Original article

Prevalence of exposure to pharmacogenetic drugs by the Saudis treated at the health care centers of the Ministry of National Guard

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ABSTRACT

Background: The drugs impacted by genetic variants are known as pharmacogenetic (PGx) drugs. Patients' responses to these drugs may vary according to the variability in patients' genetic makeup. Hence, exploring the pharmacogenes that affect drug treatment is vital to ensure optimal therapy and patients' safety. This study aimed to describe the usage rate of PGx drugs and the frequency of relevant variants in the Saudi population.

Methodology: Prescription patterns over seven years (2015–2021) for Saudi patients on PGx drugs treated at the Ministry of National Guard-Health Affairs (MNG-HA) were investigated. Only registered drugs in the MNG-HA formulary (n = 78) were included. The patients were subgrouped into four age groups: ≤24, 25–44, 45–64, and ≥65 years. Further subgrouping was made according to gender and drugs' therapeutic categories following anatomical therapeutic chemical (ATC) classification.

Furthermore, an online searching was carried out to identify the pharmacogenes reported in the literature among healthy Saudis. The search included 45 genes that may affect drug outcomes based on evidence rated by either CPIC (A-B levels) or PharmGKB (1–2 levels).

Results: The screened patients were 1,483,905. Patients on PGx drugs accounted for 46.7% (n = 693,077 patients). The analgesic group was the most prescribed drug category (47%), which included ibuprofen (20.5%), celecoxib (6.3%), tramadol (5.8%), and others. Cardiovascular agents were the second-most utilized drug class (24.4%). Omeprazole was the second most commonly used medication (11.1%) but ranked third as a class (gastroenterology). Females used PGx drugs more frequently than males (53.5% versus 46.5%) and a higher usage rate by patients aged 45–64 years (31.3%) was noted. The cytochrome P450 genes (CYP2C9, CYP2C19, and CYP2D6) were estimated to impact responses of 54.3% (n = 1,156,113) of the used drugs (27.2% are possibly affected by CYP2C9, 12.8% by CYP2C19, and 14.3% by CYP2D6). Thirty-five pharmacogenes that characterize Saudi population and their variants' allele frequencies were identified from previous reports. This study presents the largest reported number of genes that may affect drug therapies among Saudis.

Conclusion: This study confirmed that a high percentage of Saudi patients use PGx drugs and various genotypes of certain pharmacogenes are inherited by the Saudi population.

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1. Introduction

The adoption of pharmacogenomics (PGx), the study of genetic variations related to different drug responses, is increasing at the population level. Although 60% of global PGx research projects are conducted by North Americans and Europeans, other countries, particularly in East Asia showed more concern towards this field of research science (Klein et al., 2017). The increase in PGx research adoption is motivated by the importance of PGx in elucidating the effect of genes on the pharmacokinetics and pharmacodynamics of medications (Franconi and Campesi, 2014). PGx aid in individualizing therapies according to the genotypes of patients, through which the genetic variations attributed to medication disposition can be tested upfront to predict variability of patients' responses to the administered drugs (Kisor et al., 2019). The incorporation of pharmacogenetic testing might contribute to better patient outcomes by reducing side effects and improving the overall effectiveness of the prescribed medications (Polasek et al., 2019).

Different international PGx guidelines are publicly available and widely used in clinical practice, in particular the guidelines established by the Dutch Pharmacogenetics Working Group (DPWG) and those published by the international Clinical Pharmacogenetics Implementation Consortium (CPIC) (Swen et al., 2011, Bank et al., 2018). These consortia in addition to Pharmacogenomics Knowledge Base (PharmGKB) (Thorn et al., 2013), provide a thorough assessment of the possible associations between various drug-gene pairs. The associations of 50 pharmacogenes with 152 drugs were ranked among the top two levels of evidence according to CPIC (levels A-B) and PharmGKB (levels 1–2) (Whirl-Carrillo, 2021).

To our knowledge, no study on the Saudi population has provided focus statistics related to the prescription patterns of drugs impacted by genetic variants, and no previous estimation has been made on the overall genes predicted to influence Saudi patients who carry selected genotypes. In addition, the age groups of patients who are frequently exposed to PGx drugs have not yet been identified in Saudi society. Several previous reports about Western populations indicated that patients older than 45 years are more likely to use PGx treatments than younger patients (Alshabeeb et al., 2019, Samwald et al., 2016). In Saudi Arabia, the estimated total number of individuals aged ≥45 years was 626,431, representing 3% of the general population in 2000 while in 2016 they represented 19.16% of the population (Statistics, 2016). Almost 67% of the elderly in Saudi Arabia administer at least one medication, with total spending on medications in 2010 of SAR 13.5 billion (Khoja et al., 2018, AlKhamees et al., 2018, Saudi FDA and WHO, 2012). Using multiple drugs at a time, polypharmacy, which is common among older age patients, is associated with an increased tendency of drug ineffectiveness, low compliance, and high level of unacceptable adverse drug reactions (ADRs) (Bjerrum et al., 1998, Marcum and Gellad, 2012). This is due to the nature of chronic diseases in elderly which require complex drug regimen and continuous social and family care. Failure to provide this care in addition to elderly susceptibility to forgetfulness may result in lower compliance rate, drug interactions, and inadequate therapy outcomes (Shruthi et al., 2016).

Identification of genes associated with ADRs development is essential to apply the appropriate precautionary measures to avoid predictable incidents. In the Kingdom of Saudi Arabia, three previous studies emphasized the common pharmacogenes and discussed the allele frequency distribution of PGx variants, which are expected to influence drug efficacy and toxicity. The studies were conducted at King Faisal Specialist Hospital and Research Center (KFSHRC) in Riyadh by Bu et al. (2004), Mizzi et al.

(2016), and recently by Goljan et al. (2022) but they were focused on a limited number of pharmacogenes (n = 8, 9 and 8, respectively) harbored by the Saudi population. Other Saudi studies have tested a much lower number of pharmacogenes (only one or two) as they aimed to identify the causal relationship of each gene with certain disease phenotypes rather than determining its association with the variable drug responses.

This study aimed to (i) estimate the percentage of Saudi patients on PGx drugs in MNG-HA, (ii) determine the age group categories at higher risk of exposure to PGx drugs, and (iii) identify the investigated pharmacogenes among the Saudi population reported in the literature. We will also highlight the major genes predicted to influence the response of patients to the given drugs.

2. Methodology

Prescription data of Saudi patients who were eligible for treatment in the Ministry of National Guard Health Affairs (MNG-HA) were screened. The involved patients were followed up in seven medical hospitals located in different regions around the kingdom (three hospitals in the central region (King Fahad Hospital, King Abdullah Specialist Children Hospital, and Military Field Hospital in Riyadh), two in the eastern region (Imam Abdulrahman Bin Faisal Hospital in Dammam and King Abdulaziz Hospital in Alhasa), one in the western region (King Khalid Hospital in Jeddah), and one in Madinah (Prince Mohammed Bin Abdulaziz Hospital) plus another 31 primary care centers; 38 sites in total; for more details of all patients recruitment sites see Table 1). The BESTCare system, a patient database platform built by MNG-HA that provides access to patient's electronic medical records (Marwah, 2016), was used to identify patients' prescription patterns over seven years (2015–2021). The number of patients using PGx drugs in MNG-HA medical sites, age, and sex were verified.

