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Exploring the Genetic Inheritance of Novel Pharmacogenetic Markers in the Saudi Population

Petra Novakova[1], Jana Kralova[1]*, Lucie Vesela[1]

[1]Department of Pharmacognosy, Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic.

***E-mail** ✉ jana.kralova.pg@yahoo.com

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ABSTRACT

Variants in pharmacogenes can profoundly influence drug responses, but data on their occurrence in Middle Eastern populations, particularly Saudis, are scarce. This study investigated the inheritance patterns of selected pharmacogenetic markers in healthy individuals from Saudi Arabia. A total of 95 unrelated healthy Saudi participants provided DNA samples, which were genotyped using the Affymetrix Axiom Precision Medicine Diversity Array. Thirty-eight variants in 15 pharmacogenes were chosen for analysis based on their clinical significance and the lack of previous reports in the Saudi population. Among the 37 variants tested, 26 were completely absent. Eight markers in six genes—DPYD (rs1801268), CACNA1S (rs772226819), EGFR (rs121434568), RYR1 (rs193922816), CYP2B6 (rs3826711), and MT-RNR1 (rs267606617, rs267606618, rs267606619)—were not detected in any participant. Eleven variants spanning nine pharmacogenes were observed with variable prevalence. Notably, ATIC (rs4673993, MAF = 0.71) and SLC19A1 (rs1051266, MAF = 0.48), both relevant to methotrexate response, were highly frequent. CYP3A4 exhibited three alleles, including a common variant (rs2242480) and two rare alleles (*3 and *22). Other widely distributed variants included CHRNA5 (rs16969968, MAF = 0.35), IFNL3/IL28B (rs11881222, MAF = 0.30), and SLCO1B114 (MAF = 0.14), while CYP2A6*2, NAT2*14, and CFTR (rs115545701) were present at low frequencies (MAF = 0.021, 0.011, 0.005). Comparisons with global populations revealed significant differences for eight variants relative to Africans, five relative to East Asians, and two relative to Europeans. This study uncovers previously unreported pharmacogenetic profiles in Saudis, providing a foundation for tailoring therapies for diseases such as rheumatoid arthritis, cystic fibrosis, and hepatitis C. The findings can guide the development of Saudi-specific pharmacogenomic panels and inform precision medicine strategies.

Keywords: Saudis, Pharmacogenomics (PGx), ATIC, IFNL3, CHRNA5, CYP3A4

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Introduction

An individual's genetic makeup can profoundly influence drug response, including differences in metabolism, therapeutic effectiveness, and susceptibility to adverse drug reactions (ADRs) [1]. Genetic variations often differ between populations, leading to population-specific drug responses [2]. Over the last two decades, numerous studies have cataloged pharmacogenomic (PGx) variants and their allele frequencies, primarily in European, American, African, and East/Southeast Asian populations, including Japanese and Chinese cohorts. While countries in Europe and North America benefit from well-established research infrastructure [3, 4], PGx studies in Middle Eastern populations remain limited, with few investigations into variant inheritance and ancestral diversity [5, 6]. Understanding the prevalence and distribution of pharmacogenetic variants is essential for implementing precision medicine, ensuring patients receive treatments tailored to their genetic profiles [7]. Economic analyses further support the utility of genetic testing, as it can reduce healthcare costs by preventing ADRs and treatment failures [8-10].

Previous reports have explored common and rare variants across 35 pharmacogenes in the Saudi population [11-13]. Frequently observed alleles include those in cytochrome P450 genes, such as CYP2D6 (*2, *4, *10, *41), CYP2C9 (*2, *3), CYP2C19 (*2, *17), CYP3A5 (*3), and CYP4F2 (*3). Additional common variants were reported in other pharmacogenes, including ABCG2 (rs2231142), ACE (rs1799752), ADD1 (rs4961), ADRB2 (rs1042713), APOE (rs7412), HLA-A (*31:01), and HLA-C (*04:01). Rare variants were also identified in CES1 (rs71647871), CYP2D6 (*5, *6, *17, 29), CYP3A53, DPYD (1236G>A), TPMT (*3A, 3C), and NUDT153. Importantly, several pharmacogenetic markers with known clinical impact remain unexplored in the Saudi population [14]. The present study aimed to evaluate the inheritance of selected variants and star alleles in 15 candidate pharmacogenes in Saudis for the first time. Verification of these variants could facilitate the design of an optimized PGx testing panel tailored to the genetic profile of Saudi patients in clinical settings [13].

