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Pharmacogenomic Landscape of South Korea: Implications for Tailored Medical Treatments

José Almeida[1], Paulo Santos[1], Ricardo Neves[1]*, Bruno Costa[1]

[1]Department of Pharmacognosy, Faculty of Pharmacy, University of Porto, Porto, Portugal.

***E-mail** ✉ ricardo.neves.pg@outlook.com

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ABSTRACT

Adverse drug reactions (ADRs) continue to challenge healthcare systems worldwide, largely due to genetic differences in drug-metabolizing enzymes across populations. To address this, we conducted a comprehensive pharmacogenomic (PGx) survey of the South Korean (SKR) population, focusing on 21 clinically relevant pharmacogenes. Whole genome sequencing (WGS) was performed on 396 individuals, including healthy volunteers (n = 99), patients with chronic diseases (n = 95), and cancer patients with colon (n = 81), breast (n = 81), or gastric cancer (n = 40), aiming to establish genotype-informed drug dosing guidelines. High-throughput genotyping (HTG) of CYP2D6, along with comparisons to the 1,000 Genomes Project (1 KG) and the US National Marrow Donor Program (NMDP), revealed substantial variability in genes such as CYP2B6, CYP2C19, CYP4F2, NUDT15, and CYP2D6. For instance, intermediate metabolizer status for CYP2B6 was observed in 3.28% of SKR participants, resembling rates in Europeans (5.77%) and East Asians (5.36%), yet diverging significantly from other populations globally ($p < 0.01$). Nearly half of the SKR cohort (48.74%) were intermediate metabolizers for CYP2C19, with the *35 allele (2.02%) being uniquely present in SKR. The high-risk CYP4F2 *3 allele was considerably more prevalent in SKR (34.72%) compared to other East Asian groups ($p < 0.01$). NUDT15 poor metabolizers were identified in 0.76% of SKR individuals, similar to other East Asian populations (1.59%), whereas TPMT poor metabolizers were rare, mainly found in Europeans and Africans, with a single case in SKR. Notable differences were also detected in CYP2D6 variants rs1065852 and rs1135840.Among 72 drugs evaluated, the vast majority of patients (93.43%, n = 370) required at least one dosage adjustment, averaging 4.5 medications per individual, and 31.31% (n = 124) needed adjustments for more than five drugs. These findings underscore the high degree of pharmacogenetic diversity in SKR and highlight the critical importance of integrating population-specific PGx information into clinical practice to improve drug safety and therapeutic outcomes. This extensive profiling lays the groundwork for precision medicine in South Korea and offers insights with potential global relevance.

Keywords: PGx profiling, Pharmacogenomics, Pharmacogenetics, South Korean, Drug dosing recommendation

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Introduction

Adverse drug reactions (ADRs) and insufficient therapeutic responses continue to pose major challenges for healthcare systems worldwide [1, 2]. Beyond the direct clinical impact, ADRs substantially increase the costs and resource demands associated with pharmacological treatments [3, 4], and lack of drug efficacy further exacerbates these burdens across multiple diseases and medication classes [5-12]. Pharmacogenomics (PGx) offers a strategic solution, aiming to tailor drug selection and dosing to an individual's genetic profile to reduce ADRs and enhance treatment effectiveness [13, 14]. Genetic differences that influence drug absorption, metabolism, distribution, excretion, and toxicity have been repeatedly shown to significantly affect therapeutic outcomes. However, variations in the prevalence of PGx alleles across populations hinder universal implementation, emphasizing the need for population-specific pharmacogenomic studies [15-19].

Advances in next-generation sequencing (NGS) have enabled large-scale PGx profiling, with many studies employing whole exome sequencing (WES) or targeted NGS panels [15, 20]. Yet, these approaches often fail to capture non-coding genomic regions that may influence drug response [21]. Whole genome sequencing (WGS), by contrast, offers the most comprehensive assessment of pharmacogenes, overcoming the limitations of WES and targeted panels [21].

Over 500 drugs now carry pharmacogenomic information recognized by the US Food and Drug Administration (FDA) [22]. Resources such as the Pharmacogenomics KnowledgeBase [23] and the Clinical Pharmacogenetics Implementation Consortium (CPIC) [24, 25] provide guidance for applying PGx data in clinical practice, often using the star-allele nomenclature system [26]. Nevertheless, the clinical prioritization of drug-gene pairs can vary across populations [27-29], and population-specific dosing strategies—such as CPIC recommendations for warfarin—are increasingly recognized as essential [30]. Despite shared cultural, lifestyle, and phenotypic traits among East Asian groups, including Han Chinese and Japanese populations, genetic evidence supports treating South Koreans as a distinct population in PGx research [31].

The Korean Variant Archive 2 (KOVA2) represents a rich genomic resource with 1,896 WGS and 3,409 WES datasets, totaling 5,305 individuals [32]. However, pharmacogenomic analyses leveraging this dataset remain limited, especially for highly polymorphic genes such as CYP2D6. Here, we supplement prior efforts by employing high-throughput genotyping (HTG) for CYP2D6, providing a more detailed characterization of the pharmacogenomic landscape in the South Korean (SKR) population.

By illuminating population-specific PGx variation, this study aims to inform clinicians and improve drug therapy outcomes, emphasizing the integration of SKR-specific pharmacogenomic data into personalized treatment strategies to achieve safer and more effective care.

