Pharmacogenomics and Personalized Medicine

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ORIGINAL RESEARCH

Analysis of Comprehensive Pharmacogenomic Profiling of VIP Variants Among the Genetically Isolated Chechen Subpopulation from Jordan

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Laith N AL-Eitan[1,2]
Doaa M Rababa'h[1]
Nancy M Hakooz[3]
Mansour A Alghamdi[4,5]
Rana B Dajani[6–8]

[1]Department of Applied Biological Sciences, Jordan University of Science and Technology, Irbid, Jordan; [2]Department of Biotechnology and Genetic Engineering, Jordan University of Science and Technology, Irbid, Jordan; [3]Department of Biopharmaceutics and Clinical Pharmacy, School of Pharmacy, University of Jordan, Amman, Jordan; [4]Department of Anatomy, College of Medicine, King Khalid University, Abha, Saudi Arabia; [5]Genomics and Personalized Medicine Unit, College of Medicine, King Khalid University, Abha, Saudi Arabia; [6]Department of Biology and Biotechnology, Hashemite University, Zarqa, Jordan; [7]Radcliffe Institute for Advanced Studies, Harvard University, Cambridge, MA, USA; [8]Jepson School of Leadership, Richmond University, Richmond, VA, USA

Background: Profiling rare variants in isolated populations can significantly clarify and understand the development of a clinically relevant process. Therefore, leading to a better identifying novel targeted treatment.

Objective: This study aimed to determine the allele frequencies of 56 single nucleotide polymorphisms (SNPs) within several important pharmacogenes.

Methods: This study consisted of 166 unrelated subjects from a genetically isolated group (Chechen) who were living in Jordan. In this study, the distribution of the variants among Chechen was compared to other ethnic groups available at two databases (Genome 1000 and (ExAC)). The frequency of genotypes and alleles was calculated and tested using the chi-square test and the Hardy–Weinberg equilibrium equation (HWE).

Results: Our results revealed that the distribution of allele frequencies within different pharmacogenes among Chechen showed different similarities with other populations. The CEU and TSI showed the highest resemblance with the Chechen population (75% similarity), in contrast to LWK which had the lowest similarity (30%).

Conclusion: This study sheds light on clinically relevant SNPs to enhance medical research and apply pharmacogenomics in clinical settings.

Keywords: pharmacogenomics, VIP polymorphism, Phase I enzymes, Phase II enzymes, metabolizing

Introduction

Pharmacogenomics has become a promising future to enhance individuals' response to treatment.[1] Single nucleotide polymorphisms (SNPs) are one of the most common variants among populations that affect enzyme activity as well as drug metabolism.[2] Consequently, clinical significant SNPs have been studied and screened extensively in different genes in different ethnic backgrounds and given the term very important pharmacogenomic (VIP) variants.[3]

These VIP variants help in drug dose optimization for patients relevant to their genetic makeup and lead to enhanced therapy outcomes and maintain the efficacy of drug treatment.[4] Remarkably, the frequency distribution of these VIP variants varies among different ethnic groups.[5] The importance of the VIP variants depends on their presence within critical genes including drug-metabolizing genes.[6] However, the underlying mechanism of the correlation between the genetic variants and drug response is still beyond clinical practice.[7] Rare variants that impact gene function may account for some uncovered differences in the pharmacological response and

Correspondence: Laith N AL-Eitan
Department of Applied Biological Sciences, Jordan University of Science and Technology, PO Box 3030, Irbid 22110, Jordan
Tel +962 -2 -7201000
Fax +962-2-7201071
Email laeitan@just.edu.jo

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metabolism process.[8] Genetic variants in drug target enzymes; metabolizing, transporters, receptors help in predicting toxicity and treatment failure among patients.[9]

Genetically isolated populations, such as Chechen, can help medical research to overcome the extensive allelic heterogeneity which is a major cause of complex diseases.[10] Chechen, a Caucasian ethnic group of the Nakh peoples, lived in the highlands of the North Caucasus region of Eastern Europe.[11] In 1860 they immigrated to Ottoman lands; however, today, tens of thousands of Chechens live in Turkey, Jordan, Syria, Iraq, Egypt, Saudi Arabia and other Persian Gulf countries.[12] Not many genetic studies have been conducted on Chechens and Circassians living in Jordan. As a genetically isolated population, they can provide a baseline for future studies to discover novel markers associated with diseases.[13–16] Moreover, there is an urgent need for pharmacogenetic research as not many studies conducted in Jordan.[17,18] Therefore, this study aimed to determine the allele frequencies of 52 SNPs within several pharmacogenes in Chechen living in Jordan in comparison to other ethnic groups.

Materials and Methods

Study Subjects

This study was subjected to and in agreement with the Human ethics committee at National Center for Diabetes, Endocrinology and Genetics (NCDEG) and Jordan University of Science and Technology (JUST). Details about subjects and written informed consent were obtained from all volunteers in the study. Ten milliliters of venous blood was collected from unrelated healthy 166 Chechen subjects living in Jordan.

This study was conducted in agreement with the Human ethics committee at National Center for Diabetes, Endocrinology and Genetics (NCDEG) and Jordan University of Science and Technology (JUST), policy number (GM7601). Written informed consent was obtained from all volunteers in the study. This research was also conducted in accordance with the Declaration of Helsinki.

DNA Extraction and Genotyping

Blood samples were drawn from subject and then stored at 4°C for 24 hours before the purification of the genetic material. The extracted DNA was then stored at −20°C.

Genotyping was performed using Agena Bioscience MassARRAY® on a Compact Spectrometer iPLEX GOLD chemistry by Australian Genome Research Facility. Genomic DNA was extracted from each blood sample using the Wizard® Genomic DNA Purification Kit (Promega Corporation, USA) according to the manufacturer's instructions. The quality and quantity of the purified DNA were ascertained via agarose gel electrophoresis and the Nano-Drop ND-1000 UV-Vis Spectrophotometer (BioDrop, UK), respectively.

Candidate genes polymorphisms were analyzed using Sequencing technique. Loci of candidate SNPs were amplified using Multiplex PCR followed by Mass EXTEND which is a primer extension process is resulting in allele-specific DNA products. The genotyping after the minisequencing reaction product analysis was reported by Mass spectrometry. After that, the extension PCR products were separated onto a 384 well spectroCHIP and placed into the MALDI-TOF (Matrix-Assisted Laser Desorption/Ionization Time-of-Flight) mass spectrometer. Lastly, a software system (SpectroTYPER-RT (RT for real-time)) was used to analyze the results.

Variants Selection

The studied VIP variants were selected from the public databases including the PharmGKB database (https://www.pharmgkb.org/), the SNP database of the National Centre for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov/SNP/), and the International HapMap Project (http://www.hapmap.org/). SNPs selected within significant genes that play roles in drug metabolism which make their variants clinically important variants. Finally, the primers were used to genotype these VIP variants were shown in the Supplementary Material.

Population's Variation Data

The allele counts variation data for other populations were obtained from HapMap Project website: CHE: Chechens from Jordan, ASW: African ancestry in Southwest USA, CEU: Utah, USA residents with Northern and Western European ancestry from the CEPH collection, CHB: Han Chinese in Beijing, China, CDX: Chinese Dai in Xishuangbanna, China, GIH: Gujarati Indians in Houston, Texas, USA, GBR: British in England and Scotland, JPT: Japanese in Tokyo, Japan, LWK: Luhya in Webuye, Kenya, MXL: Mexican ancestry in Los Angeles, California, USA, TSI: Toscani in Italy, YRI: Yoruba in Ibadan, Nigeria, CAR: Circassian from Jordan (unpublished data), ACB; African

Table 1 List of Genes, Their VIP Variants, Positions, and Genotyping Data Based on the Whole Cohort (N= 166)

