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IN-SILICO PHARMACOGENOMIC ANALYSIS OF SLC5A2 AND UGT1A9 VARIANTS RELEVANT TO SGLT2 INHIBITOR RESPONSE IN THE INDIAN DIABETIC POPULATION

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Keywords:

Pharmacogenomics, SGLT2 inhibitors, SLC5A2, UGT1A9, Diabetes mellitus, *In-silico* study, Indian population, Precision medicine

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ABSTRACT: Background: Interindividual variability in response to sodium-glucose cotransporter-2 (*SGLT2*) inhibitors may be influenced by genetic polymorphisms affecting drug transport and metabolism. Variants in the *SLC5A2* and *UGT1A9* genes may influence therapeutic response, pharmacokinetics, and susceptibility to adverse effects associated with *SGLT2* inhibitors. However, population-specific pharmacogenomic data for the Indian population remain limited. **Objective:** To compare allele frequencies of selected *SLC5A2* and *UGT1A9* variants and predict their potential pharmacogenetic implications for *SGLT2* inhibitor response in the Indian population using *in-silico* analysis. **Methods:** This *in-silico* pharmacogenomic study analyzed selected *SLC5A2* variants (rs9934336, rs3813008) and *UGT1A9* variants (rs2741049, rs72551330) using publicly available genomic databases including IndiGenomes and the 1000 Genomes Project. Functional annotation and pathogenicity prediction were performed using dbSNP, Ensembl, SIFT, PolyPhen-2, Mutation Assessor, and MutationTaster tools. Hardy–Weinberg equilibrium-based genotype simulations were used to estimate potential pharmacodynamic and pharmacokinetic variability associated with SGLT2 inhibitor therapy. All findings represent computational predictions derived from publicly available genomic datasets. **Results:** The Indian population demonstrated distinct allele frequencies for rs9934336 (0.1753), rs3813008 (0.2889), rs2741049 (0.6791), and rs72551330 (0.0019). Compared with East Asian and European populations, Indian individuals showed intermediate allele distribution patterns. HWE-based genotype simulation in an Indian population (n = 1000) suggested variability in predicted transporter expression and metabolic activity associated with SGLT2 inhibitor response. Integrated genotype-based analysis indicated potential variability in predicted pharmacodynamic and pharmacokinetic response patterns among individuals in the Indian population. **Conclusion:** Selected *SLC5A2* and *UGT1A9* polymorphisms may contribute to variability in predicted pharmacodynamic and pharmacokinetic responses to SGLT2 inhibitors. These findings support the potential relevance of population-specific pharmacogenomic profiling for future precision-medicine research in diabetes management. However, clinical validation studies are required to confirm these *in-silico* observations.

INTRODUCTION: Type 2 diabetes mellitus (T2DM) continues to be a major global health burden associated with significant cardiovascular, renal, and metabolic complications [1].

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Among recently developed antidiabetic therapies, sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as highly effective agents because of their glucose-lowering, cardioprotective, and renoprotective effects [2].

These drugs act primarily by inhibiting the sodium-glucose cotransporter-2 protein encoded by the *SLC5A2* gene in the proximal renal tubules, thereby reducing renal glucose reabsorption and promoting glucosuria[3]. Despite their clinical efficacy, substantial interindividual variability exists in

therapeutic response, adverse effects, and tolerability to SGLT2 inhibitors [4]. Increasing pharmacogenomic evidence suggests that genetic polymorphisms in drug transporter and metabolic pathway genes may significantly influence these differences [5]. Variants within *SLC5A2* have been associated with altered transporter expression and functional activity, potentially modifying glucose-lowering response and renal outcomes following SGLT2 inhibitor therapy [6].

Among the important *SLC5A2* polymorphisms, rs9934336 and rs3813008 are regulatory variants that may influence transcriptional activity and transporter expression [6, 7]. Individuals carrying low-expression genotypes may demonstrate enhanced urinary glucose excretion and improved glycemic response to therapy [8]. In addition to transporter-related variability, drug metabolism also contributes to differences in pharmacokinetic response. The *UGT1A9* enzyme plays a major role in the glucuronidation and metabolism of several SGLT2 inhibitors including dapagliflozin and canagliflozin [9].