Of the 152 drugs impacted by pharmacogenes with high association evidence (Whirl-Carrillo, 2021), this study assessed the usage level of the registered drugs in the MNG-HA formulary (n = 78). Some of the registered PGx drugs were excluded from this study for the following reasons:

1. The prescribed amounts of the drugs were not precisely known. This included the anesthetic agents: enfluran, desflurane, isoflurane, and sevoflurane.
2. This study aimed to focus on medications that are affected by genes but not regularly tested to raise awareness of genetic testing. The drugs (n = 17) affected by the *G6PD* gene (chloramphenicol, ciprofloxacin, glibenclamide, glipizide, mesalazine, methylene blue, moxifloxacin, nitrofurantoin, norfloxacin, phenazopyridine, primaquine, quinine, rasburicase, sulfacetamide, sulfadiazine, sulfamethoxazole /trimethoprim, and sulfasalazine) were not included here as *G6PD* enzyme activity is routinely assessed among Saudis, using the standard quantitative (spectrophotometric) or qualitative (fluorometric) assays (Albagshi et al., 2020). Usage of these assays help the prescribers to be cautious when treating *G6PD* deficient patients who are in need for medications that are substrates for *G6PD* enzyme.

The recruited patients were divided based on age into four groups: children and youth (0–24 years), young adults (25–44 years), middle age group (45–64 years), and seniors (≥65 years). Quit similar age distributions were used previously (Lin et al., 2020, Peng et al., 2020, Alshabeeb et al., 2019) which is supported by the age standards classified by the World Health Organization (Dyussenbayev, 2017). The data were also sub-categorized according to gender differences to identify the impact of gender factor on

Table 1
Number of followed up patients in all health care facilities of MNGHA in various regions around the kingdom of Saudi Arabia over the period 2015–2021.

Region	Hospital/Clinic Name	Number of Patients	
Central (18 centers)	Arar Clinic	9,733	
	Battalion and Brigade Clinic	6,405	
	Hail Clinic	23,580	
	Hail Dialysis Center	103	
	Iskan Yarmouk Clinic	53,585	
	Khashm Alan Clinic	87,073	
	King Abdullah Specialist Children Hospital	141,016	
	King Fahad Hospital	356,425	
	King Khalid Military Academy Clinic	1,947	
	King Saud City (Dirab) Clinic	53,125	
	Military Field Hospital	2,980	
	Ministry of National Guard Clinic	3,362	
	Najran Clinic	6,637	
	Prince Bader Residental City Clinic (PBRC)	4,108	
	Qassim Clinic	24,238	
	Rafha Clinic	11,381	
	Riyadh Dialysis North Center	282	
	Um Alhamam Clinic	64,750	
	Subtotal		**850,730**
Eastern (4 centers)	Imam Abdulrahman Bin Faisal Hospital (Dammam)	63,503	
	Dammam Primary Health Care Center	31,315	
	King Abdulaziz Hospital (Al Ahsa)	100,985	
	Al Ahsa Primary Health Care Center	35,717	
	Subtotal		**231,520**
Madinah (4 centers)	Iskan Madinah Clinic	20,065	
	Madina Dialysis Center	103	
	Prince Mohammed Bin Abdulaziz Hospital	65,125	
	Yanbu Clinic	5,848	
	Subtotal		**91,141**
Western (12 centers)	Bahra Clinic	17,560	
	Iskan Jeddah Clinic	12,758	
	Iskan Taif Clinic	34,871	
	Jizan Clinic	2,667	
	Jeddah Dialysis Center	248	
	King Khalid Hospital	188,510	
	Makkah Dialysis Center	87	
	Preventive Medicine (Jeddah) Clinic	967	
	Sharaie Clinic	14,256	
	Specialized Polyclinic (SP)	36,369	
	Training Center	1,222	
	Um Assalam Clinic	999	
	Subtotal		**310,514**
38 centers	Overall Total		1,483,905

the level of PGx drug prescription patterns. Further subgrouping was performed according to drugs' therapeutic categories based on the anatomical therapeutic chemical (ATC) classification.

To explore the pharmacogenes reported in the literature among the Saudis, systematic online searching was carried out using multiple medical scientific websites, particularly MEDLINE (PubMed) database. The search involved all previous genetic association studies, published up to the end of 2021, conducted on healthy Saudi individuals. Patients from various age groups (pediatrics and adults) were included in the study. The inclusion was restricted to studies that reported variant allele frequency of the targeted genes which were categorized under the upper-two high levels of association evidence suggested by CPIC and PharmGKB (levels A-B in CPIC or 1–2 in PharmGKB). Four genes (*CFTR*, *GBA*, *HLA-DRB1*, and *KIF6*) interact with non-formulary drugs (ivacaftor, velaglucerase alfa, nevirapine, and pravastatin, respectively); therefore, they were excluded in addition to *G6PD* for the reason mentioned above.

Medical Subject Headings (MeSH) terms were used such as Saudi AND gene names (n = 45) AND rs number of each unique variant AND healthy OR controls. Other Keywords like pharmacogenetics OR pharmacogenomics OR genetic association OR genetic testing were explored too. To ensure no studies had been

neglected, different electronic databases including the Cochrane Library, Web of Science, and EMBASE were searched. The same major terms searched in PubMed were searched among other databases to maintain a more targeted search.

This research study obtained the ethical approval from the Institutional Review Board (IRB) committee (ref RC18/292/R) at King Abdullah International Medical Research Centre (KAIMRC), King Saud Bin Abdulaziz University for Health Sciences (KSAU-HS), MNG-HA, Riyadh, Saudi Arabia.

3. Results

Analysis of the data showed that 1,483,905 patients were followed up over the designated 7-year period (2015–2021) across various MNG-HA health facilities (Table 1). The patients in the central region represented 57.3% of the examined cohort. The western region came next in terms of the number of visiting patients (20.9%), followed by eastern province and Madinah city (15.6% and 6.1%, respectively). Among the whole group, 693,077 patients (46.7%) used at least one of the prescribed PGx drugs (n = 78) (Table 2). Ibuprofen and omeprazole were the most commonly prescribed drugs (20.5% and 11.1%, respectively). These were followed by atorvastatin (7.7%), aspirin (6.8%), celecoxib (6.3%), tramadol

Table 2
Number of patients on various PGx drugs prescribed at MNGHA medical canters during 2015–2021.

