Identification of Drug Inhibition of UGT Enzymes as a Risk Factor for Drug-Induced Liver Injury

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Background

- Drug-induced liver injury (DILI) can exert a significant burden on human health and the economy.
- Drug metabolism can play a significant role in the induction of DILI.
- With drug development efforts increasingly adopting methods to avoid drug candidates that are liable to cytochrome P450 (CYP) metabolism, non-cytochrome P450 (non-CYP) enzymes are becoming more important in drug pharmacokinetics.
- Associations between DILI risk and CYP enzymes have been investigated[1]. However, there has been no comprehensive study to assess drugs' DILI risks with various non-CYP enzymes.
- In this study, we investigate the associations between drugs' DILI risk and their interactions with 42 non-CYP enzymes as substrates, inducers and/or inhibitors.

Methods

- **Data collection.**
  - DILI classification of 317 drugs (no-DILI-concern, less-DILI-concern or most-DILI-concern) was obtained from the Liver Toxicity Knowledge Base (LTKB) dataset[2].
  - Data on the drugs' interactions with 42 non-CYP enzymes was collected from *in vitro* reports in historical FDA regulatory documents obtained from Elsevier's PharmaPendium database.
  - Daily doses and log P values of the drugs were retrieved from an in-house dataset.
- **Data analysis.**
  - Associations between DILI risk and drug-enzyme interactions were examined using binomial classification with the response variables: high DILI concern (most-DILI-concern) and low DILI concern (no- and less-DILI concern).
  - Different sets of predictor variables examined were type of drug-enzyme interaction, individual enzymes and enzyme families.
  - Multivariate logistic regression was used to identify statistically significant associations with DILI risks. The odds ratios (OR), 95% confidence intervals (95% CI) and statistical significance (*p*-value) were obtained from the logistic regression.
  - R software was used to perform all statistical analyses.

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Table 1. DILI risk and type of interaction with non-CYP enzymes

Non-CYP Enzyme Interaction		DILI Concern: Low	DILI Concern: High	OR (95% CI)	p-Value
Substrate	No	214	75	1.71 (0.65 – 4.36)	0.2620
	Yes	12	16		
Inhibitor	No	217	69	**6.18 (2.58 – 15.87)**	**< 0.0001**
	Yes	9	22		
Inducer #	No	226	88	NA	NA
	Yes	0	3		

Table 2. DILI risk and non-CYP enzyme families

Enzyme family		DILI Concern: Low	DILI Concern: High	OR (95% CI)	p-Value
AKR	No	224	88	2.82 (0.35 – 24.37)	0.3088
	Yes	2	3		
BChE	No	225	91	5.19E-8 (NA – 2.8E70)	0.9848
	Yes	1	0		
CES	No	224	88	5.07 (0.52 – 111.15)	0.1896
	Yes	2	3		
FMO	No	224	89	1.41 (0.13 – 17.11)	0.7702
	Yes	2	2		
GGT	No	226	90	1.18E6 (0.00 – NA)	0.9874
	Yes	0	1		
MAO	No	224	90	0.81 (0.03 – 11.55)	0.8839
	Yes	2	1		
SULT	No	223	87	0.79 (0.10 – 6.06)	0.8241
	Yes	3	4		
UGT	No	214	68	**5.81 (2.60 – 13.74)**	**< 0.0001**
	Yes	12	23		

Table 3a. DILI risk and type of interaction with UGT enzymes

UGT Enzyme Interaction		DILI Concern: Low	DILI Concern: High	OR (95% CI)	p-Value
Substrate	No	221	77	**3.38 (1.02 – 12.03)**	**0.0482**
	Yes	5	14		
Inhibitor	No	218	71	**4.88 (1.89 – 13.30)**	**0.0012**
	Yes	8	20		
Inducer #	No	226	88	NA	NA
	Yes	0	3		

Table 3b. DILI risk and type of interaction with UGT enzymes

UGT Enzyme Interaction		DILI Concern: Low	DILI Concern: High	OR (95% CI)	p-Value
Pure substrates	No	221	82	1.18 (0.16 – 5.65)	0.8472
	Yes	5	9		
Dual substrate-inhibitors	No	225	79	**13.39 (1.64 – 314.64)**	**0.0255**
	Yes	1	12		
Pure inhibitors	No	218	73	**3.21 (1.14 – 9.10)**	**0.0373**
	Yes	8	18		