However, the metabolic contribution of *UGT1A9* differs among individual SGLT2 inhibitors, and currently available pharmacogenomic evidence is more substantial for selected drugs such as dapagliflozin and canagliflozin than for the entire SGLT2 inhibitor class. Therefore, interpretation of *UGT1A9*-related pharmacogenetic variability should be considered drug-specific and exploratory rather than universally applicable to all SGLT2 inhibitors. Functional polymorphisms within *UGT1A9*, such as rs2741049 and rs72551330, may reduce enzymatic activity and alter systemic drug exposure [4]. Reduced metabolic clearance can increase plasma drug concentration, thereby enhancing therapeutic effect but also increasing susceptibility to adverse effects [2]. Recent pharmacogenomic studies have emphasized that combined variations in *SLC5A2* and *UGT1A9* may collectively influence efficacy, safety, and clinical outcomes of SGLT2 inhibitor therapy [5]. Population-based studies further demonstrate marked ethnic variation in the distribution of these pharmacogenetically relevant alleles [7]. However, data regarding Indian population-specific distribution and predicted therapeutic implications remain limited despite the rapidly increasing diabetes burden in India[1]. Therefore, understanding population-specific pharmacogenomic profiles may support the development of genotype-guided precision therapy and optimize individualized diabetes management.

Accordingly, this study aimed to:

1. Compare allele frequencies of selected *SLC5A2* and *UGT1A9* variants between Indian and global populations using publicly available genomic datasets.
2. Evaluate the potential functional relevance of these variants using established *in-silico* prediction tools.
3. Predict possible pharmacogenetic implications of these variants in relation to SGLT2 inhibitor pharmacodynamics and pharmacokinetics.

METHODOLOGY:

Data Sources: This study was conducted as an in-silico pharmacogenomic analysis using publicly available genomic and pharmacogenetic databases. Allele-frequency data for selected *SLC5A2* and *UGT1A9* variants were obtained from the IndiGenomes database and the 1000 Genomes Project Phase 3 dataset. Data extraction and analysis were performed between January and March 2026.

The IndiGenomes database contains whole-genome sequencing data from 1029 Indian individuals representing diverse ethnic and geographic populations across India. Global population frequency data were obtained from the 1000 Genomes Project Phase 3 release, including East Asian (EAS), South Asian (SAS), and European (EUR) population groups.

Variant annotation, chromosomal localization, and genomic validation were performed using dbSNP Build 155 and Ensembl Genome Browser Release 111 mapped to the GRCh38/hg38 human reference genome. Functional prediction tools including SIFT, PolyPhen-2, Mutation Assessor, and MutationTaster were accessed through their publicly available web servers during the study period. Allele-frequency data were manually extracted using rsID-based queries from the respective genomic databases.

Alternate allele frequencies reported by the databases were directly recorded for comparative analysis across populations. Since only publicly available secondary genomic datasets and computational prediction tools were utilized, institutional ethical approval was not required.

Allele Frequency Definition: Allele frequencies reported in this study represent alternate allele frequencies (AAF) as provided by the source databases. For each rsID, the reference allele and alternate allele were identified according to dbSNP Build 155 annotations mapped to the GRCh38/hg38 reference genome. The alternate allele frequency obtained from IndiGenomes and the 1000 Genomes Project was used for interpopulation comparison.

Functional interpretation of genotype categories was based on previously published pharmacogenomic evidence regarding predicted effects on transporter expression, transcriptional regulation, or metabolic activity. Since the alternate allele does not necessarily correspond to the minor allele or functional-risk allele in every population, genotype-effect assignments were interpreted cautiously and presented as hypothesis-generating computational predictions rather than clinically validated classifications.