Drug List (n = 78)		Gender	≤24 years	25–44 years	45–64 years	≥65 years	Total females	Total males	Total Patients (%)
1	Allopurinol	F	450	751	2,905	2,027	6,133		15,355
		M	827	2,941	3,214	2,240		9,222	(0.86)
2	Amikacin	F	1,217	319	563	387	2,486		5,284
		M	1,539	341	457	461		2,798	(0.30)
3	Amitriptyline	F	734	4,057	6,906	2,594	14,291		21,443
		M	493	2,615	2,514	1,530		7,152	(1.20)
4	Aripiprazole	F	235	326	217	84	862		1,874
		M	378	383	143	108		1,012	(0.10)
5	Aspirin	F	2,216	15,478	24,188	18,734	60,616		121,699
		M	1,535	6,894	28,662	23,992		61,083	(6.80)
6	Atorvastatin	F	581	7,993	39,805	20,950	69,329		137,957
		M	512	12,129	33,012	22,975		68,628	(7.70)
7	Azathioprine	F	264	708	435	96	1,503		2,506
		M	254	445	225	79		1,003	(0.14)
8	Capecitabine	F	4	220	603	217	1,044		1,980
		M	7	119	473	337		936	(0.11)
9	Captopril	F	1,213	532	2,399	1,463	5,607		10,653
		M	1,360	862	1,552	1,272		5,046	(0.59)
10	Carbamazepine	F	741	769	757	318	2,585		5,227
		M	963	759	557	363		2,642	(0.29)
11	Carglumic acid	F	24	0	0	0	24		61
		M	37	0	0	0		37	(0.00)
12	Celecoxib	F	2,806	18,043	35,171	10,525	66,545		112,935
		M	4,203	19,268	15,045	7,874		46,390	(6.31)
13	Citalopram	F	1,221	3,576	4,810	2,694	12,301		20,129
		M	1,058	2,769	2,126	1,875		7,828	(1.12)
14	Clomipramine	F	29	88	65	17	199		358
		M	26	62	54	17		159	(0.02)
15	Clopidogrel	F	55	515	4,113	5,333	10,016		30,037
		M	76	1,753	8,775	9,417		20,021	(1.68)
16	Codeine	F	7,447	19,200	17,094	7,001	50,742		91,089
		M	8,401	15,604	9,817	6,525		40,347	(5.09)
17	Dapsone	F	49	70	38	9	166		406
		M	83	88	59	10		240	(0.02)
18	Diane-35	F	1,335	2,144	111	0	3,590		3,593
		M	2	0	1	0		3	(0.20)
19	Doxepin	F	4	13	24	17	58		112
		M	5	17	18	14		54	(0.01)
20	Efavirenz	F	0	7	13	0	20		85
		M	3	37	21	4		65	(0.00)
21	Erlotinib	F	0	2	28	13	43		77
		M	0	3	13	18		34	(0.00)
22	Etanercept	F	48	173	342	114	677		847
		M	25	51	68	26		170	(0.05)
23	Ethambutol	F	62	72	99	105	338		969
		M	122	162	142	205		631	(0.05)
24	Femoston	F	53	287	127	1	468		468
		M	0	0	0	0		0	(0.03)
25	Fentanyl	F	8,830	18,383	9,040	6,299	42,552		74,590
		M	6,810	7,162	9,797	8,269		32,038	(4.16)
26	Flecainide	F	17	46	89	21	173		394
		M	29	79	97	16		221	(0.02)
27	Flucloxacillin	F	1,083	176	157	108	1,524		3,422
		M	1,389	208	156	145		1,898	(0.19)
28	Fluorouracil	F	17	144	242	66	469		789
		M	14	50	166	90		320	(0.04)
29	Fluvoxamine	F	93	169	170	55	487		878
		M	82	173	101	35		391	(0.05)
30	Gentamicin	F	11,298	4,778	3,431	1,868	21,375		43,811
		M	13,038	4,439	2,778	2,181		22,436	(2.45)
31	Gynera	F	2,947	14,205	1,122	2	18,276		18,276
		M	0	0	0	0		0	(1.02)
32	Haloperidol	F	176	422	876	1,301	2,775		7,252
		M	475	808	1,089	2,105		4,477	(0.40)
33	Hydralazine	F	871	1,362	2,493	3,795	8,521		18,086
		M	858	897	2,911	4,899		9,565	(1.01)
34	Hydrochlorothiazide	F	257	247	2,534	2,091	5,129		9,131
		M	290	346	1,606	1,760		4,002	(0.51)
35	Ibuprofen	F	85,133	67,581	26,941	4,211	183,866		366,533
		M	100,324	58,745	18,813	4,785		182,667	(20.47)
36	Imipramine	F	246	74	91	46	457		960
		M	384	55	46	18		503	(0.05)
37	Irinotecan	F	13	47	137	32	229		532
		M	16	37	158	92		303	(0.03)

Table 2 (*continued*)

Drug List (n = 78)		Gender	≤24 years	25–44 years	45–64 years	≥65 years	Total females	Total males	Total Patients (%)
38	Isoniazid	F	406	544	336	157	1,443		2,860
		M	342	467	318	290		1,417	(0.16)
39	Marvelon	F	1,340	6,319	369	0	8,028		8,031
		M	1	2	0	0		3	(0.45)
40	Meloxicam	F	2,235	13,432	28,118	8,045	51,830		86,461
		M	3,456	13,210	11,851	6,114		34,631	(4.83)
41	Mercaptopurine	F	237	21	7	5	270		710
		M	394	36	5	5		440	(0.04)
42	Methadone	F	60	25	17	11	113		234
		M	71	15	25	10		121	(0.01)
43	Methotrexate	F	703	1,254	1,483	417	3,857		5,331
		M	668	281	349	176		1,474	(0.30)
44	Metoprolol	F	536	1,992	7,155	7,945	17,628		42,575
		M	639	3,086	10,217	11,005		24,947	(2.38)
45	Mirtazapine	F	258	1,254	2,110	1,665	5,287		9,373
		M	231	1,380	1,203	1,272		4,086	(0.52)
46	Mycophenolic acid	F	313	455	471	126	1,365		3,052
		M	332	441	648	266		1,687	(0.17)
47	Neomycin	F	5,716	4,757	5,054	2,158	17,685		32,885
		M	6,025	3,925	3,249	2,001		15,200	(1.84)
48	Nicotine	F	0	8	7	4	19		428
		M	33	203	137	36		409	(0.02)
49	Omeprazole	F	19,264	34,099	40,728	17,506	111,597		198,154
		M	16,231	31,613	22,722	15,991		86,557	(11.06)
50	Oxcarbazepine	F	156	55	23	17	251		540
		M	184	54	36	15		289	(0.03)
51	Oxycodone	F	211	789	1,298	653	2,951		5,097
		M	243	661	705	537		2,146	(0.28)
52	Paromomycin	F	8	4	3	2	17		38
		M	10	5	4	2		21	(0.00)
53	Paroxetine	F	336	1,409	1,740	511	3,996		8,298
		M	419	2,360	1,183	340		4,302	(0.46)
54	Peginterferon alfa-2a	F	9	28	13	8	58		132
		M	4	39	25	6		74	(0.01)
55	Peginterferon alfa-2b	F	0	3	1	0	4		10
		M	1	2	2	1		6	(0.00)
56	Phenytoin	F	521	298	423	414	1,656		4,471
		M	951	681	540	643		2,815	(0.25)
57	Progyluton	F	301	691	146	0	1,138		1,139
		M	1	0	0	0		1	(0.06)
58	Pyrazinamide	F	50	66	96	93	305		875
		M	103	156	122	189		570	(0.05)
59	Ribavirin	F	342	1,043	1,549	2,170	5,104		11,787
		M	784	1,958	1,440	2,501		6,683	(0.66)
60	Quetiapine	F	12	46	153	147	358		686
		M	19	44	127	138		328	(0.04)
61	Rifampin	F	23	63	67	49	202		581
		M	52	120	94	113		379	(0.03)
62	Risperidone	F	948	464	445	688	2,545		6,824
		M	2,480	796	401	602		4,279	(0.38)
63	Rituximab	F	192	253	263	142	850		1,559
		M	166	191	193	159		709	(0.09)
64	Rosuvastatin	F	148	1,740	9,092	4,276	15,256		32,509
		M	148	3,318	8,974	4,813		17,253	(1.82)
65	Salmeterol	F	945	2,266	3,946	2,963	10,120		16,749
		M	1,452	1,264	1,787	2,126		6,629	(0.94)
66	Simvastatin	F	112	1,690	9,345	3,936	15,083		25,185
		M	82	2,024	5,073	2,923		10,102	(1.41)
67	Streptomycin	F	25	62	130	44	261		1,015
		M	166	207	258	123		754	(0.06)
68	Succinylcholine	F	176	89	147	240	652		2,537
		M	609	588	356	332		1,885	(0.14)
69	Tacrolimus	F	2,201	2,025	1,530	375	6,131		11,592
		M	1,933	1,629	1,312	587		5,461	(0.65)
70	Tamoxifen	F	3	472	935	89	1,499		1,578
		M	2	40	22	15		79	(0.09)
71	Thioguanine	F	137	0	4	2	143		349
		M	202	2	1	1		206	(0.02)
72	Tobramycin	F	2,386	2,585	2,278	1,256	8,505		15,809
		M	2,423	2,189	1,559	1,133		7,304	(0.88)
73	Tramadol	F	7,392	25,763	17,280	7,915	58,350		103,897
		M	9,758	15,279	11,575	8,935		45,547	(5.80)
74	Valproic acid	F	858	519	500	294	2,171		5,243 (0.29)
		M	1,369	912	445	346		3,072	

