the growing anticipation that genotyping the *CYP2D6* gene may be useful when making treatment decisions with drugs for which this enzyme represents a major metabolic pathway [142]. *CYP2D6* allele and phenotype frequencies were previously studied in healthy volunteers from Costa Rica, Nicaragua and Panama, showing a high frequency of predicted ultrarapid metabolizers in Guatuso and Admixed from Costa Rica [4].

In this sense, the Iberoamerican Network of Pharmacogenetics (RIBEF [145]) has increased the pharmacogenetic knowledge in Latin American populations and its possible clinical implication by performing studies in Central America [4] – Costa Rica [37], Cuba [28,38,39] and Nicaragua [38,39]. Particularly, has investigated in Cuban, Mexican and Spanish populations the association of *CYP2D6* genotype and phenotype with psychological factors and neurocognition [40,146], with eating disorders [41,147] and with depression and suicide [148–151], among others.

HLA-A and *-B* were the most studied biomarkers among patients (Figure 5). Both *HLA* genes are

among the most studied ones in worldwide trend of pharmacogenetic studies. This might be related to their importance in organ transplantation.

Overall, only 47 out of 104 biomarkers – including DMEs – have been studied in the population of this region (Figures 4 & 5). Moreover, despite that *CYP2C19*, *ABCB1*, *CYP2C9* and *TP53* are among the most intensively investigated biomarkers worldwide [10], the information available about them in Central America and the Caribbean is scarce. Thus, further pharmacogenetics studies should be performed to characterize the populations in this region, which are in some instances unique. The uniqueness of the population of Central America and the Caribbean calls for a departure from ‘inherited’ results obtained from very distinct populations. Instead, pharmacogenetic studies should be conducted to characterize its inhabitants. The characterization of these populations in terms of ‘required’ or ‘recommended’ biomarkers is necessary to validate their usefulness and for the future implementation of such tests in the clinical management of patients. This eventually would promote a safer and more effective use of medications.

Finally, it is noteworthy that to the best of our knowledge, these biomarkers are not included as part of the clinical practice in countries from Central American and the Caribbean region. Thus, the information con-

Figure 4. Number of studies involving healthy volunteers from Central America and the Caribbean classified by pharmacogenetic biomarker and country studied.

Figure 5. Number of studies of patients from Central America and the Caribbean clustered by pharmacogenetic biomarker and country studied.

tained in this review only refers to pharmacogenetic biomarkers studied in scientific research.

Conclusion

Costa Rica is the country with the most intense research activity related to pharmacogenetic biomarkers in Central America and the Caribbean. Moreover, following the global trend, oncology is the most studied medical therapeutic area. CYP2D6 is the most investigated pharmacogenetic biomarker in healthy volunteers, whereas *HLA-A* and *-B* are the most studied biomarkers in patients from Central America and the Caribbean. So far, only 45% of the most relevant pharmacogenetic biomarkers have been investigated in individuals from this region, which excludes some important markers for therapeutic areas that address medical needs in these countries. In the light of the present data, research activity on pharmacogenetics in Central American and the Caribbean populations is limited or absent. Therefore, strategies to promote effective collaborations and foster interregional initiatives and research efforts are mandatory in order to fill

the gaps in this evolving field in Central America and the Caribbean.

Future perspective

The pharmacogenetic research in Central America and the Caribbean will evolve promoting links among research groups of the countries. Moreover, further studies should mostly focus on priority medical therapeutic areas according to the needs of the region, such as oncology, cardiovascular and infectious diseases. The pharmacogenetic biomarkers *CYP2D6*, *CYP2C19*, *TP53* and *ERBB2* should be studied not only in healthy volunteers but also in patients in accordance to the global trend, as well as, relevant biomarkers not yet studied ought to be investigated. Additionally, research efforts should also focus on the translation of pharmacogenetic information into clinical guidelines.

