Human pharmacogenomic variation of antihypertensive drugs: from population genetics to personalized medicine

Aim: To investigate the human pharmacogenetic variation related to antihypertensive drugs, providing a survey of functional interpopulation differences in hypertension pharmacogenes. **Materials & methods:** The study was divided into two stages. In the first stage, we analyzed 1249 variants located in 57 hypertension pharmacogenes. This first-stage analysis confirmed that geographic origin strongly affects hypertension pharmacogenomic variation and that 31 pharmacogenes are geographically differentiated. In the second stage, we focused our attention on the ethnic-differentiated pharmacogenes, investigating 55,521 genetic variants. *In silico* analyses were performed to predict the effect of genetic variation. **Results:** Our analyses indicated functional interpopulation differences, suggesting insight into the mechanisms of antihypertensive drug response. Moreover, our data suggested that rare variants mainly determine the functionality of genes related to antihypertensive drugs. **Conclusion:** Our study provided important knowledge about the genetics of the antihypertensive drug response, suggesting that next-generation sequencing technologies may develop reliable pharmacogenetic tests for antihypertensive drugs.

Original submitted 19 September 2013; Revision submitted 14 November 2013

KEYWORDS: bioinformatics ▪ blood pressure ▪ drugs ▪ geographic origin ▪ hypertension ▪ pharmacogenomics

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Arterial hypertension is a major risk factor for many disorders (i.e., coronary artery disease, myocardial infarction, heart failure, stroke and renal failure), and drug therapy can effectively prevent these risks [1]. As demonstrated by molecular studies and family history, genetic variation affects both predisposition to the disease and drug response [2]. Several pharmacological medications are available for its treatment, but hypertension-associated diseases remain one of the main burdens of healthcare [3]. Furthermore, the prevalence of the disease is steadily growing. In 2025, it is estimated that 1.56 billion adults worldwide will have been diagnosed with hypertension [4]. Accordingly, hypertension has the highest rate of recurrent drug therapy [5]. Moreover, less than 50% of hypertension patients manage to control their blood pressure. Current therapy strategies in the general hypertensive population have not shown the same effectiveness as was observed in clinical trials [6]. These data suggest that the optimal investigative approach to produce the best antihypertensive therapies has not yet been established, and relevant enhancements in this field must be made in order to improve patient care and treatment efficacy. Indeed, the control of the economic cost related to the management of hypertension and its adverse sequalae is an important objective for all national health systems [7]. In particular, relevant improvements should be made to the selection criteria of antihypertensive drugs and their related dosages. The study of genetic predisposition to drug response – pharmacogenomics – may produce useful tools to predict the most effective antihypertensive drug for a patient prior to the initiation of therapy. In recent years, the number of studies on the pharmacogenetics of antihypertensive drugs has rapidly increased, and several genetic variants were found to be associated with the response of different antihypertensive drugs [8,9]. Unfortunately, although hypertension pharmacogenetic data promises to play an important role in patient management, this information is not yet ready to be transferred from the bench to the bedside. Indeed, several confounding factors are present in the correlation between genotype (i.e., genomic background) and phenotype (i.e., response to antihypertensive drugs), such as environment and epigenetics [10]. This leads us to believe that multiple rare variants determine a great portion of the complex phenotype predisposition, shifting the attention from common genetic variants to rare ones [11]. This assumption strongly suggests that multiple rare variants with a high functional impact may

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play a key role in pharmacogenomic research developments. To date, most of the hypertension pharmacogenomic studies conducted have been gene-candidate investigations or genome-wide association studies [10]. These approaches are not suitable for identifying rare variants, as they likely result in missing heritability in the genetic predisposition to antihypertensive drug response. The application of high-throughput and next-generation sequencing (NGS) technologies, coupled with bioinformatic analysis to predict the functional impact of genomic variation, may result in a useful approach that could help us investigate the genomic architecture of complex phenotypes, such as drug response [12,13]. An interesting field, on which this analysis may provide remarkable information, is population-related investigation. Indeed, a number of studies have suggested that geographic origin is a relevant influencing factor in antihypertensive drug response and that geographic differences have also been observed in pharmacogenomic studies [14,15]. Furthermore, there are public genomic databases of international projects, such as the HapMap Project, the Human Genome Diversity Project (HGDP), and the 1000 Genomes Project, which provide a great deal of information on human genetic variation. This information is regularly used by researchers to investigate the relationships between geographic origin, genome variability and health [16–18]. Using these public data, we performed an *in silico* analysis of human pharmacogenomic variation in relation to antihypertensive drug response. Population genetics are coupled with a functional prediction analysis that may result in new knowledge on hypertension pharmacogenomics, uncovering a portion of the genetic mechanisms of antihypertensive drug response.

The aim of the present study was to provide a survey of functional geographic differences in hypertension pharmacogenes in order to understand the genetic basis of geographic differences in antihypertensive drug response, and to obtain useful insights that could help move hypertension care into the 'personalized medicine' era.