Materials and Methods

Blood samples were collected from 95 unrelated, healthy Saudi volunteers who provided informed consent through the Biobank at King Abdullah International Medical Research Center (KAIMRC), Ministry of National Guard Health Affairs (MNGHA), Riyadh, Saudi Arabia. Genomic DNA was extracted from whole blood using Puregene Blood Kits (Qiagen, Hilden, Germany, Catalog #158389) following the manufacturer's instructions, with automated extraction performed on the KingFisher™ magnetic system (Thermo Fisher Scientific, Fresno, CA, USA). DNA concentration and purity were measured at 260 nm using a DanoDrop 2000/2000c spectrophotometer (Thermo Fisher Scientific). DNA samples were aliquoted at 50 ng/µL and stored at 4°C.
Genotyping was conducted using the Affymetrix Axiom™ Precision Medicine Diversity Array (PMDA) Plus Kit (Thermo Fisher Scientific, Catalog #951961). The study focused on 38 genetic markers across 15 pharmacogenes, as detailed in **Tables 1 and 2**, mapped to the latest human genome reference GRCh38.p14. The analyzed genes included ATIC (rs4673993), CACNA1S (rs772226819), CFTR (11 SNPs), CHRNA5 (rs16969968), CYP2A6 (6 SNPs), CYP2B6 (rs3826711), CYP3A4 (5 SNPs), DPYD (rs1801268), EGFR (rs121434568), IFNL3 (rs11881222), MT-RNR1 (rs267606617, rs267606618, rs267606619), NAT2 (*14, rs1801279 + rs1208), RYR1 (rs193922816), SLC19A1 (rs1051266), and SLCO1B1 (*9, rs59502379; *14, rs11045819 + rs2306283).
Markers were selected based on two criteria: (1) robust association with drug response in established PGx databases (CPIC levels A–B, DPWG levels 3–4, or PharmGKB levels 1–2), and (2) lack of previously reported frequency data in Saudis. SNPs with genotyping call rates <95% or Hardy-Weinberg equilibrium p-values <0.05 were excluded. Linkage disequilibrium was assessed using r^2, retaining only markers with $r^2 \geq 0.6$ to ensure moderate-to-strong allelic correlation. Allele frequencies in the Saudi cohort were compared to African, East Asian, and European populations using data from Ensembl and PharmGKB [15, 16]. Statistical significance of frequency differences was determined with Fisher's exact test. Haplotype frequencies for NAT2*14 and SLCO1B1*14 were estimated using haplotype analysis software version 1.05 [17].

Table 1. Absent pharmacogenetic markers (MAF = 0.0) among the Saudi cohort (n = 95).

Genes	SNPs (n = 26)
DPYD	rs1801268
CACNA1S	rs772226819
EGFR	rs121434568
CYP3A4	rs28371759 (*18), rs67666821 (*20)
CFTR	rs368505753, rs80282562, rs121908757, rs121909005, rs121909013, rs75527207, rs397508442, rs74503330, rs121909041, rs193922525
SLCO1B1	rs59502379 (*9)
RYR1	rs193922816
CYP2A6	rs568811809 (*20), rs143731390 (*24), rs28399440 (*27), rs8192730 (*28), rs148166815 (*38)
CYP2B6	rs3826711
MT-RNR1	rs267606617, rs267606618, rs267606619

Table 2. Detected variants and alleles in nine pharmacogenes and their associated therapeutic agents. Drug/gen associations were derived from PharmGKB and CPIC databases.

Genes (n = 9)	Alleles/SNPs (n = 11)	MAF	Interacting drugs (n = 11)	No. of affected drugs
ATIC	rs4673993 (T)	0.71	Methotrexate	1
CFTR	rs115545701 (T)	0.005	Ivacaftor	1
CHRNA5	rs16969968 (A)	0.35	Nicotine	1
CYP2A6	rs1801272 (T, *2)	0.021	Nicotine	
CYP3A4	rs2242480 (T)	0.21	Fentanyl	3
	rs35599367 (A, *22)	0.016	Quetiapine	
	rs4986910 (G, *3) rs35599367 (A, *22) rs2242480 (T)	0.005 0.016 0.21	Tacrolimus	
IFNL3 (IL28B)	rs11881222 (rs368234815, G)	0.30	Peginterferon Alfa-2a, Peginterferon Alfa-2b, Ribavirin	3
NAT2	*14 (rs1801279, A+ rs1208, A)	0.011	Isoniazid	1
SLC19A1	rs1051266 (C)	0.48	Methotrexate	1
SLCO1B1	*14 (rs11045819, A+ rs2306283, G)	0.14	Rosuvastatin	1