#Variable excluded from multivariate analyses

Results and Discussion

- A drug has a higher likelihood of having high DILI concern if the drug
  - Is an inhibitor of a non-CYP enzyme (Table 1).
  - Interacts with an enzyme in the UDP-glucuronosyltransferase (UGT) family (Table 2).
  - Is an inhibitor of a UGT enzyme (Table 3a).
  - Is a dual substrate-inhibitor of a UGT enzyme (Table 3b).
    - Pure substrates of UGT enzymes are not associated with high DILI concern.
- Association between drug-UGT interaction and DILI risk cuts across drugs of various pharmacological or therapeutic groups (Figure 1).
- Comparing drug-UGT interaction with the previously published rule-of-two (RO2)[3] as sole predictors of high DILI concern shows that RO2 rule has lower specificity and a higher sensitivity than drug-UGT interaction (Figure 2).
  - However, combining both rules such that a positive prediction is true either for drug-UGT interaction or RO2 improves the overall performance for DILI prediction.

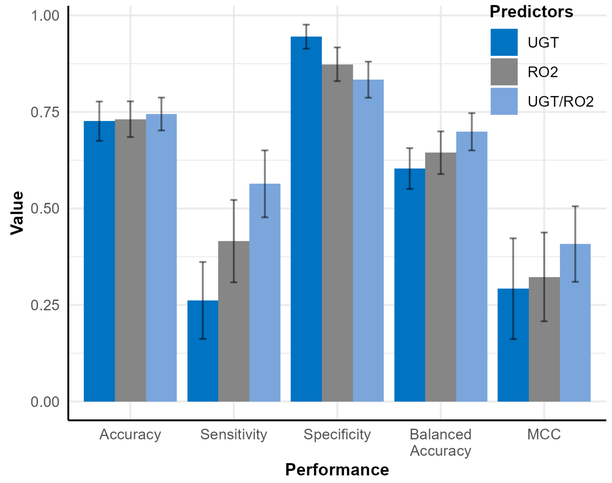


Figure 2. Performance metrics of our predictor (UGT), the previously published rule-of-two (RO2), and a predictor obtained by merging both predictors (UGT/RO2).

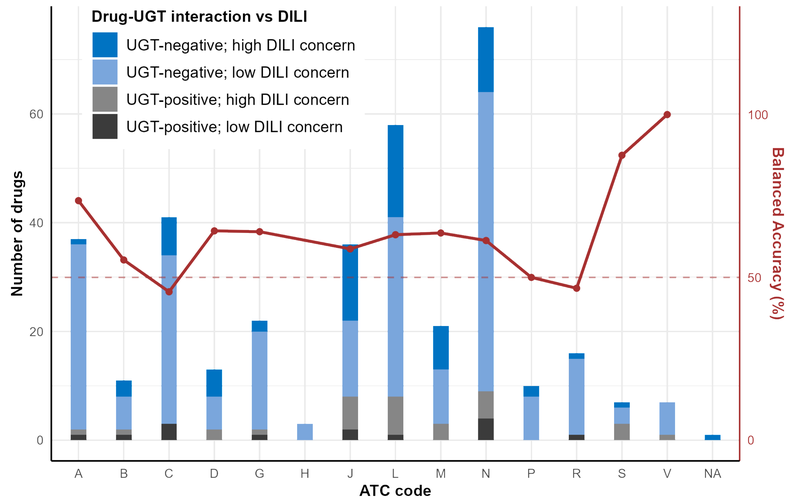


Figure 1. Drug-UGT enzyme interaction as a sole predictor of DILI across the 14 main anatomical/pharmacological groups of the WHO ATC classification system. Balanced accuracy (average of sensitivity and specificity) of the predictor for each group is shown via the line graph.

References

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Conclusions

- A drug acting as dual substrate-inhibitors or pure inhibitors of UGT enzymes increases its likelihood of being associated with severe DILI.
- Drug interaction with UGT enzymes can act as an important predictor of DILI risk.
- Combining drug-UGT interaction and RO2 creates a new DILI predictor that outperforms either predictor.