Materials & methods

Literature search

To find pharmacogenes related to antihypertensive drugs, an analysis of the Medline database was performed in April 2012 using combinations of the following keywords: 'pharmacogenetics', 'pharmacogenomics', 'hypertension', 'drugs', 'antihypertensive', 'genes', 'genetics', 'genomics', 'response to', 'blood pressure' and 'therapy'. A total of 59 articles were identified. From these, we selected 24 articles on the basis of the presence of significant associations between genetic variants and drug response (Supplementary Table 1, see www.futuremedicine.com/doi/suppl/10.2217/pgs.13.231). Genes significantly related to one of the four principal antihypertensive drug classes (i.e., ACE inhibitors, β-blockers, calcium channel blockers and diuretics) in patients affected by arterial hypertension were considered (Supplementary Table 1).

Population information & genomic data

Data were obtained from the HGDP and the 1000 Genomes Project, which provides information on human genetic variation [16,18]. In the first stage of the study, we considered 57 pharmacogenes that we identified using a literature search, and we made use of the genetic information available from the HGDP. In particular, information about 1249 SNPs analyzed in 1043 individuals belonging to 51 human populations within seven different geographical origins was used [101]. The definition of the HGDP population structure is based on seven geographic origin groups: Africa, Europe, Middle East, central Asia, east Asia, America and Oceania. Further details can be found in our previous study [19]. In the second stage, phase 1 of the 1000 Genomes Project was used to obtain genotypic data and haplotypic information [102]. Details pertaining to the 1000 Genomes populations are available at [103]. In this stage, a restricted number of pharmacogenes were considered on the basis of the first-stage analysis. The total number of the pharmacogenes and of the considered variants is 31 and 55,521, respectively.

Functional prediction analysis

The impact of single variants and of haplotypes on gene function was evaluated with various *in silico* tools and with a previously published algorithm. Details of the analysis were described in an earlier study [20]. This approach permits the distinguishing of functional haplotypes (i.e., haplotype-containing genetic variants associated with normal gene function) from non-functional haplotypes (i.e., haplotype-containing genetic variants associated with abnormal gene function).

To identify potential gene–gene interactions, the following databases were used: PharmGKB (available at [104]) [21]; STRING (available

at [105]) [22]; MINT (available at [106]) [23]; and KEGG (available at [107]) [24].

Statistical analysis

Analyses of molecular variance and F-statistics tests were performed by Arlequin 3.5.1.3 (University of Bern, Bern, Switzerland) [25]. The F-statistics test was carried out by accounting for a hierarchical island model [26]. The calculation settings were: 50,000 simulations, 100 demes to simulate and ten groups to simulate. The p-value of the F-statistics tests considered significant was $p < 0.05$.

To perform the cluster analysis and to construct the correspondence plots, Structure 2.3.3 (Stanford University, CA, USA) and Distruct 1.1 (Stanford University) were used, respectively [27,28]. For each run, 10,000 iterations after a burn-in period of 10,000 iterations were utilized, and cluster coefficients (K) from 2 to 7 were considered.

To identify the most divergent geographic origin group in the functionality-based haplotype analysis, we used the method proposed by Hofer and colleagues [29]. For each nonfunctional haplotype *i*, we computed the average nonfunctional haplotype frequency p_{ij} within each geographic origin group *j*, as well as the difference in the average frequency computed over all other populations via the following equation:

$$DF = p_{ij} - p_{-ij}$$

where p_{-ij} is the average frequency of the nonfunctional haplotype *i* in all populations not belonging to the geographic region *j*. To estimate the significance of nonfunctional haplotype frequency differences, we applied a test based