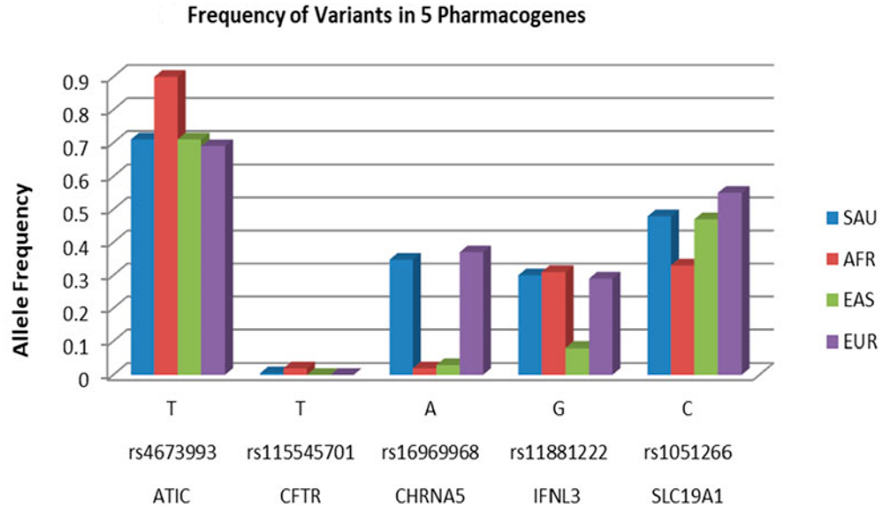
Results and Discussion

The study cohort included 60 male and 35 female participants, with mean ages of 30.4 ± 7.4 years for males and 32.3 ± 8.9 years for females (P = 0.87). Genotyping was highly successful, with an average call rate of 99.8%, and no sample falling below 96.5%. As summarized in **Table 1**, variants in six genes—DPYD (rs1801268), CACNA1S (rs772226819), EGFR (rs121434568), RYR1 (rs193922816), CYP2B6 (rs3826711), and MT-RNR1 (rs267606617, rs267606618, rs267606619)—were completely absent in the participants. Additional markers were also undetected, including rs28371759 and rs67666821 in CYP3A4, 10 SNPs in CFTR, rs59502379 in SLCO1B1, and five alleles (*20, *24, *27, *28, *38) in CYP2A6. Overall, 26 of the 37 tested markers were not observed in the cohort.

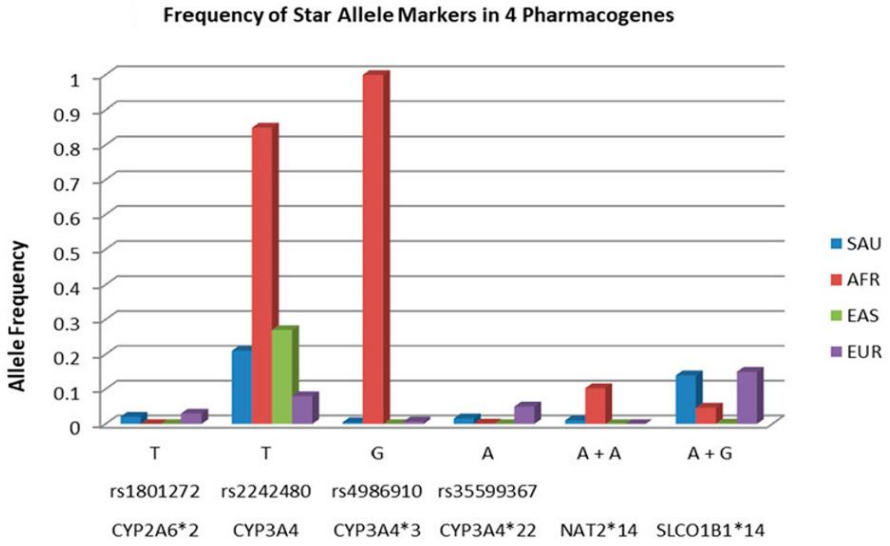
Conversely, 11 variants across nine pharmacogenes were identified. Eight markers were found in distinct genes: ATIC (rs4673993, MAF = 0.71), CFTR (rs115545701, MAF = 0.005), CHRNA5 (rs16969968, MAF = 0.35), CYP2A6 (*2, rs1801272, MAF = 0.021), IFNL3 (rs11881222, MAF = 0.30), NAT2 (*14, rs1801279 A + rs1208 A, MAF = 0.011), SLC19A1 (rs1051266, MAF = 0.48), and SLCO1B1 (*14, rs11045819 A + rs2306283 G, MAF = 0.14) **(Table 2)**. In CYP3A4, three alleles were detected: *3 (rs4986910, MAF = 0.005), rs2242480 (MAF = 0.21), and *22 (rs35599367, MAF = 0.016). Linkage analysis demonstrated a strong correlation between IFNL3 variants rs11881222 and rs12979860 ($r^2 = 0.97$).