Table 2 (*continued*)

Drug List (n = 78)		Gender	≤24 years	25–44 years	45–64 years	≥65 years	Total females	Total males	Total Patients (%)
75	Venlafaxine	F	119	586	674	151	1,530		2,773
		M	118	728	307	90		1,243	(0.15)
76	Voriconazole	F	254	91	153	120	618		1,432
		M	337	118	170	189		814	(0.08)
77	Warfarin	F	276	677	1,427	1,753	4,133		8,272
		M	353	683	1,389	1,714		4,139	(0.46)
78	Zuclopenthixol	F	2	11	2	0	15		41
		M	5	15	6	0		26	(0.00)
Total (%)			379,395 (21.14)	521,948 (29.14)	561,150 (31.33)	328,417 (18.34)	958,500 (53.52)	832,410 (46.48)	1,790,910 (100)

(5.8%), codeine (5.1%), meloxicam (4.8%), fentanyl (4.2%), and gentamicin (2.5%). Prescribing of these top ten consumed items represented collectively 74.7% of the total used PGx drugs.

The PGx drugs were subcategorized into eight therapeutic groups according to ATC criteria as detailed in the Supplementary Tables (S1-S6). Analgesic agents (8 drugs) were the most commonly used (47%, Fig. 1). The second prescribed drug class was the cardiovascular agents (24.4%), such as the statins e.g. atorvastatin, rosuvastatin, and simvastatin, while the gastroenterology class which included a single PGx medication (omeprazole) in this study, was the third top issued class (11.1%). The antimicrobials and psychiatry/neurology medications accounted for 6.2% and 6.0% of the total drug usage, respectively. In contrast, the endocrinology group (estrogen containing contraceptives) and oncology agents showed lower prescribing rates (1.8% and 1.7%, respectively). Additional breakdown of the data based on different

genders exhibited greater intake of PGx drugs by females (53.5%) than males (46.5%) (Table 2). Subgrouping of the patients into various age groups indicated a higher consumption of PGx drugs by patients aged ≥45–64 years, then the younger adults (≥25-44 years); 31.3% and 29.1%, respectively. Children and youth patients aged <25 years used relatively lower amount of PGx medications and those aged ≥65 years were the lowest users (21.2% and 18.3%, respectively).

Among the screened pharmacogenes, the cytochrome P450 genes (*CYP2C9*, *CYP2C19*, and *CYP2D6*) were estimated to affect patients' responses to 1,156,113 unique prescriptions of the selected PGx drugs which are substares for the three mentioned pharmacgenes (Table 3). These may impact the outcomes of 54.3% of the used drugs (27.2% are possibly affected by *CYP2C9* mutations, 12.8% by *CYP2C19* and, 14.3% by *CYP2D6*) throughout the 7 years. *SLCO1B1* was the fourth most common gene with a
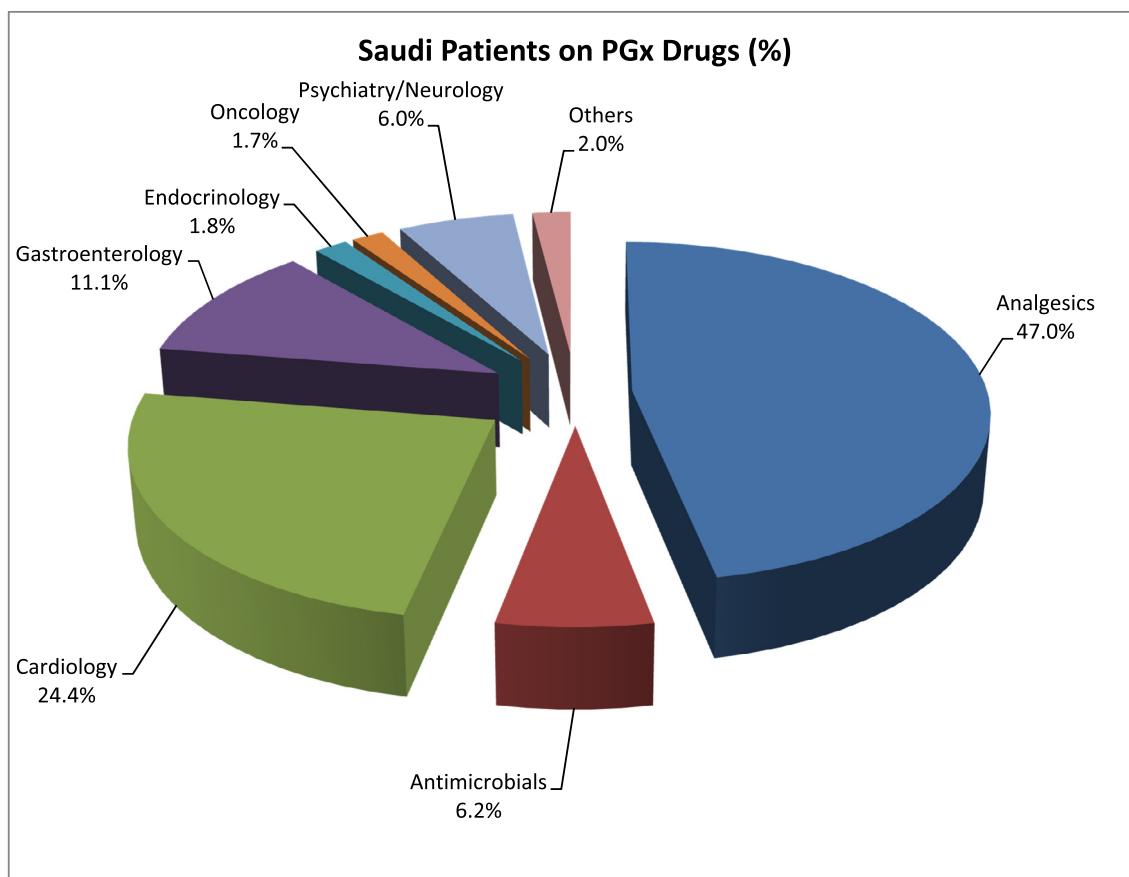
Fig. 1. Venn diagram showing the percentage of different categories of PGx drugs used by Saudi patients treated at MNG-HA.