Allele Coding and Functional Interpretation: Reference alleles and alternate alleles for all selected variants were identified according to dbSNP Build 155 annotations mapped to the GRCh38/hg38 reference genome. Because alternate allele frequency (AAF) rather than minor allele frequency (MAF) was used for population comparison, the alternate allele was not automatically assumed to represent the functional-risk allele in every population.

Functional interpretation of genotype categories was therefore based on previously published pharmacogenomic and regulatory evidence rather than allele frequency alone.

For SLC5A2 variants, genotype-effect direction was interpreted according to reported associations with altered transporter expression and glucosuric response patterns. For UGT1A9 variants, interpretation was based on reported effects on glucuronidation activity and predicted metabolic capacity. Since available evidence regarding functional direction remains limited and partially inconsistent across studies, genotype classifications such as “predicted lower expression,” “predicted higher expression,” or “predicted reduced metabolic activity” were used as exploratory computational descriptors rather than clinically validated functional phenotypes.

Variant Selection:

Variants were selected based on the following criteria:

- Availability of allele frequency data in Indian and global genomic datasets
- Functional relevance to SGLT2 inhibitor pharmacodynamics or pharmacokinetics
- Inclusion of both regulatory and coding polymorphisms associated with therapeutic variability

The final variant panel included:

SLC5A2 Variants:

- rs9934336 (intronic/regulatory variant)
- rs3813008 (promoter regulatory SNP)

UGT1A9 variants

- rs2741049 (promoter regulatory SNP)
- rs72551330 (missense coding variant, these variants were selected based on available literature suggesting potential functional or pharmacogenomic relevance and the availability of population-frequency data in both Indian and global genomic repositories.)

The selected variants were chosen based on previously reported pharmacogenomic relevance involving SGLT2 inhibitor pharmacodynamics or glucuronidation pathways.

The *SLC5A2* variants rs9934336 and rs3813008 have been investigated for their potential influence on renal glucose transporter expression, transcriptional regulation, and variability in glucosuric response following SGLT2 inhibitor therapy. Similarly, the *UGT1A9* variants rs2741049

and rs72551330 were selected because of their reported association with altered glucuronidation activity and possible effects on systemic drug exposure for selected SGLT2 inhibitors, particularly dapagliflozin and canagliflozin. However, the functional and clinical relevance of these variants is not uniformly established across all drugs within the SGLT2 inhibitor class, and available evidence remains limited. Therefore, the present analysis should be interpreted as exploratory and hypothesis-generating rather than clinically definitive.

Functional Prediction Tools: Functional significance of coding variants was evaluated using established in-silico prediction tools:

SIFT (Sorting Intolerant from Tolerant) (v6.2.1):

- Database: UniProt and RefSeq protein sequences
- Output: SIFT score (0–1)
- Threshold: ≤0.05 = deleterious; >0.05 = tolerated

PolyPhen-2 (v2.2.3):

- Models used: HumDiv and HumVar
- Output categories:
  - Probably damaging (>0.85)
  - Possibly damaging (0.15–0.85)
  - Benign (<0.15)

Mutation Assessor:

- Evaluates functional impact based on evolutionary conservation
- Output categories: high, medium, low, or neutral functional impact

Mutation Taster:

- Database: Ensembl Variant Database and RefSeq annotations
- Output: qualitative prediction ("disease causing" or "polymorphism")

Annotation of Regulatory Variants: For intronic and promoter-region variants, direct protein-impact prediction tools are not applicable.

Therefore, functional interpretation was based on published evidence regarding transcriptional regulation, gene expression, transporter activity, enzyme expression, and linkage disequilibrium with functionally relevant variants. Regulatory variants were interpreted according to their predicted influence on SLC5A2 transporter expression or UGT1A9 metabolic activity rather than structural protein alteration.

Functional Interpretation Criteria: Functional interpretation was based on an integrative approach combining computational predictions with existing pharmacogenomic evidence.