Materials and Methods

Study cohort

This investigation, carried out from 2019 to 2021, involved assembling a diverse group of South Korean (SKR) participants from five medical institutions. The cohort included healthy volunteers as well as patients diagnosed with chronic diseases, colon cancer, breast cancer, or gastric cancer. Ethical oversight was provided by the Institutional Review Board at each participating site, and written informed consent was obtained whenever possible (SKKU 2020-03-019-001, 2019-0909-011, 2003-119-1110, 3-2020-0257, B-2006-621-303). Peripheral blood samples were collected from all participants for genomic analyses.

A total of 356 unrelated individuals were recruited prospectively, covering healthy participants and patients with chronic illnesses, colon cancer, or breast cancer, while an additional 40 unrelated participants were included retrospectively **(Figure 1)**. The cohort was curated as part of "The Korean Healthcare Bigdata Showcase Project," coordinated by the Korea Health Industry Development Institute (KHIDI). The study design intentionally targeted a wide spectrum of clinical backgrounds to provide a comprehensive and representative dataset for subsequent pharmacogenomic investigations, ensuring inclusion of both healthy individuals and patients affected by various chronic and malignant conditions.

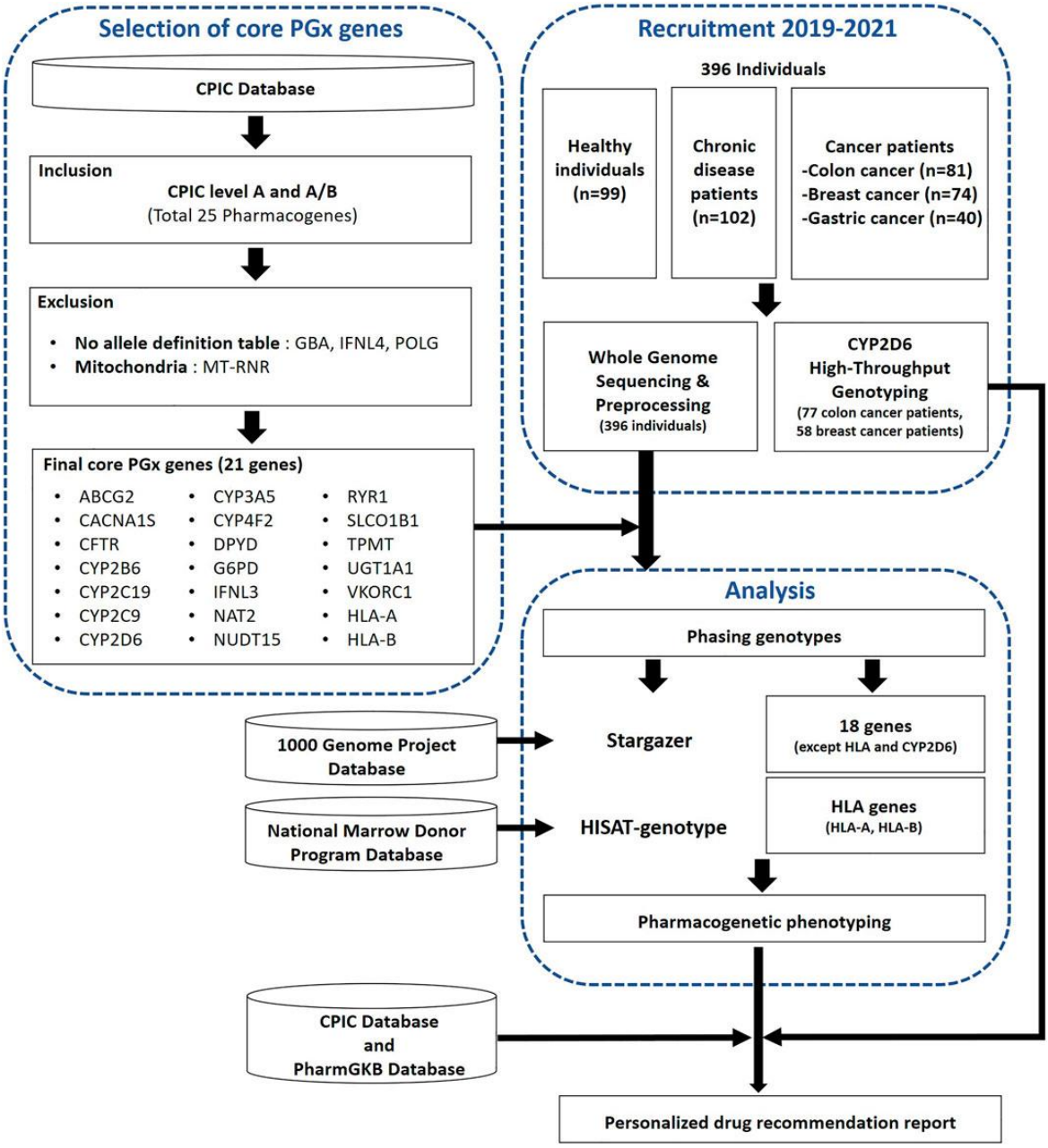


Figure 1. Schematic overview of the workflow used to select core pharmacogenes and characterize pharmacogenomic (PGx) profiles in the study cohort. The process involved whole genome sequencing (WGS) for 396 participants and high-throughput genotyping (HTG) of CYP2D6 in 135 of these individuals. The diagram also illustrates the downstream application of PGx data for generating individualized drug recommendation reports.