Gene	SNP_ID	Position[a]	SNP	SNP Location	Assay Pass Rate[b]	Call Rate[c]
MTHFR	rs1801131 rs1801133	1:11794419 1:11796321	A>C^{MA} C>T^{MA}	Missense variant Missense variant	100% 100%	100% 99.7%
DPYD	rs3918290	1:97450058	C>T^{MA}	Splice donor variant	100%	99.7%
PTGS2	rs689466	1:186681619	G>A^{MA}	2KB Upstream variant	100%	100%
SCN5A	rs7626962 rs1805124 rs6791924	3:38579416 3:38603929 3:38633208	G>A/G>T T>C^{MA} G>A^{MA}	Missense variant Missense variant Missense variant	100% 100% 100%	100% 100% 100%
NR1I2	rs3814055	3:119781188	C>T^{MA}	5 Prime UTR variant	100%	100%
P2RY12	rs2046934	3:151339854	G^{MA}>A	Intron variant	99%	99.2%
P2RY1	rs1065776 rs701265	3:152835839 3:152836568	C>T^{MA} A>G^{MA}	Synonymous variant Synonymous variant	100% 100%	100% 100%
ADH1A	rs975833	4:99280582	G>C^{MA}	Intron variant	100%	99.7%
ADH1B	rs2066702 rs1229984	4:99307860 4:99318162	G>A^{MA} T^{MA}>C	Missense variant Missense variant	100% 100%	100% 100%
ADH1C	rs698	4:99339632	T>C^{MA}	Missense variant	99%	99.2%
HMGCR	rs17244841 rs3846662 rs17238540	5:75347030 5:75355259 5:75359673	A>T^{MA} A^{MA}>G T>G^{MA}	Intron variant Intron variant Intron variant	99% 100% 100%	98.6% 99.7% 100%
ADRB2	rs1042713 rs1042714 rs1800888	5:148826877 5:148826910 5:148827322	G>A^{MA} G^{MA}>C C>T^{MA}	Missense variant Stop gained Missense variant	100% 100% 100%	100% 100% 99.7%
AHR	rs2066853	7:17339486	G>A^{MA}	Missense variant	100%	99.7%
KCNH2	rs3815459 rs3807375	7:150947306 7:150970122	C>T^{MA} C>T^{MA}	Intron variant Intron variant	100% 100%	99.7% 100%
KCNJ11	rs5219	11:17388025	T^{MA}>C	Stop gained	100%	100%
SLCO1B1	rs4149056	12:21178615	T>C^{MA}	Missense variant	100%	100%
VKORC1	rs7294 rs9934438	16:31091000 16:31093557	C>T^{MA} G>A^{MA}	3 Prime UTR variant Intron variant	100% 100%	100% 100%
SLC19A1	rs12659 rs1051266 rs1131596	21:45531642 21:45537880 21:45538002	A^{MA}>G T>C^{MA} G>A^{MA}	Synonymous variant Missense variant Missense variant	100% 99% 100%	100% 98.6% 99.7%
CYP2J2	rs890293	1:59926822	C>A^{MA}	Upstream variant	100%	100%
CYP3A4	rs4986913 rs4986910 rs4986909 rs12721634 rs2740574	7:99760836 7:99760901 7:99762047 7:99784038 7:99784473	G>A^{MA} A>G^{MA} G>A ^{MA} A>G C^{MA}>T	Missense variant Missense variant Missense variant Missense variant Upstream variant	100% 100% 100% 100% 100%	100% 100% 100% 100% 100%
CYP2C19	rs4986893 rs4244285	10:94780653 10:94781859	G>A^{MA} G>A^{MA}	Stop gained Synonymous variant	100% 100%	100% 99.7%
CYP2C9	rs1799853	10:94942290	C>T^{MA}	Missense variant	100%	100%

(*Continued*)

Table 1 (Continued).

Gene	SNP_ID	Position[a]	SNP	SNP Location	Assay Pass Rate[b]	Call Rate[c]
CYP2A6	rs28399454	19:40845362	C>T^{MA}	Missense variant	100%	100%
	rs1801272	19:40848628	A>T^{MA}	Missense variant	100%	100%
	rs28399433	19:40850474	A>C^{MA}	Upstream Variant	99%	99.2%
CYP2B6	rs3745274	19:41006936	G>T^{MA}	Missense variant	96%	96.5%
	rs28399499	19:41012316	T>C^{MA}	Missense variant	100%	100%
CYP2D6	rs59421388	22:42127608	C>T^{MA}	Missense variant	100%	100%
	rs28371725	22:42127803	C>T^{MA}	Intron variant	98%	98.4%
	rs61736512	22:42129132	C>T^{MA}	Missense variant	100%	100%
	rs28371706	22:42129770	G>A^{MA}	Missense variant	100%	100%
	rs5030656	22:42128174–42128178	delTCT	Inframe deletion	100%	100%
CYP3A5	rs776746	7:99672916	C>T^{MA}	Splice Acceptor Variant	100%	99%
UGT1A1	rs4124874	2:233757013	T^{MA}>G	Intronic variant	100%	100%
	rs10929302	2:23375713	G>A^{MA}	Intronic variant	100%	100%
	rs4148323	2:233760498	G>A^{MA}	Missense variant	100%	100%
COMT	rs4680	22:19963748	G>A^{MA}	Missense variant	100%	99.7%
GSTP1	rs1695	11:67585218	A>G^{MA}	Missense variant	100%	100%
	rs1138272	11:67586108	C>T^{MA}	Missense variant	100%	100%

Notes: [a]Chromosome positions are based on NCBI Human Genome Assembly Build. [b]Ratio of the number of discordant genotypes to the number of duplicates. [c]Ratio of the number of valid genotypes to the number of subjects genotyped. MA: Global minor allele <1.

Caribbeans in Barbados. Also, the allele count data of populations around the world were obtained from the Exome Aggregation Consortium (ExAC): African, East Asian, Latino, European (non-Finnish), South Asian and European (Finnish).

Statistical Analysis

Statistical Package for Social Sciences SPSS (version 19) was used to statistically analyze the data. The genotypes and alleles frequency was calculated and tested using the chi-square test and the Hardy–Weinberg equilibrium equation (HWE) and all p-values accepted as p-value <0.05. Fisher exact test was used for the correction of small sizes.

Results

Table 1 shows basic information about the selected variants within 28 studied genes, in addition to describe the quality control of samples' genotyping. Genotype call rates ranged from 96.5% to 100%. Allele and genotype frequencies of the selected variants among 166 Chechen subjects are listed in Table 2. SNPs were tested for Hardy–Weinberg Equilibrium (HWE), all the studied polymorphisms met the HWE standards (P-value > 0.05) except for rs1801131 within *MTHFR* (P-value = 0.027) did not fulfil the HWE equation (Figure 1).

Table 3 compares minor allele frequencies (MAF) of the significant polymorphisms among Chechens and other populations. For example, the MAF of rs776746 (T) of the *CYP3A5* gene within the Chechen group was similar to both CEU and GBR but different from ASW, CHB, CDX, GIH, and others. Also, Table 3 compares the allelic distribution of selected variants among Chechens and Circassians and other populations by estimating the *P*-value. We found that each studied variant distribution within Chechens in Jordan is significantly different from various populations. For example, Rs1229984 and rs28371725 had a highly different distribution with around 90% of the compared populations.

It is also clear from Table 3 that the similarity of the studied polymorphisms within the Chechens population with other compared population varied from one to another. The CEU Utah (USA residents with Northern and Western European ancestry from the CEPH collection) and TSI (Toscani in Italy) had the highest similarity among the studied population with around 25% differences; ie, around 75% of the studied variants had the same frequency and distribution in Chechens and other

Table 2 The Minor Allele Frequencies and HWE p Values for the VIP Variants in Chechen (N= 166)

Gene	SNP_ID	Allele	Allelic Frequency	Genotype	Genotypic Frequency	P-value
MTHFR	rs1801131	C	0.64	AA	0.37	0.027
		A	0.36	CA	0.54	
				CC	0.08	
	rs1801133	T	0.18	CC	0.67	0.88
		C	0.82	CT	0.3	
				TT	0.03	
DPYD	rs3918290	C	99.7	CC	0.99	0.96
		T	0.003	CT	0.01	
PTGS2	rs689466	T	0.89	CC	0.01	0.7
		C	0.11	CT	0.21	
				TT	0.78	
SCN5A	rs7626962	G	1.0	GG	1.0	NA
	rs1805124	T	0.75	CC	0.04	0.22
		C	0.25	CT	0.42	
				TT	0.54	
	rs6791924	G	1.0	GG	1.0	NA
NR1I2	rs3814055	C	0.67	CC	0.46	0.39
		T	0.33	CT	0.42	
				TT	0.13	
P2RY12	rs2046934	A	0.85	AA	0.72	0.97
		G	0.15	AG	0.26	
				GG	0.02	
P2RY1	rs1065776	C	0.99	CC	0.98	0.90
		T	0.01	CT	0.02	
	rs701265	A	0.83	AA	0.69	0.75
		G	0.17	AG	0.28	
				GG	0.02	
ADH1A	rs975833	G	0.76	CC	0.05	0.78
		C	0.24	CG	0.37	
				GG	0.57	
ADH1B	rs2066702	G	0.99	GA	0.02	0.87
		A	0.01	GG	0.98	
	rs1229984	C	0.88	CC	0.75	0.14
		T	0.12	CT	0.25	

(*Continued*)

Table 2 (Continued).