Comparative analysis revealed significant differences in allele frequencies for eight variants relative to African populations, five variants compared with East Asians, and two variants compared to Europeans **(Figure 1)**. Rare variants rs115545701 in CFTR and rs4986910 in CYP3A4 did not show significant interpopulation differences.

The identified pharmacogenetic variants may affect responses to a range of 11 therapeutic agents across multiple drug classes: antimicrobials (peginterferon alfa-2a and alfa-2b, ribavirin via IFNL3, and isoniazid via NAT2), psychiatric medications (quetiapine via CYP3A4, nicotine via CHRNA5 and CYP2A6), immunosuppressive/oncology drugs (methotrexate via ATIC and SLC19A1, tacrolimus via CYP3A4), analgesics (fentanyl via CYP3A4), cardiovascular drugs (rosuvastatin via SLCO1B1), and respiratory therapies (ivacaftor via CFTR).



a)



b)

Figure 1. Allele frequencies of the identified variants and star alleles among the Saudi population were compared with previously reported data from the Ensembl and PharmGKB databases for African, East Asian, and European populations [15, 16], with PGx variants illustrated in panel (a) and star allele markers in panel (b); NAT2*14 corresponds to (rs1801279, A + rs1208, A) and SLCO1B1*14 to (rs11045819, A + rs2306283, G).

This study examined multiple variants across 15 genes that have been shown to influence drug responses, supported by robust evidence from diverse population studies [5, 14, 18]. Although these variants are known to be prevalent in populations with different ancestries, their frequency in Saudis remained unclear. To our knowledge, these specific variants have not previously been screened in the Saudi population, complicating the design of an optimized pharmacogenetic testing panel tailored to local needs.

Variants in the DPYD gene can significantly affect patient responses to fluoropyrimidine-based therapies, with certain alleles predisposing individuals to severe toxicities, including gastrointestinal and hematological complications, when treated with standard doses of capecitabine or fluorouracil [19-21]. Earlier work by Goljan *et al.* [12]. identified eight rare DPYD variants in Saudis, with rs56038477 being the most frequent (MAF = 0.005) [12]. In the current study, the rs1801268 variant was screened but not detected among participants, consistent with previous reports showing that DPYD*13 (rs55886062, c.1679T>G) is also absent in Saudis [11]. Likewise, certain SNPs in EGFR (rs121434569, rs121434568) and MT-RNR1 (rs267606617, rs267606618, rs267606619) were undetected in this cohort, reflecting prior findings [13]. These preliminary results suggest that the safety and

efficacy of drugs targeting EGFR (e.g., gefitinib) and MT-RNR1 (e.g., aminoglycosides) cannot be confidently inferred for Saudis without further evaluation in larger cohorts.

The RYR1 and CACNA1S genes collaborate to regulate calcium release in skeletal muscles [22], and certain variants are linked to malignant hyperthermia and muscle-related adverse effects from anesthetics or statins [23-27]. In this study, Saudis were genotyped for rs772226819 (CACNA1S) and rs193922816 (RYR1), in addition to 20 RYR1 SNPs previously tested [13], but none were detected. This absence does not necessarily indicate lower susceptibility to anesthesia-related risks, and larger studies are needed to validate these observations.

The CYP2B6 gene, highly polymorphic among cytochrome P450 enzymes, affects the metabolism of drugs like efavirenz and methadone [28, 29]. A rare variant (rs28399499, MAF = 0.005) impacting enzyme function was previously reported among healthy Saudis [14]. In the current study, another marker (rs3826711) was tested but not observed.