Acknowledgements

The contribution of P Jacques from Ministère de la Santé Publique et de la Population, Haiti is gratefully acknowledged.

Table 3. Number of studies and subjects recruited by pharmacogenetic biomarker involving populations from Central America and the Caribbean.														
Pharmacogenetic biomarker	Country											Ref.		
	Guatemala	Honduras	El Salvador	Nicaragua	Costa Rica	Panama	Cuba	Dominican Republic	Jamaica	Haiti	Trinidad and Tobago		Guadeloupe	Puerto Rico
Enzymes														
CYP1A1	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	2 (0/962)	0 (0/0)	0 (0/0)	1 (0/235)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/132)	[11–14]
CYP1A2†	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	4 (93/2014)	0 (0/0)	0 (0/0)	1 (0/235)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[11, 14–17]
CYP2B6	0 (0/0)	0 (0/0)	1 (89/0)	1 (92/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/45)	0 (0/0)	0 (0/0)	0 (0/0)	[18,19]
CYP2C19†	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	2 (302/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	3 (320/0)	[20–24]
CYP2C9†	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (260/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	5 (190/391)	[25–30]
CYP2D6†	0 (0/0)	0 (0/0)	0 (0/0)	2 (133/0)	2 (448/0)	7 (1298/0)	5 (256/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (270/0)	0 (0/0)	3 (100/85)	[21,23, 31–46]
CYP2E1	0 (0/0)	0 (0/0)	0 (0/0)	1 (137/0)	1 (0/89)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[12,47]
CYP3A4	0 (0/0)	0 (0/0)	1 (112/0)	1 (120/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	2 (0/159)	0 (0/0)	0 (0/0)	0 (0/0)	[18, 48,49]
CYP3A5	0 (0/0)	0 (0/0)	1 (112/0)	1 (120/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/45)	0 (0/0)	0 (0/0)	0 (0/0)	[18,48]
EPHX	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/2022)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[50]
G6PD	0 (0/0)	1 (0/398)	0 (0/0)	0 (0/0)	1 (1294/0)	0 (0/0)	1 (860/0)	1 (0/238)	0 (0/0)	1 (0/168)	0 (0/0)	0 (0/0)	0 (0/0)	[51–55]
GSTM1	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/89)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/100)	0 (0/0)	0 (0/0)	2 (0/763)	1 (0/132)	[12,13, 56–58]
GSTP1	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/100)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[56,59]
GSTT1	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	2 (0/2131)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/100)	0 (0/0)	0 (0/0)	2 (0/763)	1 (0/132)	[12,13, 56–60]
MTHFR	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	2 (1424/186)	0 (0/0)	0 (0/0)	0 (0/0)	3 (0/365)	0 (0/0)	0 (0/0)	0 (0/0)	4 (0/3266)	[61–71]
NAT2†	0 (0/0)	0 (0/0)	0 (0/0)	1 (137/0)	0 (0/0)	5 (689/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[21,47, 72–75]
TPMT	1 (0/270)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[76]
UGT1A1	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/339)	0 (0/0)	0 (0/0)	1 (0/498)	0 (0/0)	[77,78]
VKORC1	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	5 (190/391)	[25–27, 29–30]
†Biomarkers (also referred to as ‘enzymes’). Numbers represent the total studies per pharmacogenetic biomarker. The number of healthy volunteers and patients included in the study is respectively shown in parentheses separated by a slash (/).														