For SLC5A2 variants, functional significance was inferred from predicted effects on renal glucose transporter expression and glucosuria. Variants reported in previous literature to influence transporter expression or glucuronidation activity were interpreted cautiously as potential contributors to variability in predicted pharmacodynamic or pharmacokinetic response patterns.

For UGT1A9 variants, interpretation focused on predicted metabolic activity and drug clearance. Reduced UGT1A9 activity was associated with increased systemic exposure to SGLT2 inhibitors, potentially resulting in enhanced therapeutic effect but increased susceptibility to adverse events. Pharmacogenomic interpretations were derived from previously published studies regarding SGLT2 inhibitor pharmacodynamics and pharmacokinetics and are presented as literature-supported trends rather than primary clinical findings.

Population Analysis: Allele frequency data for each selected variant were extracted from IndiGenomes and compared with EAS, SAS, and EUR population frequencies obtained from the 1000 Genomes Project Phase 3 dataset. Expected genotype frequencies were estimated using Hardy–Weinberg equilibrium (HWE) principles based on alternate allele frequencies obtained from the IndiGenomes dataset.

For each variant, allele frequencies were represented as p (reference allele frequency) and q (alternate allele frequency), where $p + q = 1$.

Expected genotype frequencies were calculated using the standard HWE equations: p^2 for homozygous reference genotype frequency, 2pq for heterozygous genotype frequency, and q^2 for homozygous alternate genotype frequency.

Simulated genotype counts were projected for a hypothetical population size of n = 1000 by multiplying calculated genotype frequencies by 1000. Decimal values were rounded to the nearest whole number for descriptive representation in the tables. Allele frequencies used in the calculations were derived directly from alternate allele frequencies reported in the IndiGenomes database.

The HWE-based analysis was performed as a descriptive computational simulation to estimate potential genotype distribution patterns within the Indian population.

Since the calculations were based on aggregated population-level allele-frequency data rather than individual-level genotype datasets, the simulated genotype counts should not be interpreted as observed clinical frequencies. In addition, assumptions of random mating, population equilibrium, absence of selection bias, and independent allele segregation may not fully apply across all population subgroups.

Genotype classifications were defined as follows:

- Homozygous reference genotype
- Heterozygous genotype
- Homozygous alternate genotype

No inferential statistical testing beyond HWE-based estimation was performed. Descriptive interpopulation allele-frequency comparisons were performed across Indian, EAS, SAS, and EUR populations.

Descriptive interpopulation allele-frequency comparisons were performed across Indian, East Asian (EAS), South Asian (SAS), and European (EUR) populations using publicly available aggregated genomic datasets. Since individual-level genotype data were unavailable, formal inferential statistical analysis including confidence intervals, multiple-comparison correction, and population-adjusted association testing was not performed.

Therefore, the findings are presented as exploratory descriptive comparisons intended to identify potential population-level pharmacogenomic variability patterns.

Pharmacogenomic Prediction: Genotype-based predictions of therapeutic response to SGLT2 inhibitors were inferred using integrated pharmacodynamic and pharmacokinetic interpretation.

Predictions were based on:

- Estimated SLC5A2 transporter expression
- Predicted renal glucose reabsorption capacity
- Expected glucosuric response
- Predicted UGT1A9 metabolic activity
- Expected systemic drug exposure and clearance

Combined genotype profiles involving both SLC5A2 and UGT1A9 variants were also evaluated to predict overall therapeutic efficacy, tolerability, and adverse effect susceptibility.

Haplotype Consideration: Although certain *SLC5A2* and *UGT1A9* variants may occur within functionally relevant haplotypes, haplotype frequencies were not computed because individual-level genotype data were unavailable.

Therefore, variants were analyzed independently, and functional interpretations were restricted to known regulatory or pharmacogenomic effects reported in prior literature.

Data Processing: All genotype simulations, allele frequency calculations, and tabulations were performed using Microsoft Excel (Microsoft Office 2021). Functional annotations and pharmacogenomic interpretations were manually integrated with population-frequency data to infer variant-level contributions to therapeutic response variability associated with SGLT2 inhibitors.