Gene	SNP_ID	Allele	Allelic Frequency	Genotype	Genotypic Frequency	P-value
ADH1C	rs698	C	0.27	CC	0.07	0.91
		T	0.73	CT	0.39	
				TT	0.54	
HMGCR	rs17244841	A	0.97	AA	0.94	0.72
		T	0.03	AT	0.06	
	rs3846662	G	0.43	AA	0.31	0.53
		A	0.57	GA	0.52	
				GG	0.17	
	rs17238540	G	0.03	TT	0.93	0.65
		T	0.97	GT	0.07	
ADRB2	rs1042713	G	0.63	GG	0.4	0.62
		A	0.37	GA	0.45	
				AA	0.15	
	rs1042714	C	0.69	CC	0.49	0.21
		G	0.31	CG	0.39	
				GG	0.12	
	rs1800888	C	0.99	CC	0.99	0.97
		T	0.003	CT	0.01	
AHR	rs2066853	G	0.87	GG	0.77	0.73
		A	0.13	GA	0.22	
				AA	0.02	
KCNH2	rs3815459	C	0.73	CC	0.52	0.37
		T	0.27	CT	0.43	
				TT	0.05	
	rs3807375	C	0.63	CC	0.39	0.74
		T	0.37	CT	0.48	
				TT	0.13	
KCNJ11	rs5219	C	0.54	CC	0.31	0.35
		T	0.46	CT	0.46	
				TT	0.23	
SLCO1B1	rs4149056	C	0.04	CT	0.08	0.59
		T	0.96	TT	0.92	

(*Continued*)

Table 2 (Continued).

Gene	SNP_ID	Allele	Allelic Frequency	Genotype	Genotypic Frequency	P-value
VKORC1	rs7294	C	0.62	CC	0.36	0.33
		T	0.38	CT	0.51	
				TT	0.13	
	rs9934438	G	0.59	GG	0.34	0.63
		A	0.41	GA	0.51	
				AA	0.16	
SLC19A1	rs12659	G	0.51	GG	0.27	0.54
		A	0.49	GA	0.48	
				AA	0.25	
	rs1051266	C	0.48	CC	0.23	0.86
		T	0.52	CT	0.51	
				TT	0.43	
	rs1131596	A	0.47	AA	0.22	0.88
		G	0.53	AG	0.49	
				GG	0.28	
CYP2J2	rs890293	C	0.93	CA	0.13	0.36
		A	0.07	CC	0.87	
CYP3A5	rs10264272	C	1.0	CC	1.0	N/A
	rs776746	C	0.97	CC	0.95	0.13
		T	0.03	CT	0.05	
				TT	0.01	
CYP3A4	rs4986913	G	1.0	GG	1.0	N/A
	rs4986910	A	1.0	AA	1.0	N/A
	rs4986909	G	1.0	GG	1.0	N/A
	rs12721634	A	1.0	AA	1.0	N/A
	rs2740574	T	0.99	TC	0.01	0.96
		C	0.004	TT	0.99	
CYP2C19	rs4986893	G	1.0	GG	1.0	N/A
	rs4244285	G	0.91	AA	0.02	0.13
		A	0.09	GA	0.14	
				GG	0.84	
CYP2C9	rs1799853	C	0.98	CC	0.96	0.083
		T	0.02	CT	0.04	
				TT	0.01	

(*Continued*)

Table 2 (Continued).

Gene	SNP_ID	Allele	Allelic Frequency	Genotype	Genotypic Frequency	P-value
CYP2A6	rs28399454	C	1.0	CC	1.0	N/A
	rs1801272	A	1.0	AA	1.0	N/A
	rs28399433	A	0.91	AA	0.82	0.37
		C	0.09	AC	0.18	
CYP2B6	rs3745274	G	0.69	GG	0.5	0.072
		T	0.31	GT	0.37	
				TT	0.13	
	rs28399499	T	1.0	TT	1.0	N/A
CYP2D6	rs59421388	C	1.0	CC	1.0	N/A
	rs28371725	C	0.86	CC	0.74	0.33
		T	0.14	CT	0.23	
				TT	0.03	
	rs61736512	C	1.0	CC	1.0	N/A
	rs28371706	G	1.0	GG	1.0	N/A
	rs5030656	C/T/T	1.0	-	1.0	N/A
UGT1A1	rs4124874	G	0.54	GG	0.33	0.06
		T	0.46	GT	0.41	
				TT	0.26	
	rs10929302	G	0.61	GG	0.37	0.90
		A	0.39	GA	0.47	
				AA	0.16	
	rs4148323	G	0.97	GG	0.95	0.80
		A	0.03	GA	0.05	
COMT	rs4680	G	0.59	GG	0.35	0.90
		A	0.41	GA	0.47	
				AA	0.18	
GSTP1	rs1695	A	0.67	AA	0.46	0.69
		G	0.33	AG	0.43	
				GG	0.12	
	rs1138272	C	0.84	CC	0.71	0.50
		T	0.16	CT	0.26	
				TT	0.02	

Note: *p-value > 0.05 is considered normally distributed.
Abbreviations: HWE, Hardy–Weinberg equilibrium; N/A, not applicable.

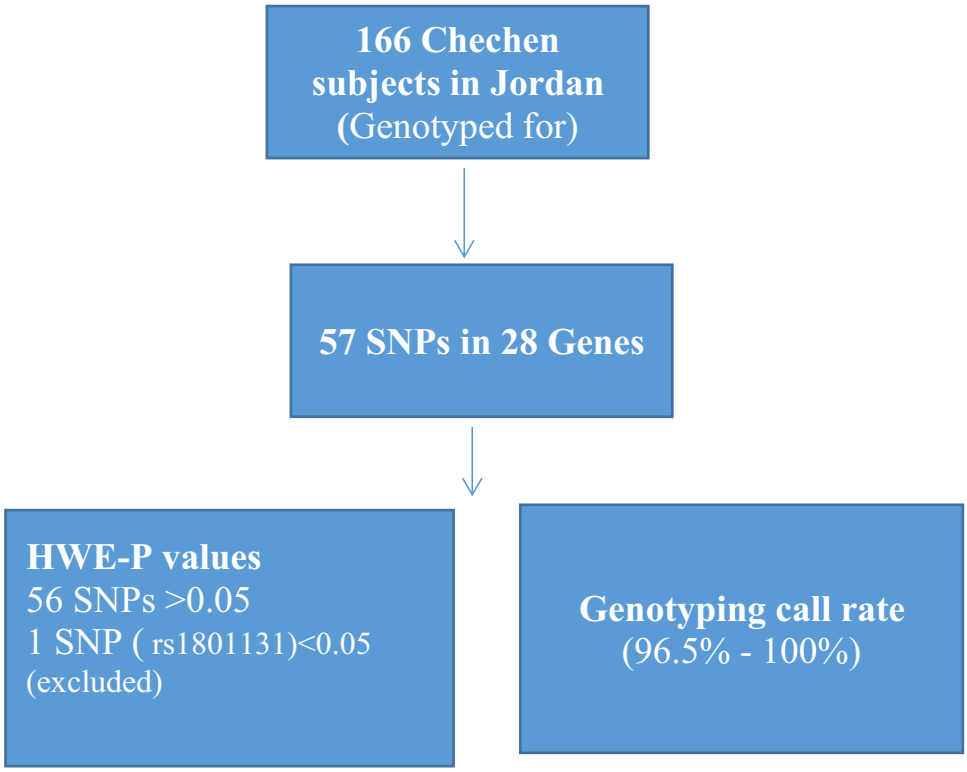

Figure 1 The number of single nucleotide polymorphisms (SNPs) in this study and their genotyping accuracy.

compared populations. This similarity in the distribution of the compared SNPs decreased to reach around 30% when compared to LWK (Luhya in Webeye).

Furthermore, the significant variants within the selected genes within Chechen were compared to the available variants within six populations listed in the Exome Aggregation Consortium (ExAC) database as shown in Table 4.

Discussion

This study was conducted on Chechens group living in Jordan. This subpopulation has a distinct genetic makeup as a genetically isolated population.[19] Our findings demonstrate that the Chechen living in Jordan may have widely varying genetic allele distribution for clinically relevant SNPs compared to other populations. Assessment of the VIP genetic polymorphism frequencies within such a minority group can attribute to studies of the theoretical basis of drug toxicity and efficacy.

Several single nucleotide variants within the *CYP450* genes have been reported as clinically significant. For example; within the *CYP2J2* gene, the variant rs890293 genotypes AA + AC have been shown to be correlated to an increased risk of nausea and vomiting when treated with tacrolimus in individuals with Kidney Transplantation as compared to genotype CC.[20]

rs4244285 (GG) genotype of *CYP2C19* is associated with increased risk of toxicity when treated with cyclophosphamide in women with Lupus Erythematosus, as compared to genotypes AA + AG.[21] Besides, patients with the genotype GG of rs4986893 and treated with phenytoin may have a decreased likelihood of drug reaction with eosinophilia and systemic symptoms (DRESS) as compared to patients with the AG and AA genotypes.[22] It also was found that allele A is associated with an increased risk of cardiovascular events when treated with clopidogrel in patients with coronary disease as compared to genotype GG.[23] Moreover, allele A of rs4986893 is associated with decreased clopidogrel inhibition of ADP-induced platelet aggregation when treated with clopidogrel in healthy individuals as compared to genotype GG.[24,25]

Furthermore, our findings reveal that the alternative allele (T) frequency of rs1229984 in *ADH1B* gene among Chechen was much less than in Latino (94%), African (99%), European non-Finnish (95%), South Asian (95%) and European Finnish (99%) according to ExAC database. rs1229984 was reported as a clinically significant variant, whereas TT genotype was associated with increased Vmax