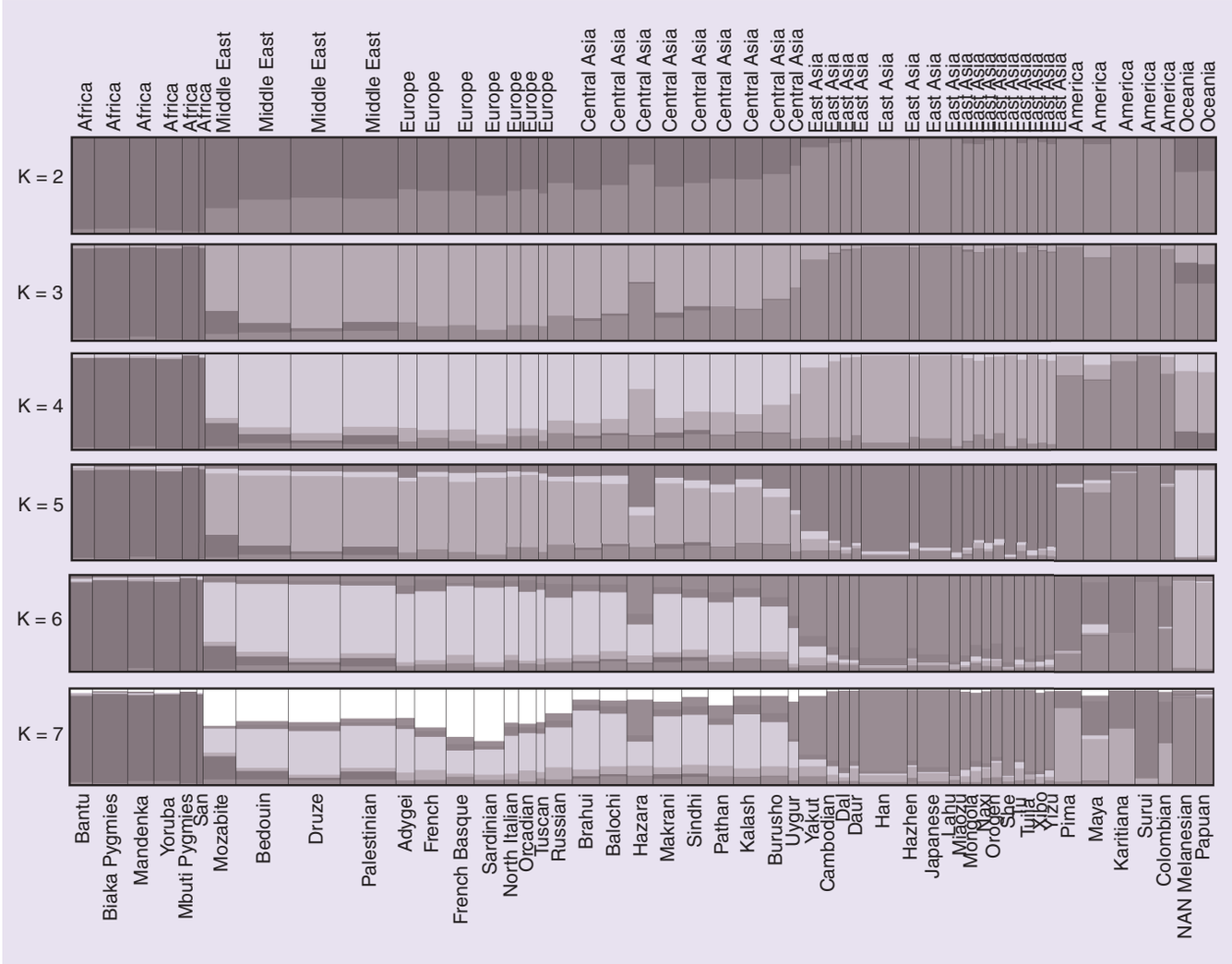

Figure 1. Population structure based on SNPs in hypertension pharmacogenes. Each population is represented by a vertical block that is partitioned into K grayscale segments that represent the population's estimated membership fractions in K clusters. Black lines separate different populations. The populations are labeled below the figure, with their geographic origin groups above it.

on 100,000 permutations, and we considered p-values <0.05 significant.

Results

The first-stage analysis was based on human genetic variation of 1249 SNPs that were located in 57 pharmacogenes (Supplementary Table 2). In order to graphically display the genetic variability of these loci among human populations, a cluster analysis was performed; Figure 1 shows the related plot. In regards to the geographical origin, differences were present among the considered populations. The largest difference was present between African and non-African populations (Figure 1, K = 2). Among non-Africans, east Asians displayed more differentiation than other geographic groups (Figure 1, K = 3). A slight differentiation was present in Eurasian populations, in which the Middle East, Europe and Central Asia groups are included (Figure 1, K = 4–7). To identify the most differentiated SNPs, an F-statistics analysis was performed. Figure 2 reports the distribution of the fixation index among populations (F_{ST}) and fixation index among defined groups (F_{CT}). Among the investigated variants, 116 SNPs showed F_{ST} and F_{CT} p-values <0.05 with F_{ST} and F_{CT} values >0.1. This led us to conclude that these loci are significantly differentiated among human populations with respect to their general distribution. Table 1 reports the 31 pharmacogenes, in which at least one differentiated SNP is located. This restricted number of geographic-differentiated pharmacogenes was analyzed with NGS data gathered from phase 1 of the 1000 Genomes Project. In this second-stage analysis, 55,521 variants were analyzed. Figure 3 shows the molecular variance among the geographic groups that results from haplotypic analyses of molecular variance, and the number of the investigated SNPs for each geographic-differentiated pharmacogene. This analysis proved that some pharmacogenes have a greater variance among geographic groups than what is considered average for the human genome (i.e., ~10%). However, this investigation does not take into account the functional impact of genetic variation and the role of rare variants in determining phenotype expression. To analyze the functional effect of all 55,521 variants and their combined effect on haplotype function, a previously described method was applied [20]. Supplementary Tables 3–64 report the results of the functional prediction analysis of the single variants and of the haplotypes. Considering the nonfunctional haplotypes, a wide array of haplotype frequency differences among geographic groups were investigated. Figure 4 reports the distribution of haplotype frequency differences among the four geographic groups. This analysis suggested that some pharmacogenes have geographic differences in nonfunctional haplotype frequencies. The greatest difference was observed in the comparison between African and non-African populations, but large differentiations were also observed in the comparisons of Europeans and Asians. To verify the statistical significance of these differences, a permutation test was applied. Table 2 reports the pharmacogenes with significant geographic differences in nonfunctional haplotype frequencies. Considering extreme nonfunctional haplotype frequency differences