RESULT:

TABLE 1: GENOMIC CHARACTERISTICS AND FUNCTIONAL RELEVANCE OF SELECTED VARIANTS

Variant (rsID)	Genomic Region	Variant Type	Effect on Gene Activity	Inference
SLC5A2 rs9934336	Intron	Intronic / regulatory	May influence SLC5A2 gene expression through regulatory mechanisms and linkage with functional variants	Moderately altered SGLT2 expression → mild variability in renal glucose reabsorption and drug response
SLC5A2 rs3813008	Promoter region	Regulatory SNP	Alters transcriptional activity of SLC5A2, affecting transporter expression in renal proximal tubules	Variable transporter expression → altered glucosuria and response to SGLT2 inhibitors
UGT1A9 rs2741049	Promoter region	Regulatory SNP	Decreased transcriptional activity of UGT1A9 leading to reduced enzyme expression	Reduced drug metabolism → increased drug exposure and enhanced pharmacological effect
UGT1A9 rs72551330	Exon (coding region)	Missense variant (Ile → Thr)	Reduced enzymatic activity due to structural protein alteration	Decreased metabolism → increased plasma drug levels and prolonged drug action

Table 1 summarizes the functional relevance of selected *SLC5A2* and *UGT1A9* variants associated with SGLT2 inhibitor response. Regulatory variants in *SLC5A2* were predicted to influence transporter expression and renal glucose reabsorption, thereby affecting glucosuric response. Similarly, *UGT1A9* variants were associated with altered drug metabolism and systemic exposure. Overall, both transporter-related and metabolic polymorphisms may contribute to variability in therapeutic efficacy and safety.

TABLE 2: ALLELE FREQUENCY COMPARISON OF VARIANTS: INDIAN POPULATION VS GLOBAL POPULATION

	rsID	Alleles	India	EAS	SAS	EUR
SLC5A2	rs9934336	G/A	0.1753	0.1151	0.181	0.2545
SLC5A2	rs3813008	G/A	0.2889	0.1865	0.2536	0.1352
UGT1A9	rs2741049	T/C	0.6791	0.4385	0.6912	0.6044
UGT1A9	rs72551330	T/C	0.0019	0	0.002	0.0169

Table 2 demonstrates clear interethnic variation in allele frequencies among Indian, East Asian, South Asian, and European populations. The Indian population showed intermediate frequencies for most variants, particularly rs3813008 and rs2741049, suggesting population-specific pharmacogenomic differences that may influence response to SGLT2 inhibitors. The rs72551330 variant remained rare across all populations.

TABLE 3: FUNCTIONAL ANNOTATION AND PATHOGENICITY PREDICTION

(rsID)	Variant Class	SIFT	Mutation Assessor	Poly Phen-2	Mutation Taster	Interpretation
rs9934336	Intronic / regulatory	N/A	N/A	N/A	N/A	Likely regulatory variant influencing SLC5A2 transcription or splicing; no direct protein structural alteration predicted
rs3813008	Regulatory SNP	N/A	N/A	N/A	N/A	Promoter-region variant potentially altering transcription factor binding and SLC5A2 expression
rs2741049	Regulatory SNP	N/A	N/A	N/A	N/A	Promoter polymorphism associated with altered UGT1A9 transcriptional activity and modified drug metabolism
rs72551330	Missense variant (Ile → Thr)	Tolerated	Low	Benign	Disease Causing	Coding variant showing discordant computational predictions, including tolerated/benign structural effects in some tools and potential functional significance in others. The possible impact on

	UGT1A9 activity and drug clearance therefore requires further experimental and clinical validation.

Table 3 indicates that most analyzed variants primarily exert regulatory effects rather than direct structural protein alterations. Variants such as rs9934336, rs3813008 and rs2741049 were predicted to affect gene transcription and expression, whereas the coding variant rs72551330 demonstrated mixed computational prediction outputs, indicating uncertain functional significance that requires further validation. These findings suggest that altered gene regulation may play a major role in therapeutic variability.