Table 3 VIP Variants Within the Pharmacogenes in Chechen Compared to HapMap Populations

SNP ID	Populations												
	CHE	ASW	CEU	CHB	CDX	GBR	GIH	JPT	LWK	MXL	TSI	YRI	ACB
rs3918290	0.003[a]	0.008[a] 0.54[b] 0.46[c]	0.005[a] 0.13[b] 0.71[c]	0.00[a] 0.62[b] 0.43[c]	0.00[a] 0.56[b] 0.45[c]	0.00[a] 0.55[b] 0.45[c]	0.146[a] 2.3[b] 0.13[c]	0.00[a] 0.63[b] 0.43[c]	0.00[a] 0.60[b] 0.44[c]	0.00[a] 0.39[b] 0.53[c]	0.005[a] 0.09[b] 0.75[c]	0.00[a] 0.65[b] 0.42[c]	0.00[a] 0.57[b] 0.45[c]
rs689466	0.11[a]	0.13[a] 0.34[b] 0.56[c]	0.19[a] 6.6[b] 0.01[c]	0.47[a] N/A[b] N/A[c]	0.52[a] N/A[b] N/A[c]	0.20[a] 7.2[b] 0.01[c]	0.13[a] 0.26[b] 0.60[c]	0.44[a] N/A[b] N/A[c]	0.03[a] 10.9[b] 1e-3[c]	0.26[a] 15.3[b] 1e-4[c]	0.20[a] 7.5[b] 0.01[c]	0.07[a] 2.1[b] 0.14[c]	0.10[a] 0.1[b] 0.79[c]
rs1805124	0.25[a]	0.26[a] 0.04[b] 0.84[c]	0.18[a] 3.5[b] 0.06[c]	0.12[a] 12.5[b] 4e-4[c]	0.07[a] 26.2[b] 3e-7[c]	0.22[a] 0.49[b] 0.48[c]	0.20[a] 1.7[b] 0.19[c]	0.13[a] 10.9[b] 1e-3[c]	0.30[a] 1.6[b] 0.21[c]	0.16[a] 4.1[b] 0.04[c]	0.23[a] 0.26[b] 0.61[c]	0.32[a] 3.7[b] 0.05[c]	0.28[a] 0.5[b] 0.47[c]
rs3814055	0.33[a]	0.29[a] 0.62[b] 0.42[c]	0.34[a] 0.01[b] 0.92[c]	0.27[a] 2.3[b] 0.12[c]	0.15[a] 19.2[b] 1e-5[c]	0.40[a] 33.2[b] 1e-8[c]	0.42[a] 3.8[b] 0.05[c]	0.25[a] 3.8[b] 0.05[c]	0.30[a] 0.55[b] 0.45[c]	0.33[a] 0.001[b] 0.97[c]	0.36[a] 0.37[b] 0.54[c]	0.27[a] 2.2[b] 0.13[c]	0.39[a] 2.0[b] 0.15[c]
rs1065776	0.01[a]	0.20[a] N/A[b] N/A[c]	0.05[a] 10.43[b] 0.001[c]	0.03[a] 4.3[b] 0.04[c]	0.02[a] 0.52[b] 0.46[c]	0.02[a] 1.4[b] 0.22[c]	0.10[a] 25.7[b] 3.9e-7[c]	0.07[a] 15.7[b] 7e-5[c]	0.21[a] N/A[b] N/A[c]	0.05[a] 6.9[b] 0.01[c]	0.03[a] 4.1[b] 0.04[c]	0.22[a] N/A[b] N/A[c]	0.20[a] N/A[b] N/A[c]
rs701265	0.17[a]	0.67[a] N/A[b] N/A[c]	0.17[a] 0.001[b] 0.97[c]	0.28[a] 11.1[b] 0.001[c]	0.19[a] 0.42[b] 0.51[c]	0.13[a] 1.0[b] 0.31[c]	0.21[a] 1.6[b] 0.21[c]	0.27[a] 9.1[b] 0.002[c]	0.80[a] N/A[b] N/A[c]	0.20[a] 0.89[b] 0.34[c]	0.16[a] 0.004[b] 0.95[c]	0.81[a] N/A[b] N/A[c]	0.72[a] N/A[b] N/A[c]
rs975833	0.24[a]	0.25[a] 0.08[b] 0.77[c]	0.24[a] 0.001[b] 0.97[c]	0.79[a] N/A[b] N/A[c]	0.75[a] N/A[b] N/A[c]	0.24[a] N/A[b] N/A[c]	0.49[a] N/A[b] N/A[c]	0.80[a] N/A[b] N/A[c]	0.19[a] 1.7[b] 0.19[c]	0.13[a] 6.5[b] 0.01[c]	0.27[a] 0.6[b] 0.43[c]	0.30[a] 2.4[b] 0.12[c]	0.28[a] 0.79[b] 0.37[c]
rs2066702	0.01[a]	0.20[a] N/A[b] N/A[c]	0.00[a] 2.4[b] 0.12[c]	0.00[a] 2.5[b] 0.11[c]	0.00[a] 2.3[b] 0.13[c]	0.00[a] 2.2[b] 0.14[c]	0.00[a] 2.5[b] 0.11[c]	0.00[a] 2.5[b] 0.11[c]	0.14[a] N/A[b] N/A[c]	0.03[a] 1.9[b] 0.16[c]	0.00[a] 2.6[b] 0.11[c]	0.28[a] N/A[b] N/A[c]	0.19[a] N/A[b] N/A[c]
rs1229984	0.12[a]	0.00[a] 16.5[b] 5e-5[c]	0.02[a] 19.1[b] 1e-5[c]	0.71[a] N/A[b] N/A[c]	0.63[a] N/A[b] N/A[c]	0.01[a] 21.8[b] 3e-6[c]	0.02[a] 16.0[b] 6e-5[c]	0.73[a] N/A[b] N/A[c]	0.00[a] 26.5[b] 2.6e-7[c]	0.08[a] 1.3[b] 0.25[c]	0.05[a] 7.8[b] 0.005[c]	0.00[a] 28.8[b] 8e-8[c]	0.01[a] 20.6[b] 6e-6[c]
rs698	0.27[a]	0.14[a] 8.1[b] 0.004[c]	0.47[a] 23.7[b] 1e-6[c]	0.05[a] N/A[b] N/A[c]	0.11[a] 16.9[b] 4e-5[c]	0.44[a] 15.9[b] 7e-5[c]	0.28[a] 0.14[b] 0.71[c]	0.07[a] 31.2[b] 2e-8[c]	0.14[a] 11.3[b] 0.001[c]	0.28[a] 0.10[b] 0.75[c]	0.31[a] 1.1[b] 0.29[c]	0.07[a] 33.1[b] 1e-8[c]	0.11[a] 18.1[b] 2e-5[c]
rs17244841	0.03[a]	0.10[a] 9.8[b] 0.002[c]	0.01[a] 0.87[b] 0.35[c]	0.00[a] 5.8[b] 0.02	0.00[a] 5.2[b] 0.02[c]	0.03[a] N/A[b] N/A[c]	0.00[a] 5.2[b] 0.02[c]	0.02[a] 0.39[b] 0.53[c]	0.08[a] 8.7[b] 0.003[c]	0.04[a] 0.38[b] 0.53[c]	0.03[a] 0.11[b] 0.74[c]	0.09[a] 10.7[b] 0.001[c]	0.10[a] 13.3[b] 3e-4[c]
rs3846662	0.43[a]	0.13[a] N/A[b] N/A[c]	0.57[a] 0.04[b] 0.83[c]	0.48 3.3[b] 0.06[c]	0.49[a] 2.5[b] 0.12[c]	0.55[a] 0.14[b] 0.17[c]	0.34[a] 26.1[b] 3.2e-7[c]	0.47[a] 7.1[b] 0.008[c]	0.03[a] N/A[b] N/A[c]	0.56[a] 0.005[b] 0.94[c]	0.57[a] 0.008[b] 0.93[c]	0.04[a] N/A[b] N/A[c]	0.11[a] N/A[b] N/A[c]
rs17238540	0.03[a]	0.10[a] 7.9[b] 0.005[c]	0.01[a] 1.5[b] 0.21[c]	0.00[a] 6.9[b] 0.008[c]	0.00[a] 6.3[b] 0.01[c]	0.02[a] 0.5[b] 0.47[c]	0.00[a] 6.9[b] 0.008[c]	0.00[a] 7.0[b] 0.008[c]	0.09[a] 8.0[b] 0.004[c]	0.04[a] 0.09[b] 0.76[c]	0.03[a] 0.001[b] 0.97[c]	0.10[a] 9.7[b] 0.002[c]	0.09[a] 8.5[b] 0.003[c]
rs1042713	0.37[a]	0.54[a] 11.3[a] 0.001[c]	0.35[a] 0.33[b] 0.56[c]	0.55[a] 15.8[b] 7e-5[c]	0.58[a] 20.7[b] 5e-6[c]	0.42[a] 0.96[b] 0.32	0.43[a] 1.8[b] 0.18[c]	0.44[a] 2.5[b] 0.11[c]	0.49[a] 7.0[b] 0.008[c]	0.48[a] 4.1[b] 0.04[c]	0.37[a] 0.01[b] 0.92[c]	0.53[a] 13.4[b] 0.0002[c]	0.51[a] 9.3[b] 0.002[c]

(*Continued*)

Table 3 (Continued).