Additionally, eleven CFTR variants commonly associated with cystic fibrosis in Caucasian and African populations were evaluated, with only rs115545701 detected in one participant (MAF = 0.005), highlighting the rarity of these alleles among healthy individuals, though they are prevalent in CF patients. A prior study of 396 CF patients across Saudi regions reported ten different CFTR variants [30]. Ivacaftor, a targeted therapy for CF, is designed specifically for patients carrying disease-causing CFTR mutations [31].

Carriage of ten additional mutations across nine genes was confirmed in the Saudi participants, with these variants potentially influencing responses to ten commonly prescribed drugs in the country's healthcare system. Notably, two variants—ATIC (rs4673993, T allele) and SLC19A1 (rs1051266, C allele), known to affect methotrexate (MTX) efficacy in rheumatoid arthritis [32]—were highly prevalent among Saudis, with allele frequencies of 71% and 48%, respectively. The high frequency of these variants suggests the need for preemptive genetic testing for patients anticipated to receive MTX, as their presence is linked to reduced treatment efficacy [33], potentially requiring higher MTX doses or consideration of alternative/additional disease-modifying antirheumatic drugs [34].

Additionally, two variants—CHRNA5 (rs16969968) and CYP2A6 (rs1801272)—associated with increased susceptibility to nicotine dependence [35, 36] were observed in the cohort, highlighting their relevance for smoking behavior and cessation strategies. Another notable mutation was NAT2*14, a slow acetylator SNP influencing isoniazid metabolism and linked to elevated risk of isoniazid-induced hepatotoxicity [37].

A substantial portion of participants (30%) carried the IFNL3 variant (rs11881222), which is associated with poorer antiviral responses in hepatitis C and HIV treatment [38]. Strong linkage disequilibrium ($r^2 = 0.97$) was observed between rs11881222 and a previously reported IFNL SNP (rs12979860) [39], consistent with patterns seen in East Asian and European populations ($r^2 = 0.95$ and 0.91, respectively) [40].

Regarding drug metabolism, CYP3A4 plays a critical role, metabolizing 50–60% of clinically prescribed drugs [41]. Two markers (−290A>G and 902T>C), previously reported among Saudis [42, 43], were confirmed, and the study further identified two rare alleles (*3 and *22) and one common allele (rs2242480). These variants may influence tacrolimus pharmacokinetics and blood concentrations [44, 45], while CYP3A4*22 and rs2242480 are associated with increased exposure to quetiapine and fentanyl, respectively [46, 47].

SLCO1B1 variants have been linked to statin-induced myopathy and rhabdomyolysis [48]. SLCO1B1*5 had been previously reported among Saudis [11, 49], and this study additionally detected **SLCO1B114** in 14% of participants. This haplotype, composed of rs11045819 and rs2306283, is associated with increased OATP1B1 activity and reduced rosuvastatin efficacy [50], and rs11045819 alone has been linked to decreased exposure to simvastatin and rifampin, warranting further validation [51, 52].

These findings highlight gaps in pharmacogenetic knowledge within the underrepresented Saudi population and emphasize the value of screening larger cohorts to assess the distribution of clinically relevant variants, ultimately enabling more informed treatment decisions [53]. The distinct genetic landscape of Saudis, shaped by unique geographic and demographic factors [54, 55], necessitates further study of drug response variability. Nine of the eleven identified markers exhibited statistically significant differences in allele frequency compared to at least one population with a different ancestral background. Although the variant selection was informed by prior studies in Caucasians, complementary next-generation sequencing approaches—such as whole-genome, exome, or targeted sequencing around actionable SNPs—are needed to fully capture Saudi-specific genetic associations. While the Axiom PMD Research Array provides a cost-effective method to detect shared variants, it has three key limitations: 1) restricted to pre-designed probes and unable to detect novel variants, 2) covers less than 5% of regulatory regions, and 3) cannot identify structural variants larger than 50 kb [56, 57].

Conclusion

Eleven variants across nine genes, potentially influencing the response to 11 therapeutic drugs, were identified in the studied Saudi cohort, and these findings can inform clinical practice in Saudi Arabia by supporting the development of guidelines for healthcare providers to personalize drug therapy based on genetic profiles.

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Ethics Statement: The study involved humans and was approved by the Institutional Review Board (IRB) Committee (reference protocol number: NRR24/011/12) at King Abdullah International Medical Research Center (KAIMRC). The study was conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

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