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Table 4. Number of studies and subjects recruited by pharmacogenetic biomarker involving populations from Central America and the Caribbean.																	
Phar- maco- genetic bio- marker	Country															Ref.	
	Guate- mala	Hon- duras	El Salva- dor	Nicara- gua	Costa Rica	Panama	Cuba	Domi- nican Re- public	Jamai- ca	Haiti	Martin- ique	Cura- çao	Trinidad and Tobago	Puerto Rico	Guade- loupe		Barba- dos
Transporters and Receptors																	
ADOR- A2A	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/968)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[16]
ADRB2	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/1893)	2 (0/744)	0 (0/0)	0 (0/0)	[79–81]
COMT	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/222)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/498)	0 (0/0)	[78,82]
CCR5	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	2 (0/225)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[83,84]
DRD2	0 (0/0)	1 (0/66)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/97)	2 (0/126)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[85–88]
EGFR	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/102)	1 (0/174)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/157)	0 (0/0)	0 (0/0)	2 (0/258)	0 (0/0)	0 (0/0)	[89–92]
FCGR3A	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/92)	0 (0/0)	0 (0/0)	[93]
HLA-A	1 (132/0)	0 (0/0)	0 (0/0)	0 (0/0)	2 (130/124)	2 (965/100)	5 (129/545)	0 (0/0)	2 (0/165)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	3 (0/2176)	0 (0/0)	1 (0/806)	[94–107]
HLA-B	1 (132/0)	0 (0/0)	0 (0/0)	0 (0/0)	3 (130/610)	3 (973/100)	3 (129/530)	0 (0/0)	2 (0/165)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	3 (0/2176)	0 (0/0)	1 (0/806)	[94–105,107–109]
HTR2A	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	2 (0/162)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[85,110]
HTR2C	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/162)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[110]
IL2R	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/771)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[111]
LDLR	0 (0/0)	0 (0/0)	0 (0/0)	1 (100/0)	2 (1335/2)	0 (0/0)	1 (0/28)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[112–115]
MDR1	0 (0/0)	0 (0/0)	1 (112/0)	1 (117/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/45)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[18,116]
SLC6A4	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	2 (0/176)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[117,118]
Numbers represent total studies per pharmacogenetic biomarker. The number of healthy volunteers and patients included in the study is shown in parentheses separated by a slash (/).																	

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Table 4. Number of studies and subjects recruited by pharmacogenetic biomarker involving populations from Central America and the Caribbean (cont.).

Phar- maco- genetic bio- marker	Country														Ref.		
	Guate- mala	Hon- duras	El Salva- dor	Nicara- gua	Costa Rica	Panama	Cuba	Domi- nican Re- public	Jamai- ca	Haiti	Martin- ique	Cura- çao	Trinidad and Tobago	Puerto Rico		Guade- loupe	Barba- dos
Other biomarkers																	
BCR-ABL	1 (0/143)	0 (0/0)	0 (0/0)	1 (0/66)	2 (0/139)	0 (0/0)	3 (0/312)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[119– 125]
BRAF	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/157)	0 (0/0)	0 (0/0)	1 (0/164)	0 (0/0)	0 (0/0)	[91,126]
c-KIT	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/39)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[127]
CFTR	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	2 (0/581)	1 (0/0)	3 (0/487)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/447)	0 (0/0)	0 (0/0)	[128– 132]
COL22A1	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/592)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[133]
IFNL3	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/259)	0 (0/0)	0 (0/0)	[134]
KRAS	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/102)	1 (0/174)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/157)	0 (0/0)	0 (0/0)	1 (0/501)	0 (0/0)	0 (0/0)	[91– 92,135]
PDGFRA	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/39)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[127]
Ph chromo- some	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	3 (0/256)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[125, 136– 137]
SOD2	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/859)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[138]
TP53	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	2 (651/844)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	[139, 140]
HPRT1	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/556)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/556)	0 (0/0)	0 (0/0)	[132]
XRCC1	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/859)	0 (0/0)	0 (0/0)	1 (0/235)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (0/117)	0 (0/0)	0 (0/0)	[14,138,– 141]
Numbers represent total studies per pharmacogenetic biomarker. The number of healthy volunteers and patients included in the study is shown in parentheses separated by a slash (/).																	