SNP ID	Populations												
	CHE	ASW	CEU	CHB	CDX	GBR	GIH	JPT	LWK	MXL	TSI	YRI	ACB
rs1042714	0.31[a]	0.12[a] 16.7[b] 4e-5[c]	0.46[a] 12.1[b] 5e-4[c]	0.11[a] 30.2[b] 4e-8[c]	0.10[a] 29.3[b] 6e-8[c]	0.39[a] 3.5[b] 0.06[c]	0.23[a] 4.6[b] 0.03[c]	0.06[a] N/A[b] N/A[c]	0.21[a] 6.3[b] 0.01[c]	0.14[a] 14.1[b] 2e-4[c]	0.14[a] 3.6[b] 0.06[c]	0.12[a] 27.0[b] 2.1e-7[c]	0.16[a] 14.6[b] 1e-4[c]
rs1800888	0.003[a]	0.00[a] 0.36[b] 0.54[c]	0.02[a] 2.4[b] 0.11[c]	0.00[a] 0.62[b] 0.43[c]	0.00[a] 0.56[b] 0.45[c]	0.02[a] 4.3[b] 0.04[c]	0.00[a] 0.62[b] 0.43[c]	0.00[a] 0.62[b] 0.42[c]	0.00[a] 0.59[b] 0.44[c]	0.00[a] 0.38[b] 0.53[c]	0.01[a] 2.2[b] 0.14[c]	0.00[a] 0.65[b] 0.42[c]	0.00[a] 0.57[b] 0.45[c]
rs2066853	0.13[a]	0.34[a] 28.0[b] 1.2e-7[c]	0.09[a] 1.5[b] 0.21[c]	0.37[a] N/A[b] N/A[c]	0.26[a] 14.4[b] 2e-4[c]	0.09[a] 0.87[b] 0.35[c]	0.12[a] 0.11[b] 0.73[c]	0.46[a] N/A[b] N/A[c]	0.48[a] N/A[b] N/A[c]	0.13[a] 0.03[b] 0.85[c]	0.09[a] 1.02[b] 0.31[c]	0.45[a] N/A[b] N/A[c]	0.47[a] N/A[b] N/A[c]
rs3815459	0.27[a]	0.42[a] 9.5[b] 0.002[c]	0.20[a] 3.2[b] 0.07[c]	0.71[a] N/A[b] N/A[c]	0.56[a] 6.6[b] 0.01[c]	0.15[a] 8.5[b] 0.003[c]	0.35[a] 3.2[b] 0.07[c]	0.80[a] N/A[b] N/A[c]	0.39[a] 8.6[b] 0.003[c]	0.39[a] 7.6[b] 0.006[c]	0.23[a] 0.74[b] 0.39[c]	0.33[a] 2.8[b] 0.09[c]	0.31[a] 1.5[b] 0.22[c]
rs3807375	0.63[a]	0.27[a] N/A[b] N/A[c]	0.65[a] 0.33[b] 0.56[c]	0.25[a] N/A[b] N/A[c]	0.26[a] N/A[b] N/A[c]	0.70[a] 3.1[b] 0.08[c]	0.61[a] 1.0[b] 0.31[c]	0.20[a] N/A[b] N/A[c]	0.20[a] N/A[b] N/A[c]	0.43[a] N/A[b] N/A[c]	0.66[a] 0.59[b] 0.44[c]	0.23[a] N/A[b] N/A[c]	0.26[a] N/A[b] N/A[c]
rs5219	0.46[a]	0.14[a] N/A[b] N/A[c]	0.38[a] 3.2[b] 0.07[c]	0.38[a] 3.7[b] 0.05[c]	0.23[a] 28.7[b] 8e-8[c]	0.26[a] 19.7[b] 1e-5[c]	0.42[a] 1.1[b] 0.29[c]	0.33[a] 9.2[b] 0.002[c]	0.01[a] N/A[b] N/A[c]	0.41[a] 1.24[b] 0.26[c]	0.29[a] 17.4[b] 3e-5[c]	0.00[a] N/A[b] N/A[c]	0.06[a] N/A[b] N/A[c]
rs4149056	0.04[a]	0.06[a] 0.38[b] 0.53[c]	0.15[a] 3.0[b] 0.08[c]	0.14[a] 2.19[b] 0.14[c]	0.14[a] 2.4[b] 0.12[c]	0.14[a] 2.6[b] 0.10[c]	0.02[a] 8.5[b] 0.004[c]	0.12[a] 1.1[b] 0.29[c]	0.02[a] 7.9[b] 0.004[c]	0.08[a] 0.05[b] 0.82[c]	0.21[a] 11.0[b] 0.001[c]	0.01[a] 13.3[b] 3e-4[c]	0.02[a] 7.6[b] 0.01[c]
rs7294	0.38[a]	0.48[a] N/A[b] N/A[c]	0.31[a] 14.5[b] 1e-4[c]	0.04[a] 0.64[b] 0.42[c]	0.17[a] 0.98[b] 0.32[c]	0.42[a] 15.2[b] 1e-4[c]	0.67[a] 0.02[b] 0.89[c]	0.09[a] 2.9[b] 0.09[c]	0.43[a] N/A[b] N/A[c]	0.35[a] 23.4[b] 1e-6[c]	0.34[a] 10.7[b] 0.001[c]	0.51[a] N/A[b] N/A[c]	0.46[a] N/A[b] N/A[c]
rs9934438	0.41[a]	0.15[a] 27.3[b] 1.7e-7[c]	0.43[a] 0.19[b] 0.65[c]	0.96[a] N/A[b] N/A[c]	0.82[a] N/A[b] N/A[c]	0.36[a] 1.4[b] 0.24[c]	0.17[a] 32.2[b] 1e-8[c]	0.90[a] N/A[b] N/A[c]	0.04[a] N/A[b] N/A[c]	0.47[a] 1.3[b] 0.25[c]	0.48[a] 2.4[b] 0.12[c]	0.03[a] N/A[b] N/A[c]	0.06[a] N/A[b] N/A[c]
rs12659	0.49[a]	0.40[a] 2.8[b] 0.09[c]	0.42[a] 2.5[b] 0.10[c]	0.49[a] 0.02[b] 0.90[c]	0.53[a] 0.81[b] 0.37[c]	0.39[a] 4.8[b] 0.03[c]	0.36[a] 8.3[b] 0.004[c]	0.54[a] 1.4[b] 0.23[c]	0.53[a] 0.77[b] 0.38[c]	0.34[a] 8.1[b] 0.004[c]	0.44[a] 1.2[b] 0.28[c]	0.48[a] 0.05[b] 0.83[c]	0.55[a] 1.8[b] 0.18[c]
rs1051266	0.48[a]	0.43[a] 0.79[b] 0.37[c]	0.57[a] 3.9[b] 0.05[c]	0.52[a] 0.92[b] 0.33[c]	0.46[a] 0.17[b] 0.68[c]	0.60[a] 4.6[b] 0.01[c]	0.60[a] 7.9[b] 0.005[c]	0.46[a] 0.31[b] 0.58[c]	0.31[a] 15.2[b] 1e-4[c]	0.65[a] 10.3[b] 0.001[c]	0.55[a] 2.5[b] 0.11[c]	0.33[a] 12.4[b] 4e-4[c]	0.31[a] 14.1[b] 2e-4[c]
rs1131596	0.47[a]	0.38[a] 3.1[b] 0.08[c]	0.57[a] 5.1[b] 0.02[c]	0.52[a] 1.5[b] 0.22[c]	0.46[a] 0.03[b] 0.87[c]	0.60[a] 7.8[b] 0.005[c]	0.61[a] 9.6[b] 0.001[c]	0.46[a] 0.09[b] 0.77[c]	0.24[a] 28.3[b] 1.1e-7[c]	0.65[a] 11.8[b] 0.001[c]	0.55[a] 3.5[b] 0.06[c]	0.28[a] 201[b] 1e-5[c]	0.28[a] 19.0[b] 1e-5[c]
rs4124874	0.44[a]	0.22[a] 47.3[b] N/A[c]	0.57[a] 7.8[b] 0.005[c]	0.72[a] 42.7[b] N/A[C]	0.55[a] 5.6[b] 0.02[c]	0.62[a] 15.4[b] 9e^{-5} [c]	0.39[a] 1.1[b] 0.28[c]	0.69[a] 31.5[b] 2e^{-8} [c]	0.11[a] 63.9[b] N/A[c]	0.48[a] 0.74[b] 0.38[c]	0.56[a] 7.04[b] 008e^{-3} [c]	0.09[a] 74.6[b] N/A [c]	0.22[a] 0.9[b] 0.3[c]
rs10929302	0.35[a]	0.33[a] 0.183[b] 0.67[c]	0.30[a] 0.95[b] 0.33[c]	0.11[a] 37.5[b] N/A[c]	0.15[a] 23.4[b] 2^{e-6} [c]	0.23[a] 7.7[b] 5^{e-3} [c]	0.44[a] 4.1[b] 0.04[c]	0.18[a] 18.5[b] 2^{e-5} [c]	0.36[a] 0.05 [b] 0.83[c]	0.34[a] 0.01[b] 0.91[c]	0.24[a] 7.7[b] 6e^{-3} [c]	0.64[a] 0.08[b] 0.78[c]	0.30[a] 0.9[b] 0.32[c]

(*Continued*)

Table 3 (Continued).

