Development of a machine learning polyvariant risk prediction model for severe cutaneous adverse drug reactions to carbamazepine and other aromatic antiseizure medications

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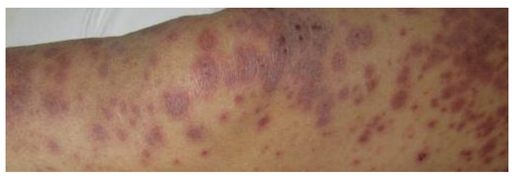
Introduction

- Carbamazepine (CBZ) is effective in epilepsy as well as pain (e.g., trigeminal neuralgia) and bipolar disease.
- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but life-threatening adverse reactions to CBZ treatment.

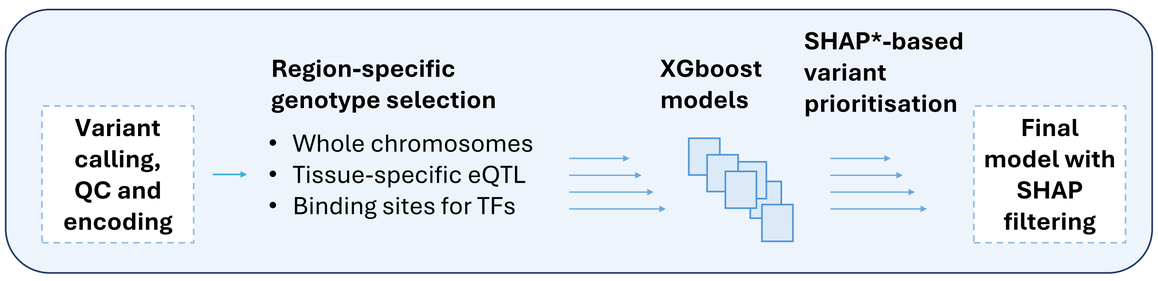


- In Asians, the *HLA-B*15:02* allele is associated with the risk of CBZ-induced SJS/TEN, however, the positive predictive value (PPV) is only 0.07[1], indicating that other genetic variants may modify the risk.

Objective: Identify additional risk-modifying variants.

Methods

Polyvariant risk identification workflow



*SHapley Additive exPlanations

Data: Whole genome data was available from Han Chinese individuals with CBZ-induced SJS/TEN (79 carriers and 33 non- carriers) or CBZ-tolerance (28 carriers, 52 non-carriers).

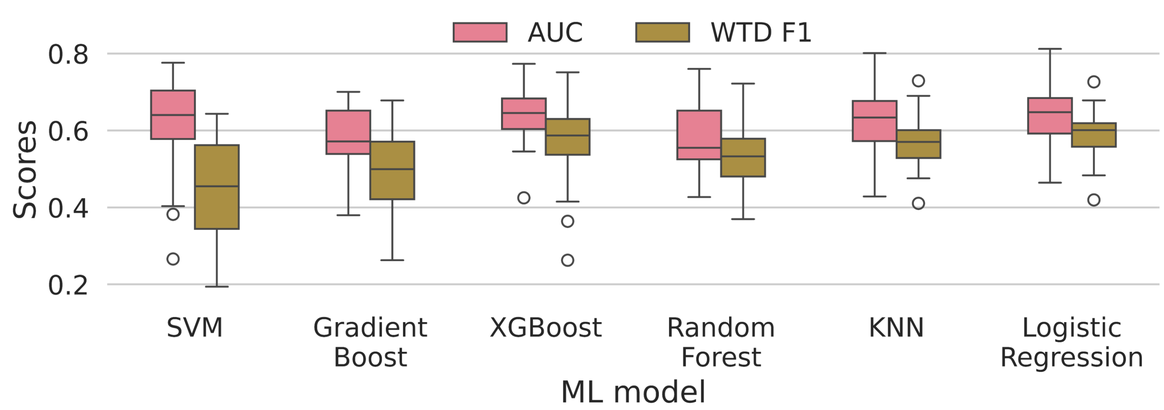
Step 1: Best predictive model for known risk regions
Six machine learning (ML) models were evaluated to determine their capacity to identify the best Area Under the Curve (AUC) and weighted F1 score (WTD F1) for the known risk region (chromosome six, containing *HLA-B*).

Step 2: Systematic screening for additional risk regions
Used the best model to systematically investigate 1,390 regions of the DNA:

- **Whole chromosomes** (to compare with chromosome six)
- **Transcription Factor Binding Sites (TFBSs)**
  - TFs bind to DNA and regulate gene expression, which is modified by genetic variants.
- **Expression Quantitative Trait Loci (eQTL) variants** for 17 tissues
- ***HLA*-regions** (eQTL variants, TFBSs specific to *HLA-B/HLA-A*, coding regions of *HLA-B*/*HLA-A*)

Step 3: Evaluated the performance of putative predictive variants
Compared the estimated PPV from the polyvariant model with that obtained from the *HLA-B*15:02* carrier status

Step 1 results: Best predictive model



XGBoost performed best with a median AUC of 0.71 and a median weighted F1 score of 0.65.

Step 2 results: Top 10 risk modifying regions

Region group	Variants	AUC	WTD F1
TF: ZNF366	38,145	0.73	0.65
TF: JUND	35,020	0.73	0.64
TF loci within 5,000 bp before and after *HLA-B*	344	0.72	0.65
Skin-Not-Sun-Exposed-Suprapubic	950,142	0.72	0.65
TF: BACH2	3,494	0.72	0.63
Colon-Sigmoid	603,214	0.72	0.63
TF: HEYL	2,145	0.71	0.66
Small-Intestine-Terminal-Ileum	300,969	0.71	0.66
Pituitary	508,964	0.71	0.66
Variants within protein-coding region of *HLA-B*	361	0.71	0.65

Step 3 results: Final model

- Identified 465 putative variants.
  - The model increased the PPV from 0.07 to 0.20.
  - The model achieved an AUC of 0.93.
- Risk beyond chromosome six/*HLA* regions
- 115 of 465 variants were classified as highly confident based on SHAP analysis.
  - 60% of these identified in TFBSs
  - Four variants modified the binding of BACH2, which is known for regulating CD8+ T cell differentiation.
  - Three eQTL variants that modify the expression of *HLA-B* also modify the expression of genes associated with skin inflammation.

Limitation: Small sample size, but high number of *HLA-B*15:02* carriers

Conclusion

- Proof of concept of a methodology for detecting polyvariant risk
- By improving the precision of genetic prediction for these potentially life-threatening adverse drug reactions, our model may enable more *HLA-B*15:02* carriers to receive CBZ treatment safely.
- Validation in an independent cohort is warranted.

Acknowledgement

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References

1. Hung, S. I., Chung, W. H. & Chen, Y. T. HLA-B genotyping to detect carbamazepine-induced Stevens Johnson syndrome: implications for personalizing medicine. Per Med 2, 225-237, doi:10.2217/17410541.2.3.225 (2005).
2. SJS image from https://dermnetnz.org/topics/sjs-ten-images licensed under Creative Commons Attribution-NonCommercial-NoDerivs 3.0 (New Zealand)

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