Table 3

Percentages of prescribed items possibly affected by various pharmacogenes.

Genes (n = 45)	Interacting drugs	Total No. of drugs	Prescribed items	%
ABCG2	Rosuvastatin	1	32,509	1.53
ACE	Captopril	1	10,653	0.50
ADD1	Hydrochlorothiazide	1	9,131	0.43
ADRB2	Salmeterol	1	16,749	0.79
APOE	Atorvastatin	1	137,957	6.49
ATIC	Methotrexate	1	5,331	0.25
CACNA1S	Succinylcholine	1	2,537	0.12
CES1	Clopidogrel	1	30,037	1.41
CHRNA5	Nicotine	1	428	0.02
CPS1	Valproic acid	1	5,243	0.25
CYP2A6	Nicotine	1	428	0.02
CYP2B6	Efavirenz, Methadone	2	319	0.01
CYP2C9	Celecoxib, Ibuprofen, Meloxicam, Phenytoin, Warfarin	5	578,672	27.21
CYP2C19	Amitriptyline, Citalopram, Clomipramine, Clopidogrel, Doxepin, Imipramine, Omeprazole, Voriconazole	8	272,625	12.82
CYP2D6	Amitriptyline, Aripiprazole, Clomipramine, Codeine, Doxepin, Flecainide, Fluvoxamine, Haloperidol, Imipramine, Metoprolol, Mirtazapine, Oxycodone, Paroxetine, Risperidone, Tamoxifen, Tramadol, Venlafaxine, Zuclopenthixol	18	304,816	14.33
CYP3A4	Fentanyl, Quetiapine, Tacrolimus	3	97,969	4.61
CYP3A5	Tacrolimus	1	11,592	0.54
CYP4F2	Warfarin	1	8,272	0.39
DPYD	Capecitabine, Fluorouracil	2	2,769	0.13
EGFR	Erlotinib	1	77	0.00
FCGR3A	Rituximab	1	1,559	0.07
FVL	Contraceptives containing estrogen	5	31,507	1.48
HLA-A	Allopurinol, Carbamazepine	2	20,582	0.97
HLA-B	Allopurinol, Dapsone, Carbamazepine, Flucloxacillin, Oxcarbazepine, Phenytoin	6	29,421	1.38
HLA-C	Allopurinol	1	15,355	0.72
HLA-DPB1	Aspirin	1	121,699	5.72
HPRT1	Mycophenolic acid	1	3,052	0.14
IFNL3 (IL28B)	Peginterferon Alpha-2a, Peginterferon Alpha-2b, Ribavirin	3	828	0.04
IFNL4	Peginterferon Alpha-2a, Peginterferon Alpha-2b, Ribavirin	3	828	0.04
ITPA	Peginterferon Alpha-2b, Ribavirin	2	696	0.03
MTHFR	Methotrexate	1	5,331	0.25
MT-RNR1	Amikacin, Gentamicin, Neomycin, Paromomycin, Streptomycin, Tobramycin	6	98,842	4.65
NAGS	Carglumic acid, Valproic acid	2	5,304	0.25
NAT2	Ethambutol, Hydralazine, Isoniazid, Pyrazinamide, Rifampin	5	23,371	1.10
NUDT15	Azathioprine, Mercaptopurine, Thioguanine	3	3,565	0.17
OTC	Valproic acid	1	5,243	0.25
POLG	Valproic acid	1	5,243	0.25
RYR1	Succinylcholine	1	2,537	0.12
SCN1A	Carbamazepine, Phenytoin	2	9,698	0.46
SLC19A1	Methotrexate	1	5,331	0.25
SLCO1B1	Atorvastatin, Rosuvastatin, Simvastatin	3	195,651	9.20
TNF-α	Etanercept	1	847	0.04
TPMT	Azathioprine, Mercaptopurine, Thioguanine	3	3,565	0.17
UGT1A1	Irinotecan	1	532	0.03
VKORC1	Warfarin	1	8,272	0.39
Total prescribed items			2,126,973	100

probable association with toxicities related to 9.2% of the given medications. Besides, *APOE* (atorvastatin substrate) and *HLA-DPB1* (aspirin substrate) came as fifth and sixth among the listed genes with the potential to be involved in predicted risks to 6.5% and 5.7% of the prescribed drugs, respectively. MT-RNR1, CYP3A4, ABCG2, and FVL were found to be among the top 10 genes list impacting the frequently used PGx drugs; they were estimated to affect 4.7%, 4.6%, 1.5%, and 1.5% of the prescribed items, respectively.

The frequency of pharmacogenetic variants that characterize Saudi population were extracted from various previous candidate gene studies, which mostly investigated a single or limited number of pharmacogenes of interest. Of the 45 selected pharmacogenes described in Table 3, data of 35 genes were identified among the tested healthy Saudis (Table 4). Bu et al. (2004) screened 513 healthy individuals to estimate the percentage of patients carrying particular genotypes of eight pharmacogenes; six of them (*CYP1A1, GSTP1, GSTM1, GSTT1, MS/MTR,* and *NQO1*) apparently lacked satis-

factory association evidence; therefore, were excluded from our study and only two genes (*MTHFR* and *NAT2*) were considered. Later on, Mizzi et al. (2016) investigated a slightly smaller number of Saudi participants (n = 499) for nine pharmacogenes (CYP2C9, CYP2C19, CYP2D6, DPYD, NAT2, SLCO1B1, TPMT, UGT1A1, and VKORC1). In the third and most recent KFSHRC large scale study on 11,889 unrelated healthy Saudis (Goljan et al., 2022), eight pharmacogenes have been investigated, two of them were tested for the first time among Saudis *(CYP4F2 and NUDT15)*, while the remaining six genes were identified previously (*CYP2C9, CYP2C19, DPYD, NAT2, TPMT,* and *VKORC1)*. Recently, 13 additional pharmacogenes (*ABCG2, ADD1, CES1, CPS1, CYP2A6, CYP2B6, EGFR, ITPA, MT-RNR1, NAGS, POLG, OTC,* and *RYR1*) were explored in healthy Saudi participants who were used as a control group in comparison to sickle cell disease patients in a genome-wide association study (GWAS) (Alshabeeb et al., 2022). In this study, the allele frequencies of three *G6PD* SNPs ((rs1050828 (202G>A), rs2230037 (1311T>C), and rs76645461 (143T>C)), were determined (mini-

Table 4
Pharmacogenes identified among Saudi healthy individuals.

