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Research Article

A Novel Analysis Technique for Affirming Drug Outcomes in Personalized Medicine

Dhruv Rishab Batra[1] | Dr. Anusha Sunder[2*] |

1. Bioinformatic Expert Data Analyst, Xcode Life Sciences Pvt. Ltd. Chennai, India.
2. Lead Scientist, Nutrigenetic Expert & Senior Data Analyst, Xcode Life Sciences Pvt. Ltd. Chennai, India.

***Corresponding Author:** Dr. Anusha Sunder, Lead Scientist, Nutrigenetic Expert & Senior Data Analyst, Xcode Life Sciences Pvt. Ltd. Chennai, India.

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Abstract: Traditional scoring systems for pharmacogenomic analysis often fail to account for variability amongst genetic markers, erroneously weighting their contributions on the same level. We introduce a novel hierarchical weighted scoring system that integrates ClinPGx Levels of Evidence/LoE (1A to 4) at the variant-gene level (https://www.pharmgkb.org/) and 'Clinical Pharmacogenetics Implementation Consortium' (CPIC) gene-drug grades (A-D) at the drug level to derive actionable suitability scores (https://cpicpgx.org/). Variant genotypes are scored +1 (favourable), -1 (unfavourable), or 0 (intermediate), LoE-weighted, and aggregated to score a gene. This continues at the gene level, with multiple genes aggregating to give a drug suitability score based on the CPIC grade of that drug-gene pair. This scoring model is applied to study the inter-individual suitability of vital drugs for various health conditions. This novel technique accommodates variable contributions at each level of analysis, promising higher accuracy and more actionable results for an end user. While for a medical practitioner, such an analysis technique ensures enhanced clinical utility, duly considering the pooled outcome of contributing gene markers for drug suitability.

Keywords: Level of Evidence/LoE, CPIC grade, drug suitability, genetic variants, pharmacogenomics.

Introduction

Traditional scoring models often treat all genetic variants as equally informative, overlooking the variability in their clinical impact. In genetic terms, variance reflects the extent to which a variant affects a phenotype. For instance, Variant A may drive the manifestation of a phenotype more strongly than Variant B, but unweighted scoring fails to account for this distinction. Weighted scoring leads one to a statistically informed score, which increases a model's confidence by accounting for differential impact. Evidence-based weights evolve data into an interpretable, clinically meaningful representation of underlying biological truth.

Methodology

Assessing drug suitability through this novel pharmacogenomics approach involves two phases, namely scoring at the gene level and scoring at the drug level. Scoring at the gene level, considers the genotype-phenotype associations for a drug based on the LoE in ClinPGx database. This is taken to phase 2, where it is weighted with CPIC grades to score at the drug level. Both the phases are explained in detail below.

Scoring at the gene level

A gene's score represents the cumulative impact of its constituent variants.

Each variant's (baseline) effect can be estimated by aligning a client's genotype for that variant with known genotype-phenotype associations as curated in ClinPGx database. Favourable genotypic concordance is assigned a nominal positive score (+1), an unfavourable concordance is assigned a nominal negative score (-1), and a moderately favourable genotype is assigned an intermediate score (0).

This score is weighted according to the variant's Level of Evidence (LoE), a reflection of the variant's strength and the reliability of its clinical annotation.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) assigns LoEs based on several statistical and clinical criteria [1]. These criteria are quantified and aggregated into a numerical score ranging from 0 to 100, which can fall into one of six categories, refer Table 1.

Table 1: Score ranges based on proposed LoE

Score Range	Proposed LoE
≥80 and supported by guideline/drug label	Level 1A
25-79.9375	Level 1B
8-24.9375 and variant in a Tier 1 VIP	Level 2A
8-24.9375	Level 2B
0-7.9375	Level 3
<0	Level 4

The proposed scoring model assigns weights to each LoE that align with each range's upper limit. Level 4 is assigned a 0.01 weight instead of a null value, reflecting its minimal yet non-negligible impact on the phenotype, as evidenced by empirical clinical research, refer Table 2.

Table 2: Proposed Weight for each LoE

Level of Evidence/LoE	Proposed Weight
1A	1.00
1B	0.8
2A	0.25
2B	0.25
3	0.08
4	0.01

The product of a variant's genotype concordance and its LoE offers a more accurate glance at its true impact on a phenotype.