Whole genome sequencing (WGS), quality control, and variant identification

Genomic DNA was isolated from peripheral blood using the Exgene Blood SV Mini Kit (GeneAll) according to standard protocols. In brief, 200 µL of blood was mixed with 20 µL of proteinase K and optionally 20 µL of RNase solution (20 mg/mL), followed by brief mixing and a 2-minute room temperature incubation. Lysis buffer BL was added, and samples were incubated at 56°C for 10 minutes. DNA was precipitated with 200 µL of ethanol (96–100%), vortexed, and applied to spin columns to enable binding. Washes with buffers BW and TW removed contaminants, and DNA was eluted in 50–100 µL of buffer AE.

DNA integrity and concentration were assessed via Qubit fluorometry (Invitrogen) and gel electrophoresis. Each sample (100 ng DNA) was fragmented to approximately 350 bp using a Qsonica 800 R2 acoustic shearing instrument. Fragments were ligated to Illumina adapters, PCR-amplified, and final libraries ranging from 500–

600 bp were validated. Library concentrations were determined using the TapeStation 4200 system (Agilent Technologies) and the KAPA Library Quantification Kit (KK4824, Kapa Biosystems).
Sequencing libraries were loaded onto Illumina flow cells for cluster generation and sequenced using 150 bp paired-end reads on an Illumina NovaSeq 6000 platform, following manufacturer guidelines.
Sequence processing included trimming adapters and low-quality reads using Trimmomatic v0.36 [33], discarding reads containing >10% N bases or with >40% of bases below Q20 quality. High-quality reads were aligned to the hg19 reference genome using BWA v0.7.17 [34] with a seed length threshold of 45. PCR duplicates were removed using GATK MarkDuplicates v4.0.11.0 [35], and base quality scores were recalibrated using GATK BaseRecalibrator. Variant calling was performed with GATK HaplotypeCaller v4.0.11.0, and variants were annotated using SnpEff v4.3t [36].

High-throughput genotyping (HTG) for CYP2D6
CYP2D6 genotyping was carried out after adjusting DNA concentrations to 50 ng/μL, with purity ratios (A260/280 and A260/230) confirmed to be between 1.5 and 2 using QuantiFluor® dsDNA (Promega) and NanoDrop ND-2000 (Biotek). HTG utilized 48-subarray plates, each containing 64 through-holes, enabling the simultaneous genotyping of 192 single-nucleotide variants (SNVs) across 16 DNA samples. Fluorescent probes labeled with VIC® and FAM® were used for allelic detection.
For each sample, 2.5 μL of DNA was combined with an equal volume of TaqMan® OpenArray™ Master Mix in a 384-well plate and loaded onto the array via the OpenArray™ AccuFill® system (Applied Biosystems). Plates were sealed and amplified in a QuantStudio 12K Flex Real-time PCR System (Applied Biosystems) for four hours. Genotype calls were determined using TaqMan® Genotyper software (Life Technologies).

Identification of core pharmacogenes
Starting from an initial pool of 25 candidate genes, 21 were ultimately selected as core pharmacogenes based on CPIC Level A and A/B evidence. The GBA and POLG genes were excluded due to incomplete CPIC allele tables, IFNL4 was removed as a polymorphic pseudogene, and MT-RNR was excluded as it is mitochondrial. The finalized core gene panel consisted of ABCG2, CYP2B6, CACNA1S, CFTR, CYP2C19, CYP2C9, CYP2D6, CYP3A5, CYP4F2, DPYD, G6PD, IFNL3, NAT2, NUDT15, RYR1, SLCO1B1, TPMT, UGT1A1, VKORC1, HLA-A, and HLA-B.

Haplotype assignment and phenotype prediction
To generate a comprehensive pharmacogenomic profile, two computational pipelines were utilized. For 18 genes (excluding CYP2D6 and HLA), star-allele calling and phenotype prediction were performed using Stargazer v1.0.8 [37]. Due to the highly polymorphic nature of HLA genes, HLA-A and HLA-B typing in 395 WGS samples was conducted with HISAT-genotype v1.3.2 [38]; one sample was excluded because of insufficient coverage. HISAT-genotype enables accurate HLA typing and DNA fingerprinting directly from standard WGS datasets.

Comparative analysis with global populations
Allelic and phenotypic distributions of 19 core pharmacogenes (excluding HLA) were compared between the SKR cohort and global populations using 1,000 Genomes Project data [39]. To refine comparisons, the East Asian (EAS) group was subdivided into CHS, JPT, CHB, KHV, and CDX populations, reflecting genetic and geographical similarities to SKR. Statistical comparisons of star-allele and phenotype frequencies were conducted using Fisher's exact test.
HLA-A and HLA-B allele frequencies were compared to eight global populations using US NMDP data [40]. Principal component analysis (PCA) of HLA allele frequencies was performed in MATLAB v19b to visualize population-specific clustering and genetic differentiation.

Drug distribution and pharmacogenomic recommendations
Drug recommendations were evaluated according to CPIC guidelines, focusing on medications requiring dose adjustments or avoidance. Each drug was categorized into one of five classes: "Standard" (no change), "Up" (dose increase), "Down" (dose decrease), "Alternative" (avoid with alternative options), and "Consider implications" (requires careful evaluation).