Gene (n = 35)	Allele	Variant location	SNP ID#	Protein activity	MAF* (%)	PMID**
ABCG2		421G>T	rs2231142	Decreased	5.6	***
ACE		del	rs1799752	Inactive	73.0	22664118
ADD1		1378G>T	rs4961	Increased	7.4	***
ADRB2		5285G>A	rs1042713	Increased sensitivity	20.0	23056045
APOE		526C>T	rs7412	Decreased	5.0	30235358
CES1		428G>A	rs71647871	Decreased	1.3	***
CPS1		4217C>A	rs1047891	Decreased	36.8	***
CYP2A6	*17	1093C>T	rs28399454	Decreased	0.7	***
CYP2B6	*18	983T>C	rs28399499	Decreased	0.5	***
CYP2C9	*2	430C>T	rs1799853	Decreased	13.4	35089958
	*3	1075A>C	rs1057910	Inactive	5.3	
	*5	1080C>G	rs28371686	Decreased	0.2	
	*6	818delA	rs9332131	Inactive	0.1	
	*8	449G>A	rs7900194	Decreased	0.5	
	*11	1003C>T	rs28371685	Decreased	0.6	
	*33	395G>A	rs200183364	Inactive	0.3	
CYP2C19	*2	681G>A	rs4244285	Inactive	9.6	
	*3	636G>A	rs4986893	Inactive	0.1	
	*8	358T>C	rs41291556	Inactive	0.1	
	*9	431G>A	rs17884712	Decreased	0.2	
	*17	−806C>T	rs12248560	Increased	25.9	
CYP2D6	*2 (duplication)	2850C>T, 4180 G>C	rs16947, rs1135840	Increased	21.0	9241658
	*3	2549delA	rs35742686	Inactive	0.3	@Conference Paper
	*4	1846G>A	rs3892097	Inactive	8.0	27636550
	*5 (deletion)	1297C>T	rs56337013	Inactive	2.0	9241658
	*6	454T>del	rs5030655	Inactive	1.0	27636550
	*9	2615delAAG	rs5030656	Decreased	0.3	Conference Paper
	*10	100C>T	rs1065852	Decreased	10.0	27636550
	*17	320C>T	rs28371706	Decreased	4.0	
	*29 (*35)	886C>T	rs16947	Decreased	3.0	24121619
	*41	2988G>A	rs28371725	Decreased	19.0	27636550
CYP3A5	*3	6986A>G	rs776746	Inactive	84.5	35089958
	*6	14,690G>A	rs10264272	Inactive	2.4	
	*7	Deletion	rs41303343	Inactive	0.4	
CYP4F2	*3	1297G>A	rs2108622	Decreased	44.4	
DPYD	*2A	1905+1G>A	rs3918290	Inactive	0.1	35089958
		1236G>A	rs56038477	Decreased	0.5	
		2846A>T	rs67376798	Decreased	<0.1	
		557A>G	rs115232898	Decreased	0.1	
	*13	1679T>G	rs55886062	Inactive	0.0	27636550
EGFR		2234C>T	rs121434569	Increased	0.0	***
FVL (F5)		1691G>A	rs6025	Decreased	1.0	22664118
HLA-A	A*31:01:02	8057A>T	rs1061235	Idiosyncratic reactions	5.3	33193311
	A*33:03:01				3.6	
HLA-B	B*13:01:01				0.2	
	B*15:02:01				0.3	
	B*15:11:01				0.0	
	B*35:01:01				2.8	
	B*38:02:01				0.2	
	B*57:01:01	733T>G	rs2395029		0.7	
	B*58:01:01				3.4	
HLA-C	C*03:02				2.8	
	C*04:01:01				12.1	
IFNL3 (IL28B)		1825C>T	rs12979860	Decreased	29.0	25811035
		1332T>G	rs8099917	Decreased	11.8	
ITPA		124+21A>C	rs7270101		7.9	***
MTHFR		677C>T	rs1801133	Decreased	15.0	19838435
						23267299
						15111988
MT-RNR1 (MT-ND1)		1555A>G	rs267606617	Decreased	0.0	***
NAT2	*5	481C>T	rs1799929	Decreased	48.0	26409796
	*6	590G>A	rs1799930	Decreased	28.0	
	*7A	857G>A	rs1799931	Decreased	12.0	
	*7B	282C>T	rs1041983	Decreased	30.0	27636550
	5D	341T>C	rs1801280	Decreased	50.0	
NAGS		337G>A	rs121912591$$	Decreased	0.2	***
		791T>C	rs104894605	Decreased	0.7	***
		473G>A	rs104894604	Decreased	0.0	***
NUDT15	*3	415C>T	rs116855232	Inactive	1.8	35089958

Table 4 (continued)

Gene (n = 35)	Allele	Variant location	SNP ID#	Protein activity	MAF* (%)	PMID**
POLG		3428A>G	rs2307441	Decreased	**6.4**	***
OTC		374C>T	rs72554356	Decreased	**0.0**	***
RYR1		20 SNPs $^{$$}$		Increased	**0.0**	***
SLCO1B1	*5	521T>C	rs4149056	Decreased	**27.0**	27636550
TNF		− 308G>A	rs1800629	Decreased	**31.0**	23884763
TPMT	*2	238G> C	rs1800462	Inactive	**<0.1**	35089958
	*3A (*3B+*3C)	460G>A & 719A>G	rs1800460 & rs1142345	Inactive	**0.3**	
	*3B	460G>A	rs1800460	Inactive	**<0.1**	
	*3C	719A>G	rs1142345	Inactive	**0.4**	
UGT1A1	*28	(−53(TA)6>7	4 (formerly rs8175347)	Decreased	**26.0**	27636550
VKORC1	*2	−1639G>A	rs9923231	Increased sensitivity	**46.0**	
		1173C>T	rs9934438	Decreased	**53.7**	35089958
		3730G>A	rs7294	Increased	**29.2**	
		106G>T	rs61742245	Increased	**2.1**	

#SNPs = Single Nucleotide Polymorphisms, SNPs shown for HLA typing are tag SNPs. *MAF = Minimum Allele Frequency. **PMID = PubMed reference number. *** = Unpublished work (Alshabeeb et al., 2022). $$ = See supplementary table for full list of SNPs. @Conference Paper by Hamsa Tayeb (2015).

mum allele frequency (MAF) = 0.02, 0.26, and 0.02, respectively), whereas the common *G6PD* variant *rs5030868* (563C>T, MAF = 0.17) was reported by Hellani et al. (2009).