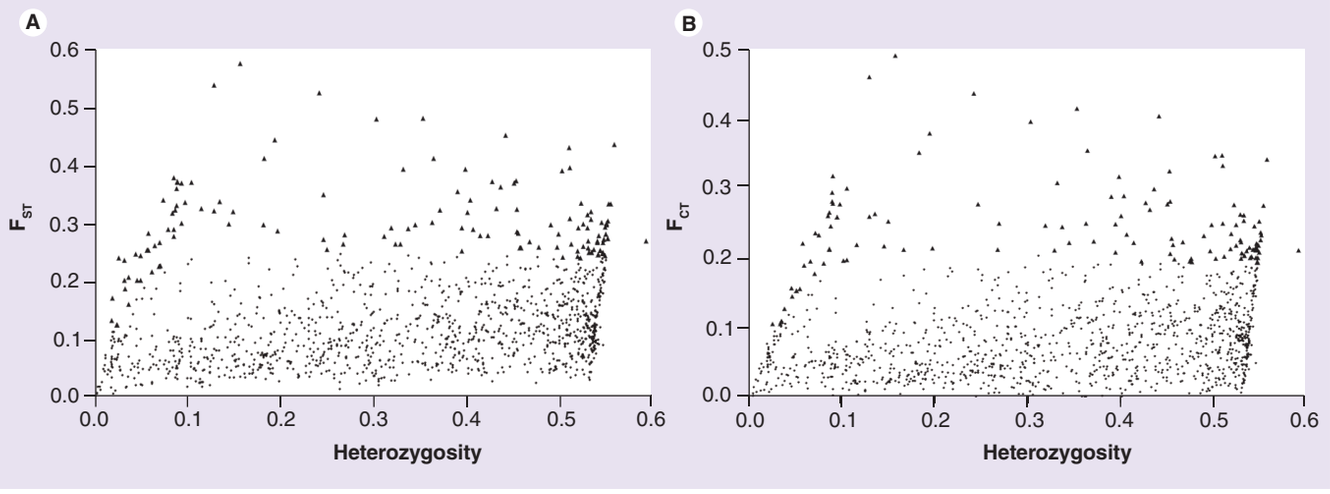

Figure 2. Analysis of F-statistics. (A) F_{ST} and **(B)** F_{CT} distributions of SNPs in hypertension pharmacogenes. Full dots represent SNPs with no significant F_{ST}/F_{CT} p-values, whereas full triangles represent SNPs with significant F_{ST}/F_{CT} p-values (<0.05) and with F_{ST}/F_{CT} values >0.1.
F_{CT}: Fixation index among defined groups; F_{ST}: Fixation index among populations.

values, we observed that the *ADRBK1* gene showed the lowest frequency of nonfunctional haplotypes in African populations (19.5%) and the highest frequency in European populations (91.1%). A reverse situation presented itself in the *PPARA* gene: its highest nonfunctional haplotype frequency was in Africans (71.3%), and its lowest was found in Asians (0.01%), in which *PPARA* nonfunctional haplotypes are rare. Other strong differences between geographic groups are: *ACE* (Africa [90.7%] vs Europe [46.0%]), *ADRA1A* (Asia [88.5%] vs Europe [45.4%]), *LIPC* (Asia [76.9%] vs Europe [36.7%]) and *TNFRSF11B* (Africa [88.6%] vs Europe [47.8%]). Our analysis also suggested that the geographic group had a nonfunctional haplotype frequency significantly different in comparison to the nonfunctional haplotype frequency of populations not belonging to this geographic group.

Considering the functional impact effect of the rare variants, we observed that variants with a functional effect on gene function are often rare. The percentage of rare variants among functional ones in the investigated pharmacogenes ranged from 60 (*PPARA*) to 100% (*ADRA1B*), with an average of 81%.

In order to identify interactions between these significant functional geographic differences, we performed an analysis of databases of protein–protein interactions and molecular pathways (Supplementary Table 65). In hypertension pharmacogenes functionally differentiated in African populations (i.e., *ABCB1*, *ACE*, *ADRBK1*, *LPL*, *PPARA* and *TNFRSF11B*), we recorded the same involvement of *ABCB1* and *LPL* in the statin pathway (PharmGKB database; Stanford University). In Asian-differentiated pharmacogenes (i.e., *ADRA1A*, *APOB*, *CACNB2*, *CYP2C8*, *LIPC*, *LYZ* and *PPARA*), our PharmGKB analysis highlighted the involvement of *APOB*, *CYP2C8* and *LIPC* in the statin pathway, and a STRING investigation confirmed the protein–protein interaction between LIPC and APOB. In Europeans, no potential interactions among geographic-differentiated pharmacogenes (i.e., *ACE*, *ADRA1A*, *ADRBK1*, *CASR*, *LIPC* and *TNFRSF11B*) were observed.