Medications were grouped into therapeutic classes, including volatile anesthetics (desflurane, sevoflurane), proton pump inhibitors (omeprazole, pantoprazole), and NSAIDs (celecoxib, ibuprofen). Special attention was given to drugs requiring pediatric dose modifications. Phenotypes labeled as "Indeterminate" were handled using standard approaches, with results presented accordingly.

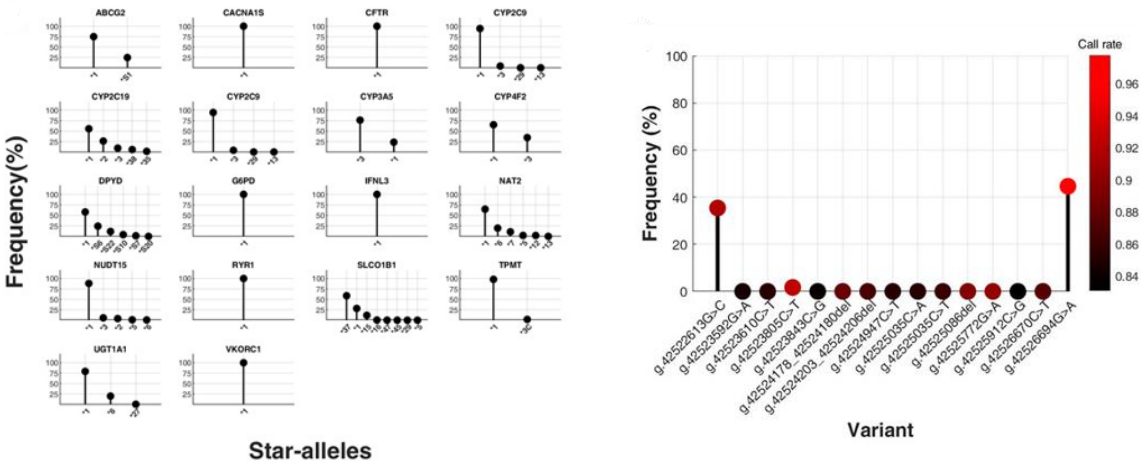
Variants in G6PD influenced the dosing of 35 medications according to the 2022 CPIC guidelines [41]. Warfarin, which requires a specific dosing algorithm, was excluded [30]. Thiopurines (mercaptopurine, azathioprine, thioguanine) required gene-specific adjustments [42]. Phenytoin doses were guided by CYP2C9 diplotypes, particularly for loading doses [43]. Adult-specific dosing guidance was applied for voriconazole and clopidogrel [44, 45].

Results and Discussion

Population-wide star-allele distributions

The study workflow encompassed the identification of core pharmacogenes followed by comprehensive genotyping and phenotype analyses **(Figure 1)**. Within the cohort of 396 SKR individuals, we examined star-allele frequencies for all core pharmacogenes, with the exception of CYP2D6 and HLA genes. As shown in **Figure 2a**, several genes—including CACNA1S, CFTR, G6PD, IFNL3, RYR1, and VKORC1—displayed a single reference star-allele at 100% frequency, reflecting remarkable genetic uniformity in these loci among the SKR population.

Conversely, genes such as CYP2B6, CYP2C9, and NUDT15 exhibited multiple star-alleles with comparatively lower frequencies, indicating notable genetic variability. Among these, DPYD, NAT2, and SLCO1B1 showed particularly heterogeneous allele patterns, with DPYD presenting six distinct alleles and SLCO1B1 encompassing eight, underscoring the extensive pharmacogenomic diversity present in the SKR cohort.



a) b)

Figure 2. Characterization of star-allele and variant frequencies across core pharmacogenes, excluding HLA genes, among South Korean individuals. (a) Star-allele distributions for core pharmacogenes, with CYP2D6 and HLA genes excluded, in 396 SKR participants. The x-axis displays the individual star-alleles for each gene, while the y-axis represents their corresponding frequency as a percentage of the cohort. (b) Distribution of CYP2D6 variants in a subset of 135 SKR individuals, with variant types indicated along the x-axis and frequencies (%) along the y-axis. Dot colors correspond to variant call rates, ranging from black (0.83) to red (0.98).

High-throughput genotyping (HTG) using the OpenArray platform was performed on 135 individuals to examine 15 CYP2D6 variants, including frameshift deletions, intronic, and missense mutations. The overall call rate averaged 93.0%, with a maximum of 97.79% and a minimum of 83.09%. Analysis revealed that, except for three of the 15 variants, all remaining loci were predominantly wild-type across participants **(Figure 2b)**.

We further compared SKR star-allele frequencies with global populations from the 1,000 Genomes Project, highlighting unique patterns in core pharmacogenes outside of CYP2D6 and HLA. Phenotype predictions based

on these star-alleles demonstrated considerable differences between SKR and global populations, including subgroups within East Asians (EAS) **(Figure 3)**. While SKR generally aligned most closely with the EAS group, notable pharmacogenomic distinctions were observed in CYP2B6, CYP2C19, CYP4F2, NUDT15, and TPMT, indicating a population-specific genetic architecture.