The frequency distribution of different *HLA* loci in Saudis was extracted from a study conducted by Jawdat et al. (2019), who performed *HLA* typing of the bone marrow collected from 2405 donors and more recently screened a very large number of donors (n = 28,927) for six genes, *HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1,* and *HLA-DPB1* using the next-generation sequencing method (Jawdat et al., 2020). It is worth mentioning that the variant *HLA-DPB1*03:01:01,* associated with aspirin-induced asthma, is common among Saudi individuals (MAF = 0.12). In addition, the *HLA-DRB1*01:01:01* variant, which was excluded in this study as it interacts with a non-formulary drug (nevirapine) at MNG-HA premises, is carried by 1.6% of Saudis. Thus, testing this variant in patients using nevirapine treated in other health care centers may be useful. The data on other pharmacogenes were verified from various candidate gene studies (McLellan et al., 1997, Hellani et al., 2009, Saour et al., 2009, Alghasham et al., 2012, Settin et al., 2012, Daghestani et al., 2012, Al-Dosari et al., 2013, Al-Harthi et al., 2013, Al-Qahtani et al., 2015, Al-Shaqha et al., 2015) (Al-Saikhan et al., 2017, Almigbal et al., 2018). The variants in *TPMT* (*2, and *3B) and *DPYD* (*2A and *13) were detected in ≤0.1% of Saudis. Furthermore, a novel variant (*rs371313778,* 2434G>A) in *DPYD* was reported in a Saudi female who experienced severe toxicity when exposed to 5-fluorouracil (Bukhari et al., 2019). Mutations in four genes (*EGFR*, OTC, *MT-RNR1,* and RYR1,) that were reported in Western societies are absent among Saudis (Alshabeeb et al., 2022). Also, *CYP2C19*3* was found to be exist in <0.1% of the Saudi population, the variants *rs121912591* and *rs104894605* in *NAGS, CYP3A5 (*7), DPYD,* selected *HLA-B* (*B*13:01, B*15:02, B*38:02,* and *B*57:01*), and *TPMT* are carried by <1%, whereas various variants of the *CYP2D6* gene *(*5, *6, *17,* and *29), CYP3A5 (*6) FVL (rs6025), CES1 (rs71647871), HLA* (*A*33:03, B*35:01, B*58:01,* and *C*03:02*), and *NUDT15*3* showed higher frequently rates between 1 and 4%.

4. Discussion

This study described the frequencies of medications affected by genetic variants used in the MNG-HA hospitals and primary care centers in Saudi Arabia over 7 years. Similar studies have been conducted on other populations, but allele frequencies and drug utilization can vary from region to region. Thus, our data are considered useful support to change medication use policy among Saudi society but may not be generalized to different populations.

Consistent with previous studies conducted on Dutch, Americans, and Canadians (Alshabeeb et al., 2019, Samwald et al., 2016, Fan et al., 2021), analgesics, cardiovascular drugs, proton pump inhibitors, and psychotropics were among the most prescribed drug categories. The analgesic group became the top category in this study as more medications belonging to the group, such as ibuprofen, celecoxib, and fentanyl were added to the screened list, wheras the psychotropic group was found to be the fifth used category as multiple agents of the group were excluded, such as clozapine, olanzapine and pimozide as a result of failure to fit the selected evidence level criteria or due to non-availability in MNG-HA formulary e.g. atomoxetine, brivaracetam, bupropion, desipramine, escitalopram, nortriptyline, and sertraline. The antimicrobial group was ranked as the fourth commonly used drug class in our study as a result of adding the aminoglycosides (amikacin, gentamicin, neomycin, paromomycin, streptomycin, and tobramycin) to the PGx drug list based on the recent strong association evidence of toxicities-induced by this group in patients positive for *rs267606617* (G allele), *rs267606618* (C allele), and *rs267606619* (T allele) in *MT-RNR1* gene (McDermott et al., 2022).

The usage of PGx medications may vary from one country to another. For instance, across Europe, 20.5% of patients in Germany used PGx drugs (de Vries et al., 2021), whereas slightly higher usage (23.6–24.2%) was observed in the Netherlands as documented in three separate studies (Alshabeeb et al., 2019, Bank et al., 2019, van der Wouden et al., 2019). On the other hand, higher consumption noticed observed in the United States (33.5%) (Samwald et al., 2016) and among Saudis (46.7%) in this study. This high percentage of exposure by Saudis to PGx drugs may be explained by the high usage among Saudi children and adolescent patients (≤24) than their counterparts in other areas e.g. in the Netherlands (Alshabeeb et al., 2019) (21.2% versus 5.3%, respectively). In the United States, only 6.9% of children (≤13) were taking PGx medications. Another reason is that the consumption of a larger number of drugs was screened in this study (n = 78) than in the Dutch study (n = 45). The elevated usage rate among the tested Saudi cohort stresses further large-scale study at a national level to confirm the findings which may potentiate the necessity for genotyping Saudi patients.

The study revealed that women consumed more PGx drugs than men, this result is consistent with the findings reported by previous studies in Europe and the United States (Alshabeeb et al., 2019, Samwald et al., 2016). The increased usage by women may refer to the nature of women who need to take certain medications not generally needed by men such as oral contraceptive pills and the pain killers used regularly at each menstrual cycle. Our data showed that women consume analgesics 19% more than men.

Omeprazole is a proton-pump inhibitor used for various purposes but widely prescribed to patients on non-steroidal anti-inflammatory analgesics which helps in minimizing the risk of gastritis and ulceration induced by these analgesics (Bishop et al., 2022). Hence, omeprazole has followed the prescribing pattern of the analgesic group and was consumed 29% more by females than males. In addition, some disease conditions are more prevalent in women than in men such as breast cancer (Giordano, 2018), which makes usage of antineoplastic agents predominantly seen in women than in men. This was confirmed in our cohort study where two thirds of the oncology medications showed an increased usage by women than men; for example, 1499 females were given tamoxifen compared to only 79 males over the past 7 years. On the other hand, the overall males' consumption of cardiovascular agents exceeded women's usage by 6%. For instance, use of the antiplatelet clopidogrel was doubled by males than females (used by 20,021 vs 10,016 patients, respectively). Our results support the historical notice that cardiovascular diseases were considered as a man's disease with high propensity to develop cardiovascular complications (Bots et al., 2017, Thompson and Daugherty, 2017). As reported in previous studies, our data showed more prescriptions introduced to patients aged ≥45–64 years than younger ones. Inconsistently, antimicrobial medications were used more commonly (43.7%) by children and youth patients than other groups. This is expected as children's immature immunity makes them less likely efficient in fighting infections and therefore exogenous antibiotics are routinely prescribed to overcome serious conditions (Chappell et al., 2021).

Lack of pharmacogenetic information is a main barrier to provide sufficient PGx counseling to patients (Rahawi et al., 2020). Hence, this research described 78 drugs impacted by variants in 45 genes based on the scientific high level evidence indicated in the CPIC and PharmGKB. Identifying the major genes involved in drug interactions would be helpful to focus on the most relevant candidates among the wide pool of suggested genes, which facilitates the design of a specific gene panel for PGx testing (Wu et al., 2012). The genes were ranked in this study based on the usage rate of the medications they interact with. However, the ranking of genes may vary between different studied populations as a result of variances in the penetrance of variants and the pattern of prescribing relevant drugs (Samwald et al., 2016). The cytochrome P450 genes (CYP2D6, CYP2C9, and CYP2C19) and SLCO1B1 were identified as the most important genes that may affect responses to PGx drugs used by the study population. The findings here match several previous studies that recommended adding the four mentioned genes to the selected gene panels and assays for testing (Dunnenberger et al., 2015, Alshabeeb et al., 2019, Dong et al., 2018, Ji et al., 2016). In a small study on 50 Saudi stroke patients, they were divided into two groups, responders and non-responders to the antiplatelet clopidogrel, and were genotyped for *2 and *3 alleles in CYP2C19 to assess their impact on therapy resistance. The results showed high frequency of both variants in non-responder arm (Alhazzani et al., 2017). Association of CYP2C9 (*2 and *3) with warfarin dose variability was also investigated among 112 Saudi patients which emphasized a need for lower doses in patients positive for the variants particularly *3 than those with wild type (Al-Saikhan et al., 2018). The studies conducted on Western population have shown that CYP2D6 genotypes was linked to the majority (46.8–60.3%) of drug response prediction in patients on PGx drugs (Alshabeeb et al., 2019, Fan et al., 2021). In contrast, the gene in our study was found to feasibly affect 14.3% of treatment outcomes among Saudi patients on PGx drugs. This is because more than half of the drugs metabolized by CYP2D6 were excluded from this study, as the study included only formulary drugs in MNG-HA which also need to fit the top two association evidence levels suggested by CPIC and PharmGKB.