Discussion

An investigation of human genomic variation, coupled with a functional prediction analysis, could help bring hypertension care into the 'personalized medicine' era. The present study provided an analysis of functional differences in hypertension pharmacogenes among human populations, and sought to understand the mechanisms of interpopulation differences in antihypertensive drug response and to obtain insights into interindividual variability.

The study was divided into two stages. In the first stage, analysis was focused on genetic variability among a large number of human populations (HGDP data: 51 populations). In the second stage, the aim was to investigate a large number of genetic variants (data from 1000 Genomes Project: 55,521 variants).

Table 1. Pharmacogenes with at least one SNP with a fixation index and F_{CT} p-value <0.05 and with a F_{ST} and F_{CT} >0.1 in Human Genome Diversity Project-based analysis.

Pharmacogene	SNP (n)	Pharmacological class
ABCB1	1	Calcium channel blocker
ACE	2	ACE inhibitor
ACE2	1	ACE inhibitor
ADRA1A	1	Angiotensin receptor blocker; β-blocker
ADRA1B	1	Angiotensin receptor blocker; β-blocker
ADRBK1	1	β-blocker
AGT	1	ACE inhibitor
AGTR1	3	Angiotensin receptor blocker; β-blocker
APOB	4	Angiotensin receptor blocker; β-blocker
CACNA1C	12	Calcium channel blocker
CACNA1D	9	Calcium channel blocker
CACNB2	13	β-blocker
CASR	5	Angiotensin receptor blocker; β-blocker
CETP	1	Angiotensin receptor blocker; β-blocker
CYP2C8	3	Calcium channel blocker
CYP2C9	1	β-blocker
CYP3A4	3	β-blocker
CYP3A5	2	Calcium channel blocker
EDN2	1	Angiotensin receptor blocker; β-blocker
EDNRA	4	Angiotensin receptor blocker; β-blocker
FRS2	1	Diuretic
GNAS	4	β-blocker
LIPC	9	Angiotensin receptor blocker; β-blocker
LPL	2	Angiotensin receptor blocker; β-blocker
LYZ	1	β-blocker
NEDD4L	4	Diuretic
NR3C2	11	Angiotensin receptor blocker; β-blocker
PPARA	6	Angiotensin receptor blocker; β-blocker
PPARG	5	Angiotensin receptor blocker; β-blocker
SCNN1B	2	Diuretic
TNFRSF11B	2	Angiotensin receptor blocker; β-blocker

The associated pharmacological class is also reported.