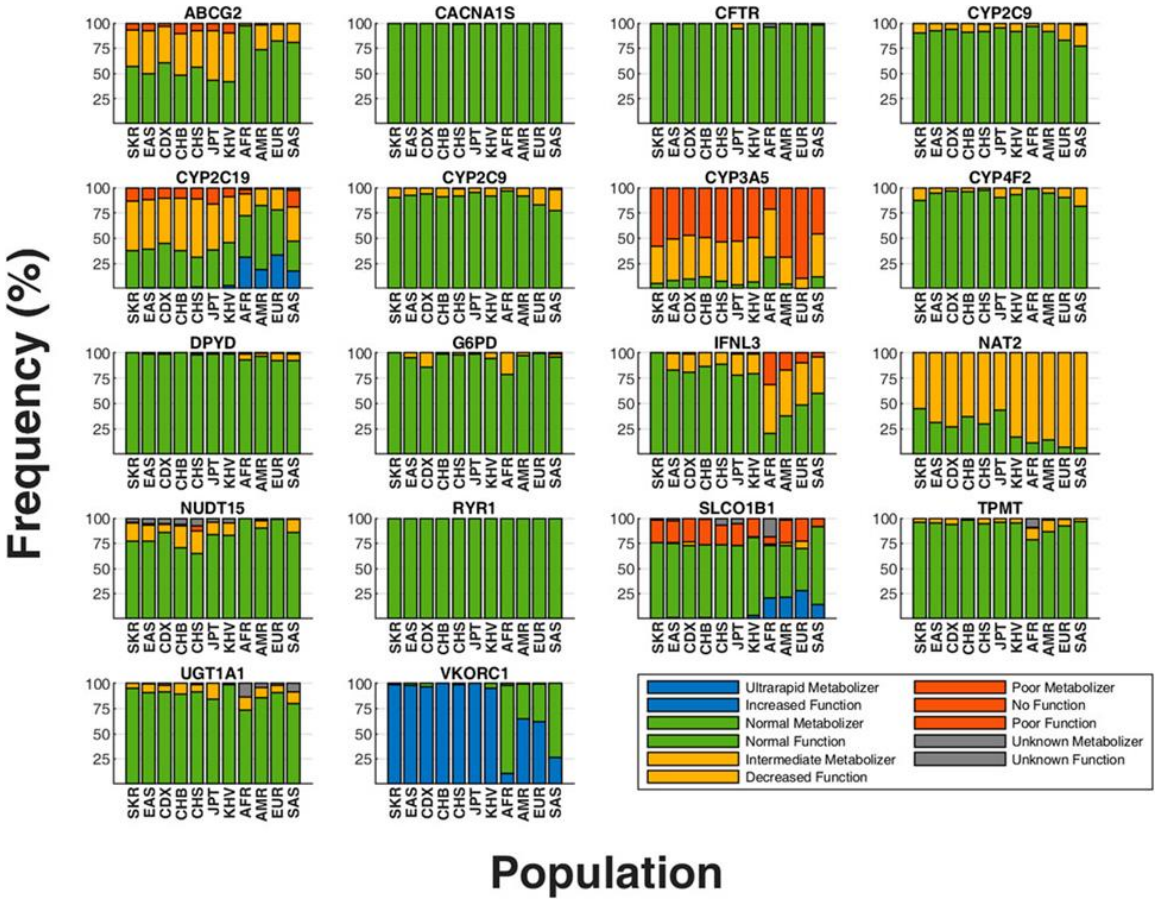


Figure 3. Comparison of predicted phenotype frequencies for core pharmacogenes (excluding CYP2D6 and HLA) between the SKR cohort and populations from the 1,000 Genomes Project. The x-axis denotes population groups, while the y-axis indicates the proportion of predicted phenotypes. Distinct colors correspond to different phenotypic classes. Population abbreviations: SKR, South Korean (this study); AFR, African; AMR, Admixed American; SAS, South Asian; EUR, European; EAS, East Asian; CHS, Southern Han Chinese; JPT, Japanese; CHB, Han Chinese; KHV, Kinh Vietnamese; CDX, Dai Chinese.

Analysis of CYP2B6 intermediate metabolizers revealed that 3.28% of the SKR population carried this phenotype, a frequency comparable to Europeans (5.77%) and EAS (5.36%) but significantly lower than AMR (17.86%), SAS (15.13%), and AFR (27.84%) ($p < 0.01$). Using Stargazer definitions [46], the *9/*9 diplotype was classified as intermediate metabolizer, reflecting close alignment with EAS populations, though notable variation exists within subgroups, with CHB at 2.91%, JPT at 7.69%, and CDX at 13.98% ($p < 0.01$). Ultrarapid metabolizers were observed in all major populations except SKR.

For CYP2C19, 48.74% of SKR individuals were intermediate metabolizers, similar to the broader EAS group (48.81%), but substantially higher than AMR (16.43%). Poor metabolizers accounted for 13.64% of SKR, slightly exceeding EAS (11.71%) and CHB (10.68%), yet lower than JPT (16.35%). The *2 allele frequency in SKR (26.39%) was lower than in other EAS populations (31.25%), and the *35 allele, absent in other EAS groups, was observed in SKR at 2.02%, highlighting unique genetic features. Clinically, these phenotypes influence drug prescriptions, with certain medications contraindicated for intermediate and poor metabolizers [44-49].

CYP4F2's high-risk *3 allele, associated with reduced enzymatic activity [50], showed a frequency of 34.72% in SKR, surpassing JPT (23.08%), CHB (21.84%), and the broader EAS group (21.43%) ($p < 0.01$). NUDT15 poor metabolizers were predominantly found in EAS, including SKR (0.76%), with very low prevalence in AMR

(0.58%) and absent in other global populations [50]. TPMT poor metabolizers were mainly observed in EUR and AFR; SKR had only one individual exhibiting this phenotype [42], emphasizing the population-specific distribution of pharmacogenomic traits.