SNP ID	Populations												
	CHE	ASW	CEU	CHB	CDX	GBR	GIH	JPT	LWK	MXL	TSI	YRI	ACB
rs4148323	0.0[a]	0.01[a] 2.7[b] 0.09[c]	0.0[a] N/A[b] N/A[c]	0.23[a] 82.9[b] N/A[c]	0.10[a] 35.2[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.02[a] 6.4[b] 0.01[c]	0.13[a] 45.3[b] N/A[c]	0.0[a] N/Ab N/A[b]	0.02[a] 7.8[b] 5^{e-3} [c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]
rs4680	0.50[a]	0.27[a] 19.0[b] $1e^{-5}$ [c]	0.46[a] 0.6[b] 0.43[c]	0.31[a] 17.6[b] 3e-5 [c]	0.26[a] 26.1[b] 3.1e-7 [c]	0.52[a] 0.3[b] 0.55[c]	0.43[a] 2.0[b] 0.15[c]	0.28[a] 24.5[b] 7.2e-7 [c]	0.28[a] 22.8[b] 1e-6[c]	0.39[a] 3.8[b] 0.05[c]	0.45[a] 1.1[b] 0.28[c]	0.30[a] 20.2[b] 6e-6 [c]	0.36[a] 15.4[b] 8e-5 [c]
rs1695	0.30[a]	0.45[a] 10.2[b] 0.001[c]	0.39[a] 5.1[b] 0.02[c]	0.18[a] 8.6[b] 0.003[c]	0.22[a] 3.6[b] 0.05[c]	0.31[a] 0.2[b] 0.62[c]	0.31[a] 0.01[b] 0.76[c]	0.10[a] 28.7[b] 8e-8 [c]	0.51[a] 23.7[b] 1e-6 [c]	0.56[a] 27.6[b] 1.5e-7[c]	0.29[a] 23.7[b] 1e-6 [c]	0.39[a] 5.8[b] 0.01[c]	0.43[a] 10.3[b] 0.001[c]
rs1138272	0.10[a]	0.00[a] 6.4[b] 0.01[c]	0.09[a] N/A N/A	0.00[a] 21.1[b] 4e-6[c]	0.00[a] 19.1[b] 1e-5[c]	0.05[a] 2.6[b] 0.1[c]	0.08[a] 0.2[b] 0.58[c]	0.00[a] N/A[b] N/A[c]	0.01[a] 13.2b 3e-4[c]	0.05[a] 2.07[b] 0.15[c]	0.05[a] 3.6[b] 0.05[c]	0.00[a] 22.1[b] 2e-6[c]	0.001[a] 17.1[b] 3e-5[c]
rs890293	0.07[a]	0.16[a] 10.1[b] 0.001[c]	0.05[a] 0.5[b] 0.46[c]	0.04[a] 1.2[b] 0.27[C]	0.02[a] 6.5[b] 0.01[c]	0.05[a] 0.6[b] 0.44 [c]	0.05[a] 0.4[b] 0.54[c]	0.02[a] 4.8[b] 0.02 [c]	0.14[a] 7.3[b] 0.007[c]	0.03[a] 2.1[b] 0.14[c]	0.05[a] 0.5[b] 0.47 [c]	0.15[a] 10.8[b] 0.001 [c]	0.10[a] 2.3[b] 0.12[c]
rs10264272	0.0[a]	0.05[a] 16.5[b] $5e^{-5}$ [c]	0.00[a] N/A[b] N/A[c]	0.00[a] N/A[b] N/A[c]	0.00[a] N/A[b] N/A[c]	0.00[a] N/A[b] N/A[c]	0.00[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.24[a] N/A[b] N/A[c]	0.02[a] 7.8[b] 0.005[c]	0.01[a] 1.6[b] 0.21[c]	0.17[a] N/A[b] N/A[c]	0.11[a] N/A[b] N/A[c]
rs776746	0.03[a]	0.68[a] N/A[b] N/A[c]	0.04[a] 0.4[b] 0.52[c]	0.31[a] N/A[b] N/A[c]	0.31[a] N/A[b] N/A[c]	0.05[a] 1.9[b] 0.16[c]	0.28[a] N/A[b] N/A[c]	0.25[a] N/A[b] N/A[c]	0.88[a] N/A[b] N/A[c]	0.23[a] N/A[b] N/A[c]	0.05[a] 1.5[b] 0.21[c]	0.83[a] N/A[b] N/A[c]	0.75[a] N/A[b] N/A[c]
rs4986913	0.0[a]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.005[a] 1.6[b] 0.20[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]
rs4986910	0.0[a]	0.0[a] N/A[b] N/A[c]	0.01[a] 3.6[b] 0.06[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.01[a] 3.6[b] 0.06[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]
rs2740574	0.004[a]	0.67[a] N/A[b] N/A[c]	0.02[a] 2.4[b] 0.12[c]	0.0[a] 0.6[b] 0.43[c]	0.0[a] 0.6[b] 0.45[c]	0.03[a] 7.8[b] 0.005[c]	0.08[a] 23.2[b] 1.4e-6[b]	0.0[a] 0.6[b] 0.43[c]	0.83[a] N/A[b] N/A[c]	0.07[a] 19.7[b] 1e-5[c]	0.03[a] 6.4[b] 0.01[c]	0.76[a] N/A[b] N/A[c]	0.66[a] N/A[b] N/A[c]
rs4986893	0.0[a]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.04[a] 14.7[b] 1.4e-4[c]	0.07[a] 25.6[b] 4e-7[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.07[a] 30.8[b] 3e-8c	0.01[a] 3.4[b] 0.07[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.005[a] 1.7[b] 0.19[c]
rs4244285	0.09[a]	0.14[a] 2.3[b] 0.12[c]	0.13[a] 2.2[b] 0.13[c]	0.33[a] N/A[b] N/A[c]	0.26[a] 27.6[b] 1.5e-7[c]	0.14[a] 3.3[b] 0.07[c]	0.33[a] N/A[b] N/A[c]	0.32[a] N/A[b] N/A[c]	0.21[a] 15.7b 8e-5[c]	0.12[a] 1.2[b] 0.27[c]	0.09[a] 0.02[b] 0.9[c]	0.17[a] 7.2[b] 0.007[c]	0.15[a] 4.5[b] 0.03[c]
rs1799853	0.02[a]	0.04[a] 0.9[b] 0.34[c]	0.15[a] 30.3[b] 4e-8c	0.0[a] 5.0[b] 0.02[c]	0.0[a] 4.5[b] 0.03[c]	0.08[a] 10.7[b] 0.001[c]	0.05[a] 2.3[b] 0.12[c]	0.0[a] 5.1[b] 0.02[c]	0.0[a] 4.8[b] 0.02[c]	0.10[a] 12.7[b] 4e-4[c]	0.15[a] 31.7[b] 2e-8[c]	0.0[a] 5.2[b] 0.02[c]	0.03[a] 0.02[b] 0.89[c]
rs28399454	0.0[a]	0.07[a] 24.9[b] 5.8e-7[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.06[a] 18.8[b] 1e-5[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.13[a] N/A[b] N/A[c]	0.15[a] N/A[b] N/A[c]

(*Continued*)

Table 3 (Continued).