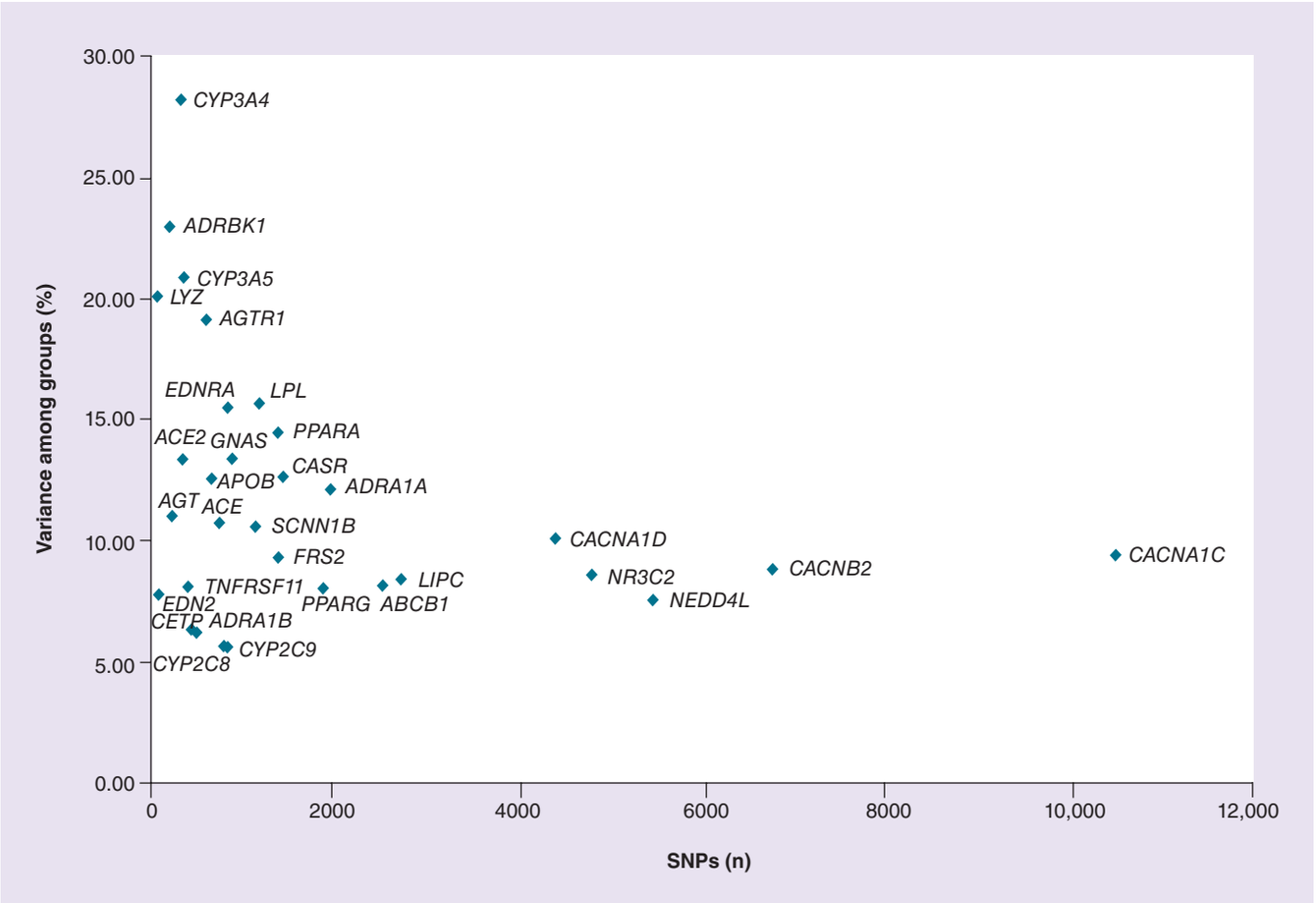

Figure 3. Molecular variance among geographic groups in origin-differentiated pharmacogenes.

The outcomes of the first-stage analysis illuminated significant interpopulation differences. Conducting a cluster analysis led us to conclude that the main differences were present between Africans and non-Africans. These results are in accordance with the great diversity of African genomes among human geographic groups and are likely owing to the African origin of humans [30,31]. An analysis of F-statistics showed that 116 of the 1249 SNPs significantly diverged among the investigated populations, suggesting that the pharmacogenes, in which these variants are located, may be functionally different among geographic groups.

The second-stage analysis highlighted that functional geographic differences are present in hypertension pharmacogenes and, in some cases, these diversities are significant. Extreme differences were observed between Africans and non-Africans, in accordance with the first-stage analysis, suggesting that these geographic functional diversities are associated with differences in response to related antihypertensive drugs. However, significant functional differences are also present in European and Asian comparisons. These findings are in agreement with previous studies that associated functional genetic differences with diversity in health-related aspects of human populations [19]. Considering each antihypertensive drug separately, we were able to relate the genetic mechanisms according to the geographic differences of their antihypertensive drug response. Atenolol is the most repeatedly used antihypertensive drug among our identified geographic-differentiated pharmacogenes: *ADRBK1* (Africa, Europe), *LPL* (Africa), *PPARA* (Africa, Asia), *TNFRSF11B* (Africa, Europe), *APOB* (Asia), *ADRA1A* (Asia, Europe), *CACNB2* (Asia), *LIPC* (Europe) and *CASR* (Europe). An ancestry-based study conducted on atenolol response made it clear that hypertensive patients with African origins are less responsive to atenolol monotherapy than patients with European origins [32]. Furthermore, a pharmacometabolomic study confirmed geographic differences in response to atenolol treatment, suggesting that dissimilar metabolomic signatures of atenolol exposure are present between African and European hypertensive patients [33]. The second antihypertensive drug associated with our geographic-differentiated

pharmacogenes is irbesartan (an angiotensin receptor blocker): *LPL* (Africa), *PPARA* (Africa, Asia), *TNFRSF11B* (Africa, Europe), *APOB* (Asia), *ADRA1A* (Asia, Europe), *LIPC* (Europe) and *CASR* (Europe). All irbesartan-related pharmacogenes are also involved in atenolol response. Geographic studies on irbesartan determined that monotherapy is less efficacious in patients with African origins than in patients with European origins [34]. The ACE inhibitor-related pharmacogenes that are analyzed in the present study are involved in lisinopril response: our data suggested that the *ACE* gene is differentiated in African (nonfunctional haplotype frequency: 90.7%) and European populations (nonfunctional haplotype frequency: 46.0%). Few data are available regarding geographic differences in ACE-inhibitor response. However, it has been demonstrated that African patients have a higher risk of angioedema and cough due to ACE-inhibitor treatment than European ones [35]. Our data regarding functional pharmacogenetic diversity among human populations seem to be in accordance with the epidemiological data gathered on interpopulation variability in the responsiveness of ACE inhibitors and β-blockers [32–35]; with similar geographic-differentiated pharmacogenes corresponding to similar geographic-differentiated drug responses.

Regarding calcium channel blockers, two pharmacogenes displayed results that were geographically differentiated: *ABCB1* (Africa) and *CYP2C8* (Asia). Epidemiological data about geographic variability in calcium channel blockers highlighted that these drugs reduce blood pressure across all patient groups, regardless of sex, geographic origin, age and dietary sodium intake [36]. Therefore, we hypothesized that functional differences observed in *ABCB1* and *CYP2C8* may be attributed to other function-homolog genes. Finally, the *LYZ* gene is the only geographically differentiated pharmacogene involved in the response of hydrochlorothiazide that showed a higher frequency of nonfunctional haplotypes in Asian populations (74.7%) than in non-Asian ones (Africa: 48.3%; America: 57.4%; Europe: 51.1%). Ancestry-based studies conducted on hydrochlorothiazide response have suggested that geographic origin plays a role in determining side effects related to this antihypertensive therapy [37]. However, little information is available about the geographic differences of hydrochlorothiazide response in Asian populations with respect to other geographic groups.