TABLE 4: HWE-BASED SIMULATION OF GENOTYPE DISTRIBUTION AND FUNCTIONAL IMPACT IN AN INDIAN POPULATION (N = 1000)

Variant (rsID)	Genotype	Predicted Functional Classification	Expected Count (n/1000)	Predicted Functional Effect	Exploratory Pharmacogenomic Interpretation
rs9934336 (*SLC5A2*)	GG	Predicted lower expression	680	Potentially reduced transporter activity	Possible increase in glucosuric response pattern
	AG	Predicted intermediate expression	289	Moderately altered transporter activity	Intermediate predicted pharmacodynamic response
	AA	Predicted higher expression	31	Potentially increased transporter expression	Possible lower glucosuric response pattern
rs3813008 (*SLC5A2*)	GG	Predicted lower expression	506	Potentially reduced *SLC5A2* transcription	Possible increase in predicted therapeutic response
	AG	Predicted intermediate expression	411	Moderately altered transcriptional activity	Intermediate predicted response pattern
	AA	Predicted higher expression	83	Potentially increased transporter expression	Possible lower urinary glucose excretion
rs2741049 (*UGT1A9*)	CC	Predicted standard metabolic activity	461	Standard enzyme expression	Predicted standard pharmacokinetic profile
	CT	Predicted intermediate metabolic activity	436	Moderately altered metabolism	Possible mild increase in systemic drug exposure
	TT	Predicted reduced metabolic activity	103	Reduced *UGT1A9* activity	Potential increase in plasma drug exposure
rs72551330 (*UGT1A9*)	TT	Predicted standard metabolic activity	996	Standard enzymatic activity	Predicted standard pharmacokinetic profile
	CT	Predicted intermediate metabolic activity	4	Mild reduction in metabolic activity	Possible mild alteration in systemic exposure
	CC	Predicted reduced metabolic activity	~0	Potentially reduced enzymatic activity	Rare predicted genotype requiring further validation

Table 4 presents the predicted genotype distribution and functional impact of selected variants in an Indian population. Most individuals were predicted to have low or intermediate *SLC5A2* expression and normal/intermediate *UGT1A9* metabolism, indicating generally favorable response to SGLT2 inhibitors. Functional genotype classifications were assigned based on literature-supported pharmacogenomic interpretation and should be considered exploratory computational predictions rather than experimentally validated phenotypes.

TABLE 5: PHARMACOGENOMIC PREDICTION OF CLINICAL OUTCOMES OF SGLT2 INHIBITORS BASED ON GENOTYPE

Variant (rsID)	Predicted Functional Classification (Genotype)	Predicted Pharmacogenomic Response Pattern	Exploratory Clinical Interpretation
rs9934336 (*SLC5A2*)	Predicted lower expression (GG)	Potentially increased glucosuric response	Possible increase in glucose-lowering response pattern

	Predicted intermediate expression (AG)	Intermediate predicted response	Moderate predicted pharmacodynamic variability
	Predicted higher expression (AA)	Potentially lower glucosuric response	Possible reduction in predicted therapeutic response
rs3813008 (*SLC5A2*)	Predicted lower expression (GG)	Potentially increased response pattern	Possible increase in urinary glucose excretion
	Predicted intermediate expression (AG)	Intermediate predicted response	Average predicted glucose-lowering variability
	Predicted higher expression (AA)	Potentially lower response pattern	Possible reduction in glucosuric effect
rs2741049 (*UGT1A9*)	Predicted reduced metabolic activity (TT)	Potential increase in systemic drug exposure	Possible alteration in pharmacokinetic response and tolerability
	Predicted intermediate metabolic activity (CT)	Moderately altered drug exposure	Intermediate predicted pharmacokinetic variability
	Predicted standard metabolic activity (CC)	Predicted standard response profile	Expected pharmacokinetic profile based on current evidence
rs72551330 (*UGT1A9*)	Predicted reduced metabolic activity (CC)	Potential increase in systemic exposure	Rare predicted genotype requiring further validation
	Predicted intermediate metabolic activity (CT)	Mildly altered pharmacokinetic response	Possible moderate alteration in drug exposure
	Predicted standard metabolic activity (TT)	Predicted standard response profile	Expected pharmacokinetic variability within standard range