SNP ID	Populations												
	CHE	ASW	CEU	CHB	CDX	GBR	GIH	JPT	LWK	MXL	TSI	YRI	ACB
rs1801272	0.0[a]	0.01[a] 2.7[b] 0.09[c]	0.04[a] 11.8[b] 6e-4[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.03[a] 9.2[b] 0.002[c]	0.01[a] 3.2[b] 0.07[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.05[a] 15.8[b] 7e-5[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]
rs28399433	0.09[a]	0.06[a] 0.2[b] 0.64[c]	0.05[a] 3.0[b] 0.08[c]	0.27[a] 28.7[b] 8e-8[c]	0.18[a] 8.0[b] 0.01[c]	0.04[a] 3.9[b] 0.04[c]	0.19[a] 10.5[b] 0.001[c]	0.28[a] 32.2[b] 1e-8[c]	0.09[a] 0.002[b] 0.96[c]	0.10[a] 0.1[b] 0.75[c]	0.06[a] 1.2[b] 0.27[c]	0.10[a] 0.1[b] 0.70[c]	0.06[a] 1.4[b] 0.23[c]
rs3745274	0.31[a]	0.35[a] 0.05[b] 0.82[c]	0.28[a] 0.6[b] 0.40[c]	0.27[a] 15.5[b] 8.4e-5[c]	0.33[a] 0.1[b] 0.71[c]	0.23[a] 3.8[b] 0.05[c]	0.23[a] 4.6[b] 0.03[c]	0.22[a] 5.3[b] 0.02[c]	0.36[a] 1.2[b] 0.27[c]	0.31[a] N/A[b] N/A[c]	0.30[a] 0.04[b] 0.83[c]	0.40[a] 4.7[b] 0.03[c]	0.38[a] 2.5[b] 0.11[c]
rs28399499	0.0[a]	0.1[a] 33.5[b] 1e-8[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.06[a] 20.6b 6e-6[c]	0.08[a] 2.5[b] 0.11[c]	0.0[a] N/A[b] N/A[c]	0.12[a] N/A[b] N/A[c]	0.05[a] 32.2[b] 1e-8[c]
rs59421388	0.0[a]	0.04[a] 13.7[b] 2e-4[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.09[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.11[a] N/A[b] N/A[c]	0.08[a] N/A[b] N/A[c]
rs28371725	0.14[a]	0.02[a] 14.8[b] 1e-4[c]	0.12[a] 0.5[b] 0.46[c]	0.03[a] 16.8[b] 4e-5[c]	0.08[a] 4.4[b] 0.03[c]	0.07[a] 5.9[b] 0.01[c]	0.15[a] 0.002[b] 0.96[c]	0.01[a] 30.1[b] 4e-8[c]	0.03[a] 17.6[b] 3e-5[c]	0.02[a] 15.8[b] 7e-5[c]	0.14[a] N/A[b] N/A[c]	0.01[a] 28.7[b] 8e-8[c]	0.05[a] 11.8[b] 6e-4[c]
rs61736512	0.0[a]	0.04[a] 13.7[b] 2e-4[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.17[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.11[a] N/A[b] N/A[c]	0.09[a] 32.2[b] 1e-8[c]
rs28371706	0.0[a]	0.15[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.19[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.25[a] N/A[b] N/A[c]	0.20[a] N/A[b] N/A[c]
rs5030656	0.0[a]	0.01[a] 2.7[b] 0.99[c]	0.02[a] 6.8[b] 0.01[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.04[a] 13.0[b] 3e-4[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.01[a] 2.6[b] 0.11[c]	0.01[a] 11.0[b] 0.001[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]

Notes: [a]Minor allele frequency, [b]Chi-square value, [c]p-value, when p-value < 0.05 is considered a significant difference. CHE: Chechens from Jordan, ASW: African ancestry in Southwest USA, CEU: Utah, USA residents with Northern and Western European ancestry from the CEPH collection, CHB: Han Chinese in Beijing, China, CDX: Chinese Dai in Xishuangbanna, China, GIH: Gujarati Indians in Houston, Texas, USA, GBR: British in England and Scotland, JPT: Japanese in Tokyo, Japan, LWK: Luhya in Webuye, Kenya, MXL: Mexican ancestry in Los Angeles, California, USA, TSI: Toscani in Italy, YRI: Yoruba in Ibadan, Nigeria, ACB; African Caribbeans in Barbados.
Abbreviation: N/A, not applicable.

of ethanol in healthy individuals as compared to genotypes CC and CT among mixed population.[26]

Furthermore, within *ADRB2* gene, the frequency of the minor allele (G) of rs1042714 among Chechen was significantly lower than it among others Latino (83%), African 82%, European non-Finnish (58%), South Asian 79 and European Finnish (63%) and East Asian (91%). It was suggested that allele G of rs1042714 was associated with an increased reduction in resting blood pressure when treated with carvedilol in healthy individuals as compared to allele G in a study conducted in a mixed population.[27] While Genotype CC was reported to be associated with decreased improvement in heart failure patients when treated with carvedilol compared to genotypes GG and CG.[28]

In this study, we found that rs5219 of *KCNJ11* gene among Chechen was distributed differently from other populations. It was proposed that the Genotype (TT) is associated with an increased likelihood of Diabetes II Mellitus.[29]

One significant limitation for this study is the sample size, large study cohort is recommended to compare the variants frequencies with other population. In addition, better designed statistical analyses should be provided for

Table 4 VIP Variants Within the Pharmacogenes in Chechen Compared to Six ExAC Populations Worldwide

SNP\Population	Chechen	African	East Asian	Latino	European (Non-Finnish)	South Asian	European (Finnish)
rs3918290	0.003[a]	0.001[a] 2.4[b] 0.12[c]	0.00[a] 26.1[b] 3.3e-7[c]	0.001[a] 2.2[b] 0.13[c]	0.006[a] 0.45[b] 0.50[c]	0.005[a] 0.20[b] 0.65[c]	0.022[a] 5.6[b] 0.02[c]
rs1065776	0.01[a]	0.18[a] N/A[b] N/A[c]	0.04[a] 9.4[b] 0.002[c]	0.05[a] 12.5[b] 4e-4[c]	0.04[a] 8.6[b] 0.003[c]	0.11[a] N/A[b] N/A[c]	0.07[a] 17.7[b] 3e-5[c]
rs701265	0.17[a]	0.69[a] N/A[b] N/A[c]	0.29[a] 22.8[b] 2e-6[c]	0.22[a] 6.4[b] 0.01[c]	0.14[a] 1.3[b] 0.26[c]	0.19[a] 1.4[b] 0.24[c]	0.15[a] 0.71[b] 0.40[c]
rs2066702	0.01[a]	0.19[a] N/A[b] N/A[c]	0.0001[a] N/A[b] N/A[c]	0.01[a] 0.46[b] 0.50[c]	0.002[a] 17.9[b] 2e-5[c]	0.002[a] 21[b] 5e-6[c]	0.00[a] N/A[b] N/A[c]
rs1229984	0.12[a]	0.99[a] N/A[b] N/A[c]	0.27[a] 34.0[b] 1e-8[c]	0.94[a] N/A[b] N/A[c]	0.95[a] N/A[b] N/A[c]	0.95[a] N/A[b] N/A[c]	0.99[a] N/A[b] N/A[c]
rs698	0.27[a]	0.15[a] 33.8[b] 1e-8[c]	0.08[a] N/A[b] N/A[c]	0.33[a] 6.2[b] 0.01[c]	0.40[a] 23.4[b] 1e-6[c]	0.32[a] 5.1[b] 0.02[c]	0.51[a] N/A[b] N/A[c]
rs3846662	0.43[a]	0.88[a] N/A[b] N/A[c]	0.53[a] 1.4[b] 0.24[c]	0.47[a] 12.2[b] 5e-4[c]	0.44[a] 19.7[b] 1e-5[c]	0.59[a] 0.50[b] 0.47[c]	0.47[a] 11.5[b] 0.001[c]
rs1042713	0.37[a]	0.49[a] 18.4[b] 2e-5[c]	0.55[a] N/A[b] N/A[c]	0.42[a] 2.9[b] 0.09[c]	0.38[a] 0.1[b] 0.78[c]	0.46[a] 8.9[b] 0.003[c]	0.45[a] 6.7[b] 0.01[c]
rs1042714	0.31[a]	0.82[a] N/A[b] N/A[c]	0.91[a] N/A[b] N/A[c]	0.83[a] N/A[b] N/A[c]	0.58[a] N/A[b] N/A[c]	0.79[a] N/A[b] N/A[c]	0.63[a] N/A[b] N/A[c]
rs1800888	0.003[a]	0.002[a] 0.05[b] 0.82[c]	0.00[a] 26.1[b] 3.3e-7[c]	0.006[a] 0.45[b] 0.49[c]	0.01[a] 3.0[b] 0.08[c]	0.004[a] 0.05[b] 0.82[c]	0.004[a] 0.1[b] 0.76[c]
rs2066853	0.13[a]	0.45[a] N/A[b] N/A[c]	0.37[a] N/A[b] N/A[c]	0.12[a] 0.1[b] 0.77[c]	0.10[a] 2.8[b] 0.09[c]	0.14[a] 0.3[b] 0.59[c]	0.11[a] 0.49[b] 0.482[c]
rs3815459	0.27[a]	0.37[a] 1.6[b] 0.21[c]	0.72[a] 33.4[b] 1e-8[c]	0.38[a] 0.59[b] 0.44[c]	0.33[a] 6.9[b] 0.01[c]	0.39[a] 0.50[b] 0.48[c]	0.44[a] 0.03[b] 0.86[c]
rs5219	0.46[a]	0.94[a] N/A[b] N/A[c]	0.64[a] N/A[b] N/A[c]	0.61[a] 29.3[b] 6e-8[c]	0.63[a] N/A[b] N/A[c]	0.63[a] N/A[b] N/A[c]	0.53[a] 4.9[b] 0.03[c]
rs4149056	0.04[a]	0.03[a] 1.3[b] 0.24[c]	0.13[a] 22.4[b] 2e-6[c]	0.11[a] 15.6[b] 1e-4[c]	0.16[a] N/A[b] N/A[c]	0.05[a] 0.84[b] 0.35[c]	0.21[a] N/A[b] N/A[c]
rs12659	0.49[a]	0.55[a] 4.0[b] 0.05[c]	0.49[a] 0.007[b] 0.93[c]	0.56[a] 7.3[b] 0.006[c]	0.58[a] 11.2[b] 0.001[c]	0.64[a] 31.7[b] 2e-8[c]	0.56[a] 5.6[b] 0.02[c]

(*Continued*)

Table 4 (Continued).