An investigation of protein–protein interaction and same-pathway involvement among geographically differentiated pharmacogenes

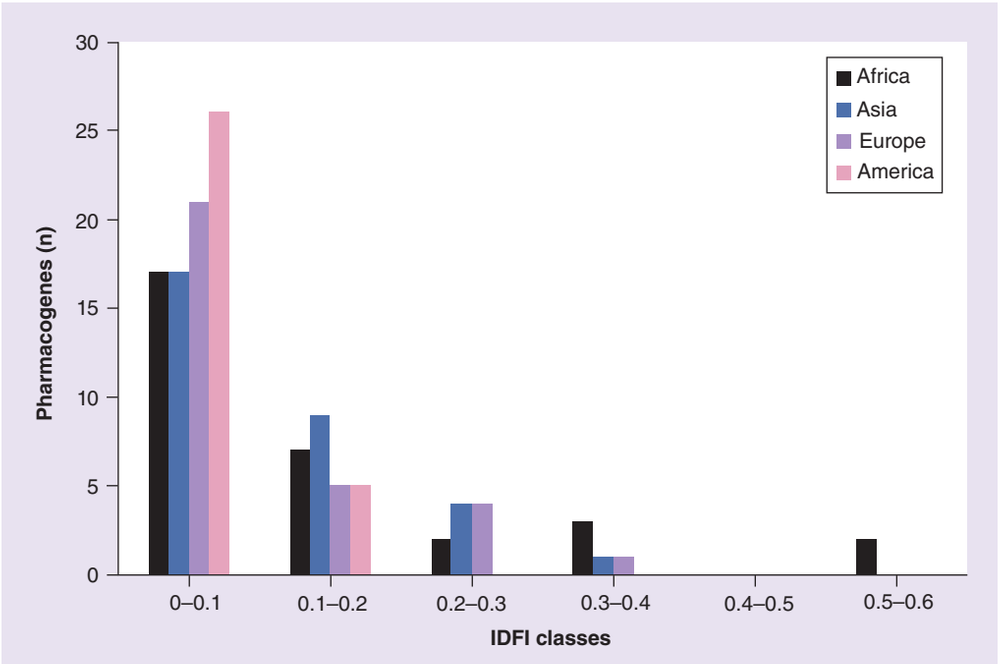

Figure 4. Nonfunctional haplotype frequency differences in geographic-differentiated pharmacogenes comparing a given geographic origin group versus the rest of the world.
The classes are based on IDFI. A semi-open IDFI interval was used to assign pharmacogenes to particular intervals (e.g., an IDFI value of 0.3 was put in the interval 0.3–0.4).
IDFI: Absolute value of nonfunctional haplotype frequency differences.

Table 2. Pharmacogenes with significant functional differences ($p < 0.05$, permutation test) among human geographic groups.

Geographic group	Pharmacogene	DF (p-value)	Drug	Pharmacological class	Ref.
Africa	*ADRBK1*	-0.577 (0.003)	Atenolol	β-blocker	[42]
	LPL	0.299 (0.010)	Irbesartan	Angiotensin receptor blocker	[43]
			Atenolol	β-blocker	[43]
	PPARA	0.574 (0.003)	Irbesartan, telmisartan	Angiotensin receptor blocker	[43,44]
			Atenolol	β-blocker	[43]
	ACE	0.343 (0.003)	Lisinopril	ACE inhibitor	[45]
	ABCB1	0.363 (0.002)	Bepridil, diltiazem, mibefradil, verapamil	Calcium channel blocker	[46,47]
	TNFRSF11B	0.311 (0.014)	Irbesartan	Angiotensin receptor blocker	[43]
			Atenolol	β-blocker	[43]
Asia	*LYZ*	0.224 (0.003)	Hydrochlorothiazide	Diuretics	[48]
	PPARA	-0.368 (0.007)	Irbesartan, telmisartan	Angiotensin receptor blocker	[43,44]
			Atenolol	β-blocker	[43]
	APOB	0.157 (0.010)	Irbesartan	Angiotensin receptor blocker	[43]
			Atenolol	β-blocker	[43]
	ADRA1A	0.296 (0.007)	Irbesartan	Angiotensin receptor blocker	[43]
			Atenolol	β-blocker	[43]
	CACNB2	0.265 (0.003)	Atenolol	β-blocker	[49]
	LIPC	0.296 (0.003)	Irbesartan	Angiotensin receptor blocker	[43]
			Atenolol	β-blocker	[43]
	CYP2C8	-0.162 (0.015)	Verapamil	Calcium channel blocker	[50]
Europe	*ADRBK1*	0.379 (0.020)	Atenolol	β-blocker	[42]
	CASR	0.198 (0.020)	Irbesartan	Angiotensin receptor blocker	[43]
			Atenolol	β-blocker	[43]
	ADRA1A	-0.278 (0.020)	Irbesartan	ACE inhibitor	[43]
			Atenolol	β-blocker	[43]
	ACE	-0.252 (0.020)	Lisinopril	ACE inhibitor	[45]
	LIPC	-0.240 (0.020)	Irbesartan	Angiotensin receptor blocker	[43]
			Atenolol	β-blocker	[43]
	TNFRSF11B	-0.234 (0.040)	Irbesartan	Angiotensin receptor blocker	[43]
			Atenolol	β-blocker	[43]