Table 5 demonstrates the pharmacogenomic influence of genotype on clinical response to SGLT2 inhibitors. Low *SLC5A2* expression genotypes were associated with enhanced glucosuria and greater glucose-lowering effect, while poor *UGT1A9* metabolizers showed increased drug exposure and a higher likelihood of adverse effects. These findings support the clinical relevance of genotype-guided therapy.

TABLE 6: COMBINED EFFECT OF SLC5A2 AND UGT1A9 GENOTYPES ON CLINICAL OUTCOME

SLC5A2 Functional Status	UGT1A9 Functional Status	Predicted Pharmacogenomic Response Pattern	Exploratory Interpretation
Predicted lower expression	Predicted reduced metabolic activity	Potentially increased response pattern	Possible increase in glucosuric effect with altered systemic drug exposure
Predicted lower expression	Predicted standard metabolic activity	Predicted higher response profile	Possible favorable pharmacodynamic response pattern
Predicted higher expression	Predicted standard metabolic activity	Potentially lower response pattern	Possible reduction in predicted glucosuric response
Predicted higher expression	Predicted reduced metabolic activity	Variable predicted response	Altered systemic exposure may partially influence pharmacodynamic variability
Predicted intermediate expression	Predicted intermediate metabolic activity	Intermediate predicted response	Balanced predicted pharmacodynamic and pharmacokinetic variability
Predicted intermediate expression	Predicted standard metabolic activity	Predicted standard response profile	Expected variability within standard predicted range

Table 6 highlights the combined impact of *SLC5A2* and *UGT1A9* genotypes on therapeutic outcome. Individuals with low transporter expression and poor metabolic activity demonstrated the highest predicted therapeutic response but also increased risk of toxicity. In contrast, high transporter expression with normal metabolism was associated with reduced glucose-lowering efficacy.

TABLE 7: POTENTIAL PHARMACOGENOMIC CONSIDERATIONS FOR FUTURE RESEARCH ON SGLT2 INHIBITOR THERAPY

Genotype Profile	Exploratory Pharmacogenomic Consideration
Predicted lower *SLC5A2* expression genotype	May be associated with altered glucosuric response patterns in selected SGLT2 inhibitors

Predicted higher *SLC5A2* expression genotype	Could demonstrate variability in predicted transporter-response patterns requiring further investigation
Predicted reduced *UGT1A9* metabolic activity genotype	May influence systemic drug exposure in selected SGLT2 inhibitors metabolized through glucuronidation pathways
Predicted intermediate metabolic activity genotype	Could demonstrate intermediate pharmacokinetic variability patterns
Predicted standard metabolic activity genotype	Expected to exhibit pharmacokinetic variability within currently predicted ranges
Predicted lower *SLC5A2* expression + predicted reduced *UGT1A9* metabolic activity	May demonstrate combined pharmacodynamic and pharmacokinetic variability patterns requiring future clinical validation
Predicted higher *SLC5A2* expression + predicted standard *UGT1A9* metabolic activity	Could exhibit comparatively lower predicted glucosuric response patterns in exploratory simulations

Table 7 summarizes exploratory pharmacogenomic considerations derived from *in-silico* analysis of selected SLC5A2 and UGT1A9 variants. These findings represent hypothesis-generating computational predictions and should not be interpreted as direct therapeutic recommendations without prospective clinical and pharmacokinetic validation.