HTG of 15 CYP2D6 variants in 135 SKR participants provided insight into inter-population allele variation. The intronic variant g.42523805C>T (rs28371725) displayed regional diversity: SKR 1.68%, CHB 3.40%, and JPT 0.48%, reflecting substantial heterogeneity among East Asian populations. Missense variants g.42526694G>A (rs1065852) and g.42522613G>C (rs1135840) were enriched in SKR at 44.64% and 35.42%, respectively, compared to JPT (36.06% and 34.18%) but lower than CHB (60.19% and 71.26%). Globally, rs1065852 and rs1135840 were most frequent in EAS (57.14% and 64.01%). Given CYP2D6's central role in hydroxylation and demethylation of clinically relevant drugs [51], these findings underscore the importance of population-specific pharmacogenomic profiling, with rs1065852 identified as the predominant CYP2D6 allele in SKR **(Figure 2b).**

HLA allele frequencies: SKR versus global populations based on NMDP data

Given the extreme variability of HLA genes, HLA-A and HLA-B typing was performed on 395 SKR WGS samples using HISAT-genotypes [38], with one sample excluded due to insufficient coverage in the HLA loci. Analysis revealed several alleles with notable prevalence: six HLA-A and five HLA-B alleles were found in more than 5% of individuals, and four HLA-A alleles were present in over 10% of the cohort. Conversely, a substantial number of alleles—42 for HLA-A and 44 for HLA-B—were detected at very low frequencies (<1%). The most frequently observed diplotypes in SKR were A31:01:A33:03 (7.59%) for HLA-A and B35:01:B35:01 (4.56%) for HLA-B, highlighting a mix of common and rare alleles within this population **(Figure 4)**.

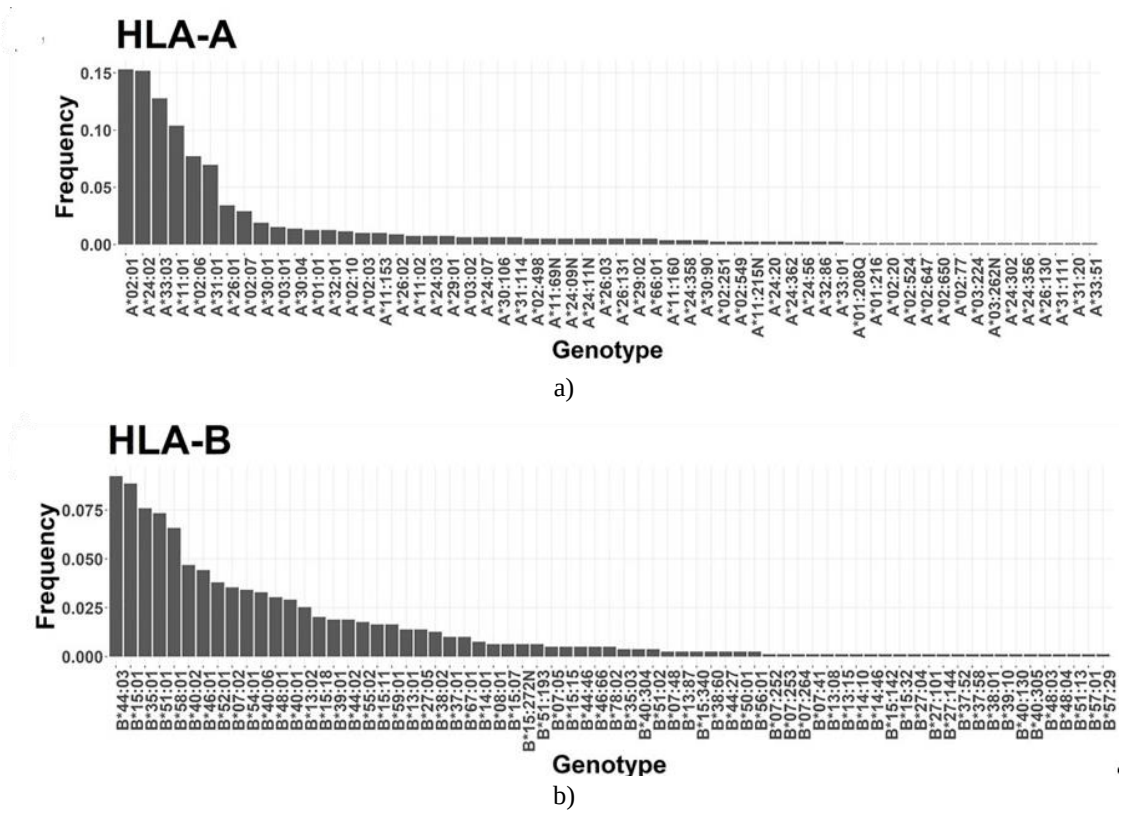


Figure 4. Frequency distribution of HLA-A and HLA-B alleles in the SKR population. Allele frequencies are displayed in descending order, with the most common alleles placed on the left side of the graph for (a) HLA-A and (b) HLA-B.