DF: Nonfunctional haplotype frequency differences.

revealed that the statin pathway may have strong functional diversity among human populations, especially in African and Asian populations. Hypercholesterolemia is a risk

factor for cardiovascular diseases and statins are the first-choice drugs for low-density lipoprotein-cholesterol reduction [38]. According to our genetic data, despite the fact that statins seem to reduce the cardiovascular events in different geographic groups, significant differences in the reduction of low-density lipoprotein levels and in the adverse rates were nevertheless present in treated individuals, especially in patients with European ancestry and African ancestry [39].

Considering the comparison between our genetic data and epidemiological information collected on antihypertensive drug response, a concordance seems to be present. However, geographic studies on drug response are mainly carried out in the USA or in other countries in which different geographic groups are present within their populations. Therefore, little information has been gathered about some human populations: for instance Middle Eastern or east Asian populations. However, our data highlighted different hypotheses to explain geographic differences in antihypertensive drug response. In particular, our data on rare variants highlighted that the pharmacogenetics of hypertension is strongly affected by personal genetic variation and common variants account for only a small percentage of functional interindividual differences in hypertension pharmacogenes. This result is in agreement with the current body of knowledge relating to human genetics, and it supports the idea that complex phenotypes can be attributed mainly to rare variants [11,40]. Moreover, recently Nelson and colleagues indicated that an abundance of rare functional variants is present in drug target genes [41]. Therefore, pharmacogenomic research should be based on NGS technologies as this could analyze the effect of individual genetic variation on drug response and bring pharmacogenomics into the 'personalized medicine' era, as suggested by recent papers [12,15]. Although NGS analysis may open up new scenarios in pharmacogenomics, the economic costs are still higher than the gene candidate or genome-wide association study approaches. The functional prediction analysis we performed on NGS data may provide the basis to design a SNP array that could analyze the role of functional rare and common variants in hypertension pharmacogenes. In this way, an explorative study, which would be less expensive than an NGS analysis, could be performed to analyze the impact of rare variants in hypertension pharmacogenomics. This kind of investigation may be a determinant in developing a reliable pharmacogenomic test that could be used to select the optimal antihypertensive therapy for each patient.

Conclusion

Our study provided relevant information on the interpopulation differences in hypertension pharmacogenes, highlighting geographically differentiated mechanisms that affect their responses to antihypertensive drugs. However, although a number of studies have been performed providing data on hypertension pharmacogenomics, the relationship between genes and antihypertensive drugs is not currently completely understood. Therefore, our outcomes, based on the current knowledge of hypertension pharmacogenomics, must be confirmed and deepened by further studies. Indeed, one of the most important results of our study was the main role of rare variants in determining the functionality of hypertension pharmacogenes. This indicates that investigations based on NGS technologies are necessary to completely understand hypertension pharmacogenomics and to produce important essential and economic improvements.

Future perspective

In the coming years, the use of high-throughput technologies in clinical practice will allow us to improve our capacity to personalize the healthcare of each individual. Regarding hypertension drugs, the application of NGS technology, together with other research fields (e.g., proteomics and metabolomics), may allow the translation of pharmacogenetic knowledge from scientific literature to clinical routine.

Acknowledgements

The authors are grateful to the research groups of HGDP and of 1000 Genomes Project for their essential contributions.

Financial & competing interests disclosure

This study was supported by RSA Grant 2009 from University of Rome Tor Vergata, by PRIN 2009-2011 (prot. n. 200975T9EW) from MIUR, and by a grant from Fatebenefratelli Association for Biomedical Research (AFaR). 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.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Background

- The analysis of interpopulation genetic differences is a useful method to investigate the predisposition to health-related phenotypes.
- A number of studies highlighted that human populations with different geographic origins have a different response to antihypertensive drugs.
- Currently, pharmacogenetic studies on antihypertensive drugs have provided few useful data to identify the optimal therapy for each patient.

Results

- Our study provided new data about the functional variation of hypertension pharmacogenes among human populations.
- This genetic outcome seems to be in accordance with the epidemiological information on the geographic variation of antihypertensive drug response.
- Moreover, the present analysis indicated that rare variants have a higher impact in determining the function of hypertension pharmacogenes with respect to common ones.

Conclusion

- Based on the present results, we provide new insights into the potential mechanisms of antihypertensive drug response.
- Further studies based on next-generation sequencing technologies may result in the development of reliable pharmacogenetic tests for antihypertensive drugs.

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Papers of special note have been highlighted as:
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