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Financial & competing interests disclosure

This study was supported by the University of Costa Rica (PhD fellowship to C Céspedes-Garro in Spain), Gobierno de Extremadura, Agencia Extremeña de Cooperación Internacional para el Desarrollo AEXCID 13IA001 (MESTIFAR; to Sociedad Iberoamericana de Farmacogenética y Farmacogenómica). This project has been coordinated in the network Red Iberoamericana de Farmacogenética y

Farmacogenómica (www.ribef.com) and MESTIFAR Project. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Costa Rica is the country with the most intense research activity related to pharmacogenetic biomarkers in Central America and the Caribbean.
- Oncology is the most studied medical therapeutic area.
- CYP2D6 is the most investigated pharmacogenetic biomarker in healthy volunteers.
- *MTHFR* is the most studied biomarker in patients from Central America and the Caribbean.
- Research activity on pharmacogenetics in Central American and the Caribbean populations is limited or absent.
- There is a 'biotechnological gap' in the development of research in pharmacogenetics in Central America and the Caribbean, and in any further implementation of actionable pharmacogenetic-guided recommendations that could benefit the population in clinical practice.
- Strategies to promote effective collaborations, and foster interregional initiatives and research efforts are mandatory in order to fill the gaps in this evolving field.

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Affiliations

Carolina Céspedes-Garro

CICAB Clinical Research Centre, Extremadura University Hospital & Medical School, Badajoz, Spain
and
RiBEF Ibero-American Network of Pharmacogenetics & Pharmacogenomics
and
Teaching & Research Department, Genetics Section, School of Biology, University of Costa Rica, San José, Costa Rica

María-Eugenia G Naranjo

CICAB Clinical Research Centre, Extremadura University Hospital & Medical School, Badajoz, Spain
and
RiBEF Ibero-American Network of Pharmacogenetics & Pharmacogenomics

Fernanda Rodrigues-Soares

RiBEF Ibero-American Network of Pharmacogenetics & Pharmacogenomics

and

Departamento de Biologia Geral, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

Adrián Llerena

CICAB Clinical Research Centre, Extremadura University Hospital & Medical School, Badajoz, Spain
and
RiBEF Ibero-American Network of Pharmacogenetics & Pharmacogenomics

Jorge Duconge

RiBEF Ibero-American Network of Pharmacogenetics & Pharmacogenomics
and
Pharmaceutical Sciences Department, School of Pharmacy, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico

Lazara K Montané-Jaime

Pharmacology Unit Department of Paraclinical Sciences, Faculty of Medical Sciences, The University of West Indies, St Augustine, Trinidad & Tobago

Hilda Roblejo

Pharmacology Unit Department of Paraclinical Sciences, Faculty of Medical Sciences, The University of West Indies, St Augustine, Trinidad & Tobago
and
Teaching & Research Department, National Center of Medical Genetics, Havana, Cuba

Humberto Fariñas

CICAB Clinical Research Centre, Extremadura University Hospital & Medical School, Badajoz, Spain

María de los A Campos

Secretaría Ejecutiva del Consejo de Ministros de Salud de Centroamérica y República Dominicana, Ciudad Merliot, El Salvador

Ronald Ramírez

RIBEF Ibero-American Network of Pharmacogenetics & Pharmacogenomics
and
Facultad de Medicina, UNAN Universidad Autónoma Nacional de Nicaragua, León, Nicaragua

Víctor Serrano

RIBEF Ibero-American Network of Pharmacogenetics & Pharmacogenomics
and
CIIMET Centro de Investigación e Información de Medicamentos y Tóxicos, Facultad de Medicina, Universidad de Panamá, Panamá, Panamá

Carmen I Villagrán

RIBEF Ibero-American Network of Pharmacogenetics & Pharmacogenomics
and
Facultad de Ciencias Médicas, Dirección de Investigación, Universidad de San Carlos de Guatemala, Guatemala

Eva M Peñas-Lledó

CICAB Clinical Research Centre, Extremadura University Hospital & Medical School, Badajoz, Spain
RIBEF Ibero-American Network of Pharmacogenetics & Pharmacogenomics