HLA-A*02:01 was found to be relatively common in the SKR population, with a frequency of 15.32%. Similar prevalence was observed in Korean (KORI) (18.57%) and Japanese (JAPI) (14.80%) populations [40], whereas it was less frequent in the Chinese (NCHI) population (9.46%), despite all being categorized as EAS. In contrast, this allele occurred at substantially lower frequencies among other Asian groups, including South Asians (AINDI, 4.92%) and other Southeast Asians (SCSEAI, 5.78%). Other HLA-A alleles in SKR with frequencies above 10%

included A*24:02 (15.19%), A*33:03 (12.79%), and A*11:01 (10.38%). Notably, A24:02 was significantly more common in JAPI (35.30%), and A11:01 was more frequent in NCHI (27.51%) compared to SKR.
Within the HLA-B locus, B*44:03 emerged as the most frequent allele in SKR (9.24%), closely matched by KORI (8.50%). Frequencies were somewhat lower in JAPI (6.05%) and markedly lower in NCHI (1.41%).
To assess variation in star-allele frequencies across nine populations, including SKR, principal component analysis (PCA) was performed **(Figure 5)**. The first three principal components explained 45.03%, 21.72%, and 16.10% of the total variation, respectively. The first component primarily distinguished populations at the continental level, while the second component effectively separated EAS populations. Notably, the PCA indicated a strong genetic similarity between SKR and the NMDP SCSEAI and JAPI populations. These results closely aligned with KORI, supporting the consistency of our findings with established data. Despite being classified under EAS, SKR showed some differences compared to JAPI and NCHI, emphasizing the importance of population-specific pharmacogenomic profiling.

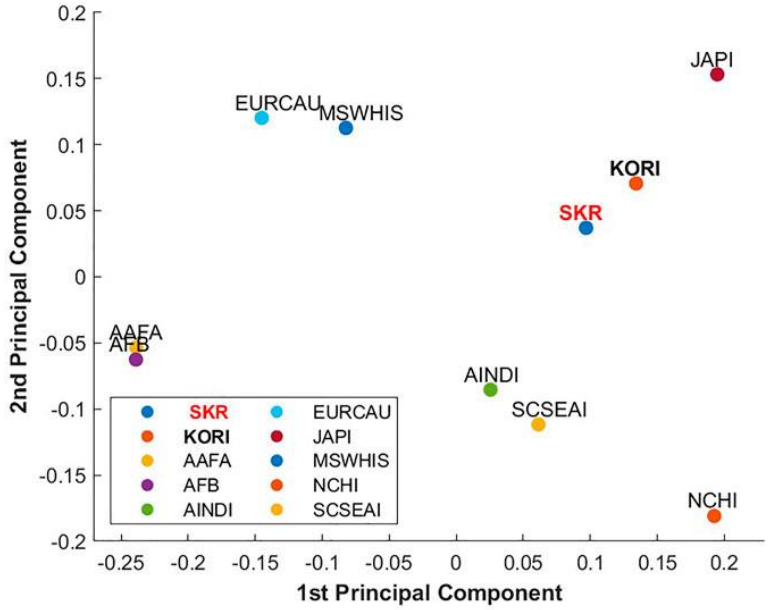


Figure 5. PCA of HLA-A and HLA-B Star-Alleles across SKR and NMDP Groups. The plot depicts the first two principal components derived from star-allele frequencies, comparing the SKR cohort (South Koreans residing in South Korea) with populations from the National Marrow Donor Program (NMDP). Population abbreviations are as follows: SKR, South Korean study group; KORI, Korean reference; JAPI, Japanese; NCHI, Chinese; AAFA, African American; AFB, African; AINDI, South Asian Indian; EURCAU, European Caucasian; SCSEAI, Other Southeast Asian; MSWHIS, Mexican or Chicano.

Distribution analysis of pharmacogene-linked phenotypes and drug guidelines
We investigated prescription guidance for 21 core pharmacogenes, applying Level A and A/B guideline recommendations with a focus on phenotype-driven decision-making. **Figure 6a** provides a broad overview of the drug-gene associations analyzed, excluding CYP2D6, and organizes the data according to drug categories alongside their corresponding guideline recommendations.

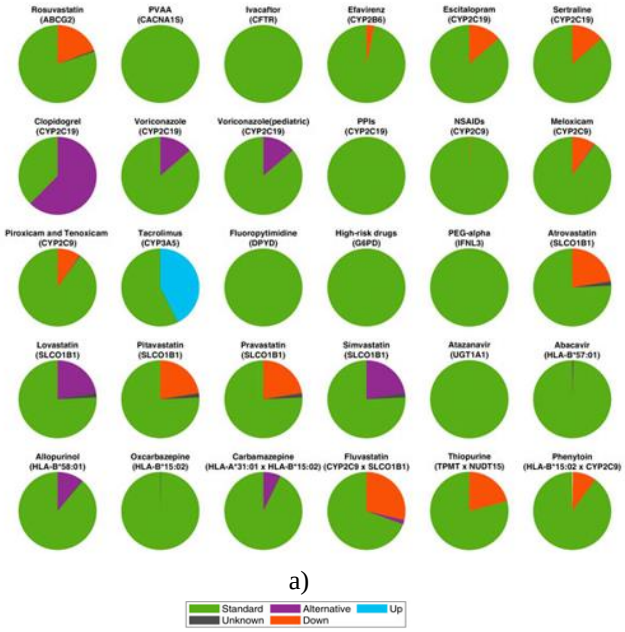


Figure 6. Personalized Medication Dosing Recommendations in the SKR Cohort. (a) Among 396 individuals in the SKR population, drug dosing recommendations were categorized as: "Standard" (no dose modification), "Down" (dose reduction), "Alternative" (drug avoidance with suggested alternatives), "Up" (dose increase), and "Unknown" (undetermined dosing for specific phenotypes). (b) The frequency of recommended dose adjustments per individual is shown according to CPIC guidelines, with the x-axis indicating the number of medications requiring modification and the y-axis representing the percentage of individuals corresponding to each count.