DISCUSSION: This study demonstrates that genetic polymorphisms in SLC5A2 and UGT1A9 may significantly influence therapeutic response to SGLT2 inhibitors through both pharmacodynamic and pharmacokinetic mechanisms [1, 5]. Variants affecting SLC5A2 expression were predicted to alter renal glucose transport efficiency, thereby modifying glucosuric response and glycemic control following SGLT2 inhibitor therapy [6]. The regulatory variants rs9934336 and rs3813008 were associated with altered transporter expression, suggesting that transcriptional modulation may contribute to interindividual variability in treatment efficacy [6, 7]. Individuals carrying low-expression genotypes demonstrated predicted enhanced urinary glucose excretion and greater glucose-lowering response, findings that are consistent with recent pharmacogenomic observations involving SGLT2 inhibitor responsiveness [8].

Similarly, UGT1A9 polymorphisms may influence predicted metabolic clearance of selected SGLT2 inhibitors, particularly agents such as dapagliflozin and canagliflozin for which glucuronidation pathways have been more extensively investigated. The promoter variant rs2741049 was associated with reduced transcriptional activity and increased systemic drug exposure [9]. The rare coding variant rs72551330 demonstrated mixed computational prediction results, with some tools suggesting tolerated or benign effects and others indicating possible functional significance. Therefore, its influence on UGT1A9-mediated metabolism remains uncertain and requires further experimental validation. Such altered metabolism may potentially influence systemic drug exposure and tolerability [2].

Cross-population analysis revealed clear ethnic differences in allele frequencies. The Indian population demonstrated intermediate frequencies for several SLC5A2 and UGT1A9 variants compared with East Asian and European populations, supporting the importance of population-specific pharmacogenomic profiling[7]. These findings highlight the growing relevance of precision medicine approaches in diabetes management, particularly in genetically diverse populations such as India [1]. The combined evaluation of transporter-related and metabolic variants suggests that therapeutic outcome may depend on the interaction between renal glucose transport activity and hepatic drug metabolism 5. Individuals with predicted lower SLC5A2 expression and predicted reduced UGT1A9 metabolic activity may demonstrate altered glucose-lowering response patterns and variability in systemic drug exposure. Such genotype combinations may become relevant in future personalized SGLT2 inhibitor pharmacogenomic research frameworks.

Strengths:

- Integration of pharmacodynamic (SLC5A2) and pharmacokinetic (UGT1A9) pathways.
- Use of cross-population pharmacogenomic comparison.
- Application of multiple *in-silico* functional prediction tools.
- Focus on Indian population pharmacogenomics.

Limitations:

- ❖ Functional effects were computationally predicted using publicly available genomic databases and *in-silico* tools without patient-level clinical validation.
- ❖ Clinical outcomes such as HbA1c reduction, renal outcomes, pharmacokinetic measurements, and adverse-event profiles were not evaluated.
- ❖ Prospective clinical validation and functional experimental studies were not performed.
- ❖ Environmental, lifestyle, and comorbidity-related factors influencing drug response were not included.
- ❖ Functional interpretation of regulatory variants remains exploratory and may vary across populations and biological contexts.
- ❖ Indian subpopulation-specific stratification could not be performed because detailed ancestry-level genotype data were unavailable.
- ❖ Rare variants require further biochemical and clinical validation studies.
- ❖ Formal inferential statistical comparison between populations was limited by the absence of individual-level genotype datasets.

CONCLUSION: This study highlights the potential role of SLC5A2 and UGT1A9 polymorphisms in influencing predicted pharmacodynamic and pharmacokinetic response variability associated with SGLT2 inhibitors. Regulatory variants affecting transporter expression and metabolic activity may contribute to variability in predicted therapeutic response patterns.

The observed pharmacogenomic implications may not apply uniformly across all SGLT2 inhibitors because metabolic pathways and glucuronidation dependence differ among individual agents. Population-specific pharmacogenomic profiling may support future precision-medicine research and individualized diabetes management strategies. However, prospective clinical and functional validation studies are required before these findings can be translated into therapeutic decision-making.

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