This study explored published literature and obtained some data from a recent unpublished study (Alshabeeb et al., 2022) to determine the frequency of variants in the 45 selected pharmacogenes among the Saudi population; however, only 35 genes were identified. Still, this number represents the wider PGx data ever published in a single study about Saudi pharmacogenes with detailed description of their alleles frequencies. These findings provide an unprecedented broader PGx background for Saudis. The results emphasized the uniqueness of the Saudi population and showed certain variances that distinguish them from other people with different ancestral heritage. For instance in CYP2C19 gene, frequency of CYP2C19*2 and CYP2C9*3 alleles is lower in the Saudi population than in the South Africans and Europeans (MAF = 0.096 vs 0.13 and 0.14, and MAF = 0.053 vs 0.36 and 0.08, respectively). In contrast, CYP2C19*17 and SLCO1B1*5 are more frequent among Saudis than their counterparts in Africa and Europe (MAF = 0.26 vs 0.18 and 0.22, and MAF = 0.27 vs 0.22 and 0.17, respectively) (Mizzi et al., 2016). In CYP2D6, low allele frequency of CYP2D6*4 and 10* were reported among Saudis than in the other tested groups (MAF = 0.08 vs 0.32 and 0.17, and MAF = 0.10 vs 0.33 and 0.19, respectively), while carriage of CYP2D6*41 is more common in the Saudis than their African and European peers (MAF = 0.19 vs 0.09 and 0.10, respectively).

Furthermore, very limited number of healthy Saudis carry the variants *3A (0.3%) and *3C (0.4%) of TPMT gene, while <0.1% of the tested Saudi cohort inherits *2 and *3B markers (Goljan et al., 2022). South Africans and Europeans appear to carry higher frequencies of TPMT*3A and *3C (3% and 8% in Africans and 2% and 4% in Europeans, respectively) but they showed an inheritance of *2 allele similar to the Saudis (Mizzi et al., 2016). Similary, the rare DYPD marker (rs55886062 (*13)) was found to be absent in the three compared populations. DPYD*2A (rs3918290), associated with myelosuppression induced by selected antineoplastic agents, is absent in Europeans and Saudis but carried by 1% of the Africans. Some DYPD rare variants were detected in Saudi individulas; for example, rs67376798 was found to be exist in <0.1% of healthy people (Goljan et al., 2022). Furthermore, a novel variant (rs371313778), which was globally reported in only 10 out of 39,500 tested participants reported by the National Center for Biotechnology Information (NCBI) SNP database (Sherry et al., 2001), was observed in a Saudi patient who developed a severe adverse reaction after administering fluorouracil treatment (Bukhari et al., 2019). This variant requires further examination among Saudis to determine its allele frequency in a representative sample size. Although, MAF of few variants was low among healthy individulas (MAF ≤ 0.4), such as *3B and *3C alleles in TPMT, rs67376798 and *2A in DPYD, *3 and *9 in CYP2D6, higher frequency distributions were noticed in cancer patients (MAF = 3% and 5% for SNPs in TPMT, 26% and 3% for SNPs in DPYD, 5% and 3% for SNPs in CYP2D6, respectively). The common mutations in ABCG2 (rs2231142), CYP2C9 (*2 and *3), CYP2C19 (*2), CYP2D6 (*4 and *10), CYP3A5 (*3), and UGT1A1 (*28) were more frequent in 181 Saudi patients with different types of tumors than healthy individulas (MAF = 21% vs 5% for ABCG2 marker, 19% vs 13% for CYP2C9*2, 9% vs 5% for CYP2C9*3, 16% vs 10% for CYP2C19*2, 15% vs 8% for CYP2D6*4, 25% vs 10% for CYP2D6*10, 91% vs 85% for CYP3A5*3, and 39% vs 26% for UGT1A1*28) (Aboul-Soud et al., 2021). This may draw an attention to the fact that some lifestyle practices and exposures to several environmental contaminants such as ciggarate smoking, sun ultraviolet radiation, air pollution, chemicals, heavy metals, or pesticides may increase the risk of mutations generation in DNA (Slote et al.).

HLA-B*59:01:01 was previously reported as a risk factor for severe cutaneous adverse reactions induced by methazolamide, a carbonic anhydrase inhibitor, in East Asian patients (Tangamornsuksan and Lohitnavy, 2019). This allele is absent

among the large examined stem cell Saudi donors (Jawdat et al., 2020). These variances in genetic makeup reflect the necessity for screening and differentiation between populations with different ancestral backgrounds. This information would help assessing the potential value and impact of implementing clinical pharmacogenomics testing guidelines in Saudi Arabia. The international PGx guidelines can be modified and tailored according to the genetic findings related to the Saudi population. Further study is needed to screen the 10 untested genes among the Saudis (*ATIC, CACNA1S, CHRNA5, CYP3A4, FCGR3A, HLA- DPB1, HPRT1, IFNL4, SCN1A*, and *SLC19A1*), this is an essential step to verify whether the mutations in these genes do exist among Saudis. This is necessary to select the appropriate gene panel that suits Saudi patients for pre-emptive testing. Consequently, this may help in reducing healthcare expenses associated with preventable genetically-related ADRs.

So far, the data reported here which showed the frequency of PGx variants are useful for reaserchers and health care practioners to optimize their genetic testing orders and pay more attention towards testing the common pharmacogenes. Hence, this would facilitate practicing a precised drug monitoring to ensure drug safety and efficacy. The indicated genotype frequencies provided a hint of the patterns of enzymatic functional activity among Saudis, which can be utilized to avoid screening non-existing and low-frequency variants unless related to serious phenotypes. Categorization of patients into different age groups will also help to focus on groups with high PGx drug usage rates. A recent Saudi surveillance study that involved 206 qualified pharmacists indicated their overall limited backgrounds about pharmacogenomics and its clinical implications (Algahtani, 2020). Thus, more efforts are needed to educate health care providers about the potential return of PGx testing prior to drug prescribing and to enhance their awareness about the local genetic data and the necessary precautions to be taken before using PGx medications. Health stakeholders in Saudi are deeply encouraged to take an advantage of the available data and plan a roadmap to prepare the health community for the implementation of international or local costumed PGx guidelines. It is important to realize that genetic predisposition is not the only contributing factor to drug poor responses and ADRs (Watkins et al., 2008). Other non-genetic factors which possibly impact responses to drugs include gender and age differences, co-morbidities, alcohol intake, smoking, drug-drug and drug-diet interactions (Haga, 2017, Lucas and Martin, 2013).

5. Conclusion

The findings of this study revealed drug prescription patterns and genetic backgrounds in the Saudi population. This study highlights the importance of understanding specific region/country drug consumption, which will allow for better pre-emptive genotyping strategies in different populations. This knowledge may bring to light more assertive treatments, with fewer adverse events and better efficacy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2022.06.013.

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