Several medications exhibited notable genetic influences requiring dose modification. Clopidogrel, widely prescribed for cardiovascular and neurovascular disease prevention, was contraindicated in 62.4% (n = 247) of SKR individuals due to CYP2C19 phenotypes [52]. Enfuvirtide, an antiretroviral for AIDS, required dosage changes in 34.8% (n = 138), including 3.2% (n = 13) needing a reduced dose of 200 mg/day [53]. Tacrolimus, crucial for post-transplant immunosuppression, demanded dose increases in 42.4% (n = 168) of participants [54]. For statins targeting LDL cholesterol, 22.5% (n = 90) of the cohort should avoid lovastatin or simvastatin, indicating alternative lipid-lowering therapy is necessary [55]. Regarding HLA-B-associated drugs, 10.9% (n = 43) of HLA-B58:01 carriers should avoid allopurinol, while abacavir was contraindicated in one individual (0.3%) carrying HLA-B57:01 [56, 57].

Overall, 72 drugs with multi-gene influences were examined **(Figure 6a)**, revealing that 93.43% (n = 370) of patients required dose modification for at least one medication, with an average of 4.5 drugs per individual **(Figure 6b)**. Notably, 31.31% (n = 124) needed adjustments for more than five medications, with the maximum reaching 15 drugs.

The rise of personalized medicine is transforming drug prescription practices by emphasizing the role of genetic testing in identifying individual metabolic differences [58]. In this study, WGS and targeted HTG were used to characterize 20 key pharmacogenes, including HLA genes and CYP2D6, in the SKR population [59]. Given the high polymorphism of CYP2D6, HTG was employed for 15 specific variants to achieve accurate genotyping, addressing the limitations of WGS in regions with repetitive sequences, high GC content, structural complexity, and large duplications, as seen in HLA genes [60].

Our results underscore the importance of genotype-guided dosing to reduce the risk of adverse drug reactions. While this study provides a summary of potential risks, individual evaluation of drug efficacy and safety remains essential, highlighting the need for additional research into the functional impact of these variants. SKR individuals displayed unique PGx characteristics compared to other EAS populations (e.g., CHB, JPT); **(Figure 3)**, including elevated frequencies of star-alleles such as CYP2C193 and CYP2C1935, which affect metabolizer status and necessitate careful dose considerations. Conversely, the low prevalence of CYP2B6*9 suggests standard Efavirenz dosing may be appropriate for most SKR, an important consideration in HIV therapy [61]. Comparisons of star-allele frequencies, supported by HLA PCA results **(Figure 5)**, validated the precision of our PGx profiling relative to KORI. These findings reinforce the value of population-specific pharmacogenomic research for tailoring drug therapy to the genetic background of SKR individuals.

This study provides a comprehensive exploration of pharmacogenomic (PGx) characteristics in the SKR population, offering novel insights that may inform future strategies for personalized medicine. By analyzing genotype distributions alongside phenotype-driven drug recommendations, we found that a large proportion of the SKR cohort requires tailored medication regimens. Among the 396 participants, 370 individuals (93.43%) were identified as needing adjustments for one or more drugs **(Figure 6b)**, underscoring the clinical relevance of population-specific PGx profiling. These findings demonstrate the potential utility of generating personalized PGx reports for SKR individuals, which could guide healthcare providers and patients in making informed therapeutic decisions, potentially streamlining treatment and improving cost-effectiveness. Future advancements in sequencing technologies, particularly long-read and cost-efficient methods, are expected to enhance genotyping accuracy for highly polymorphic pharmacogenes such as CYP2D6, enabling deeper insights into PGx variation.

Several limitations of this study warrant consideration. First, although we collected WGS data from 396 South Korean participants—a challenging task due to privacy regulations, consent barriers, and high sequencing costs—a larger cohort will be required to more accurately represent the national population. Second, this study did not integrate other PGx resources, such as PharmGKB and the Dutch Pharmacogenetics Working Group (DPWG), which use different genotype-to-phenotype mapping criteria compared to CPIC, complicating cross-database harmonization. Nonetheless, the genes designated as CPIC Level A or A/B are supported by high to moderate evidence levels in PharmGKB and DPWG [62]. Future work will aim to combine data from CPIC, PharmGKB, and DPWG for more comprehensive analyses. Third, rare variants—recognized as contributors to missing heritability in drug response—were not included in this study due to the complexity of their analysis, which requires a dedicated study design. Incorporating rare variant data represents an important avenue for subsequent research [63-66].

Conclusion

In summary, this investigation represents a pioneering effort in WGS-based PGx profiling of the SKR population, demonstrating accurate genotyping for highly polymorphic genes such as CYP2D6 using targeted HTG. Comparative analyses with global populations and among East Asian subgroups revealed notable differences, highlighting the critical need for population-specific PGx assessments to guide precision medicine initiatives.

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Conflict of Interest: None

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Ethics Statement: The studies involving humans were approved by Institutional Review Board of Kangbuk Samsung hospital, Gangnam Severance Hospital, Seoul National University Hospital, Seoul National University Bundang Hospital. The studies were 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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