SNP\Population	Chechen	African	East Asian	Latino	European (Non-Finnish)	South Asian	European (Finnish)
rs1051266	0.48[a]	0.42[a] 13.5[b] 2e-4[c]	0.52[a] 0.01[b] 0.93[c]	0.59[a] 6.6[b] 0.01[c]	0.60[a] 8.1[b] 0.004[c]	0.61[a] 10.3[b] 0.001[c]	0.60[a] 8.8[b] 0.003[c]
rs1131596	0.47[a]	0.36[a] 16.6[b] 4e-5[c]	0.51[a] 1.4[b] 0.23[c]	0.56[a] 8.1[b] 0.004[c]	0.59[a] 20.3[b] 1e-5[c]	0.58[a] N/A[b] N/A[c]	0.61[a] 12.8[b] 3e-4[c]
rs4148323	0.0[a]	0.0009[a] 0.2[b] 0.59[c]	0.15[a] 5.9[b] 0.01[c]	0.03[a] 8.9[b] 0.003[c]	0.004[a] 1.1[b] 0.27[c]	0.02[a] 6.4[b] 0.01[c]	0.05[a] 15.9[b] 7.7e-5[c]
rs4680	0.50[a]	0.32[a] N/A[b] N/A[c]	0.28[a] N/A[b] N/A[c]	0.41[a] 11.3[b] 7.6e-4[c]	0.53[a] 1.1[b] 0.30[c]	0.45[a] 3.5[b] 0.06[c]	0.57[a] 6.6[b] 0.009[c]
rs1695	0.30[a]	0.44[a] 27.7[b] 1.4e-7[c]	0.18[a] 29.3[b] 6e-8[c]	0.53[a] N/A[b] N/A[c]	0.31[a] 0.7[b] 0.41[c]	0.29[a] 0.1[b] 0.71[c]	0.27[a] 0.8[b] 0.35[c]
rs1138272	0.10[a]	0.02[a] N/A[b] N/A[c]	0.0003[a] N/A[b] N/A[c]	0.03[a] N/A[b] N/A[c]	0.08[a] 1.5[b] 0.22[c]	0.07[a] 3.6[b] 0.05[c]	0.08[a] 0.7[b] 0.41[c]
rs10264272	0.0[a]	0.12[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.01[a] 2.67[b] 0.10[c]	0.001[a] 0.27[b] 0.60[c]	0.0002[a] 0.08[b] 0.78[c]	0.0[a] N/A[b] N/A[c]
rs4986913	0.0[a]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.001[a] 0.26[b] 0.61[c]	0.0[a] N/A[b] N/A[c]
rs4986910	0.0[a]	0.001[a] 0.41[b] 0.52[c]	0.0[a] N/A[b] N/A[c]	0.002[a] 0.60[b] 0.43[c]	0.007[a] 2.5[b] 0.11[c]	0.0[a] N/A[b] N/A[c]	0.02[a] 7.0[b] 0.008[c]
rs4986909	0.0[a]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.002[a] 0.05[b] 0.81[c]	5.994e-05 0.02[b] 0.88[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]
rs4986893	0.0[a]	0.0005[a] 0.16[b] 0.68[c]	0.07[a] 23.9[b] 1e-6[c]	0.0004[a] 0.08[b] 0.76[c]	0.0002[a] 0.06[b] 0.80[c]	0.004[a] 1.2[b] 0.27[c]	0.0002[a] 0.05[b] 0.82[c]
rs4244285	0.09[a]	0.18[a] 18.0[b] 2.2e-5[c]	0.31[a] N/A[b] N/A[c]	0.10[a] 0.39[b] 0.53[c]	0.15[a] 8.6[b] 0.003[c]	0.34[a] N/A[b] N/A[c]	0.18[a] 18.3[b] 1.8e-5[c]
rs1799853	0.02[a]	0.02[a] 0.004[b] 0.94[c]	0.0003[a] N/A[b] N/A[c]	0.07[a] 9.3[b] 0.002[c]	0.13[a] 31.5[b] 2e-8[c]	0.05[a] 3.5[b] 0.05[c]	0.12[a] 27.3[b] 1.7e-7[c]
rs28399454	0.0[a]	0.11[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.006[a] 1.9[b] 0.15[c]	0.0004[a] 0.1[b] 0.73[c]	0.0[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]
rs1801272	0.0[a]	0.005[a] 1.5[b] 0.20[c]	0.0[a] N/A[b] N/A[c]	0.012[a] 4.0[b] 0.04[c]	0.025[a] 8.7[b] 0.003[c]	0.011[a] 3.8[b] 0.04[c]	0.023[a] 7.9[b] 0.004[c]

(*Continued*)

Table 4 (Continued).

SNP\Population	Chechen	African	East Asian	Latino	European (Non-Finnish)	South Asian	European (Finnish)
rs28399433	0.09[a]	0.083[a] 0.3[b] 0.57[c]	0.23[a] 0.30[b] 0.57[c]	0.138[a] 5.6[b] 0.01[c]	0.068[a] 2.8[b] 0.09[c]	0.144[a] 7.1[b] 0.007[c]	0.11[a] 1.1[b] 0.28[c]
rs3745274	0.31[a]	0.37[a] 4.1[b] 0.04[c]	0.19[a] 31.6[b] 2e-8[c]	0.32[a] 0.08[b] 0.76[c]	0.24[a] 8.9[b] 0.003[c]	0.19[a] 8.2[b] 0.004[c]	0.19[a] 29.4[b] 6e-8[c]
rs28399499	0.0[a]	0.07[a] 25.2[b] 5.1e-7[c]	0.0[a] N/A[b] N/A[c]	0.003[a] 1.1[b] 0.30[c]	0.0001[a] 0.04[b] 0.83[c]	0.0001[a] 0.04[b] 0.83[c]	0.0[a] N/A[b] N/A[c]
rs59421388	0.0[a]	0.092[a] 33.6[b] 1e-8[c]	0.0001[a] 0.04[b] 0.84[c]	0.004[a] 1.2[b] 0.26[c]	0.0003[a] 0.09[b] 0.76[c]	0.0001[a] 0.04[b] 0.84[c]	0.0[a] N/A[b] N/A[c]
rs28371725	0.14[a]	0.03[a] N/A[b] N/A[c]	0.03[a] N/A[b] N/A[c]	0.03[a] 9.3[b] 0.002[c]	0.09[a] 9.3[b] 0.002[c]	0.15[a] 0.2[b] 0.64[c]	0.03[a] N/A[b] N/A[c]
rs61736512	0.0[a]	0.10[a] N/A[b] N/A[c]	0.0005[a] 0.15[a] 0.69[c]	0.004[a] 1.3[a] 0.25[c]	0.0003[a] 0.08[a] 0.76[c]	0.0002[a] 0.08[a] 0.77[c]	0.0[a] N/A[b] N/A[c]
rs28371706	0.0[a]	0.197[a] N/A[b] N/A[c]	0.0[a] N/A[b] N/A[c]	0.007[a] 2.4[b] 0.12[c]	0.002[a] 0.71[b] 0.39[c]	0.001[a] 0.1[b] 0.75[c]	0.0002[a] 0.05[b] 0.81[c]
rs5030656	0.0[a]	0.004[a] 1.4[b] 0.22[c]	0.0[a] N/A[b] N/A[c]	0.012[a] 4.3[b] 0.04[c]	0.03[a] 10.4[b] 0.001[c]	0.002[a] 0.6[b] 0.41[c]	0.015[a] 5.2[b] 0.02[c]

Notes: [a]Minor allele frequency, [b]Chi-square value, [c]p-value, when p-value < 0.05 is considered a significant difference.
Abbreviation: N/A, not applicable.

accurate results. In conclusion, rare variants detected in isolated populations can significantly guide to understanding a potential biological process and identifying genetic loci involved in the development of clinically relevant treatment for different diseases.

Ethics Committee Approval and Patient Consent

This study was conducted in agreement with the Human ethics committee at National Center for Diabetes, Endocrinology and Genetics (NCDEG) and Jordan University of Science and Technology (JUST), policy number (GM7601). Written informed consent was obtained from all volunteers in the study.

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Disclosure

The authors declare that they have no competing interests.

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