A favourable genotype modulated by a low LoE imparts a modest positive effect, while the same genotype with a high LoE imparts a more substantial positive effect. Conversely, an unfavourable genotype with a low LoE yields a dampened negative effect, while that genotype with a high LoE can result in a more strongly negative effect on the gene's score.

Scoring at the drug level

Weighted scoring is essential at the drug level, because gene-drug interactions exhibit strong variation in their clinical relevance. Some genes directly affect pharmacokinetics, while others have more transient, peripheral roles.

The impact of a gene-drug interaction can be inferred from CPIC annotations.

At this level, the baseline effect is the percentage gene score derived from the previous calculation, which is then normalized to a continuous scale from -1 to +1. This value is then multiplied by a weight corresponding to the CPIC-assigned grade for that gene-drug interaction, refer Table 3.

Table 3: Proposed weight for each CPIC grade

CPIC Grade	Proposed Weight
A	1
A/B	0.85
B	0.7
B/C	0.35
C	0.01
C/D	0.01
D	0.01

The proposed weights reflect the CPIC's prioritization of grades A and B's higher clinical significance.

Grades C, C/D, and D are each assigned a non-zero weight, reflecting their limited yet non-negligible impact on the phenotype, as evidenced by empirical clinical research.

A favourable genotype with a low grade imparts a modest positive effect, while the same genotype with a high grade imparts a more substantial positive effect.

Conversely, an unfavourable genotype with a low grade yields a dampened negative effect, while that genotype with a high grade can result in a more strongly negative effect on the drug's score.

Thus, the proposed scoring model accounts for clinically and statistically valid factors at each level of analysis.

Results and Discussion

This model can be illustrated by studying the suitability of the beta-blocking agent Metoprolol. It is often prescribed to lower blood pressure by lowering the heart rate and contraction strength by reducing the effect of catecholamines like adrenaline and noradrenaline [3]. Research has shown a link between metoprolol's efficacy and the gene GRK4 (G protein-coupled receptor kinase 4). GRK4 regulates renal and arterial function, and several of its variants are associated with salt-sensitive or salt-resistant responses to medications that help lower blood pressure [4]. The single nucleotide polymorphisms/SNPs, namely rs1024323 [5] and rs1801058 [6] are known to modulate the gene's efficacy and thereby the drug's overall suitability.

Let's say a patient's genotype for these markers are rs1024323-CC and rs1801058-TT. Both of these are reduced function (unfavourable) variants, meaning they should adversely impact the drug's suitability. As per the model, they would receive a nominal negative score of -1. However, both markers' ClinPGX Level of Evidence is 3, which normalizes the actual effect of the "unfavourable" genotypes to 8% of their nominal effect, around -0.08 each.

When aggregated, the gene's score is -0.016 on a scale of -2 to +2, or 49.6%. At the gene level, it has been determined that GRK4 and metoprolol have a CPIC gene-drug pair grade of C [2], indicating a relatively weaker pharmacogenomic relationship between the gene and the drug. According to the proposed scoring model, the gene's score should be further normalized to 1% of its actual effect. Converting 49.6% to a number on a scale from -1 to 1 yields -0.008. 1% of this score is -0.00008, a score that accurately represents the realistic and minimal effect that these 2 markers within this gene have on the drug's overall efficacy.

Thus, we arrive at a result for one gene's contribution to a drug's overall efficacy. Similarly, the genes ADRB1 (beta-1 adrenergic receptor) and ADRA2C (alpha-2C adrenergic receptor) may be scored by this model. Let's say they yield scores of 0.005 and -0.01 respectively. The cumulative score of all 3 genes (in a [-3, 3] range) is -0.00508. Normalizing this to a percentage, we get 49.91% suitability, a moderately favourable result. While other factors such as lifestyle, concurrent medications, and medical history may be evaluated by a physician, the genetic aspect of this drug remains moderately favourable.

Similarly, a plethora of other drugs may be analysed for suitability based on known marker and gene contributions to its efficacy in vivo to comprise a novel, actionable consumer pharmacogenomic report.

Conclusion

For drug septicity and enhanced clinical utility, it is essential to compile the gene marker results, and also score them in the context of gene contributions in a drug pathway. Hence such an approach as ours can conclusively combine pharmacogenomic markers and guide in affirming drug suitability.

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