Investigating host dependency factor screening data across hemorrhagic fever and respiratory viruses to identify communalities and differences using machine learning

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Introduction

Since emerging in 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic, but it's not the only viral threat to human health. Influenza A virus (IAV) has shown pandemic potential through past outbreaks, and infections from Dengue and West Nile viruses are rising, including Europe (Logiudice, Jacopo et al. 2025). Besides vaccines, host-directed antivirals (HDA) are promising therapeutic options. While CRISPR/Cas9 or RNA interference (RNAi) screens have been employed in numerous studies to identify relevant host factors (HDF), achieving robust and consistent identification poses a challenge (Edinger et al. 2014; Wagoner et al. 2022). These studies are lacking consistency, making it difficult to interpret the results in a broad-spectrum context. In the present work, host dependency factor screening data from 76 published research articles were analyzed in an integrated approach. A boosted random forest model was employed to detect conserved patterns within each viral group, revealing reveal virus-specific and cross-viral pathways.

Methods/Results

Literature research and feature table construction

Causative agent	#data sets	Viral category
SARS corona virus 2	21	SARS2
Influenza A virus	16	IAV
Denque virus	14	Viral hemorrhagic fever (VHF)
Zika virus	11	
Ebola virus	5	
West Nile virus	4	
Yellow fever virus	4	
Rift valley fever virus	3	

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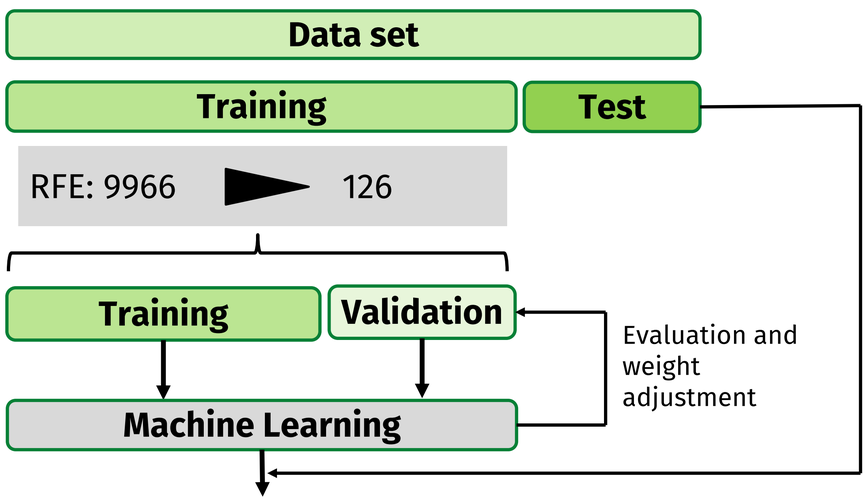
Screen	HDF1	HDF2	HDF3	Gene Set 1	Gene Set 2	Etc.	Label
Screen A	1	0	0	0	1	...	SARS2
Screen B	1	1	1	1	0	...	IAV
Screen C	0	1	1	0	1	...	VHF
Etc.	Etc.	Etc.	Etc.	Etc.	Etc.	Etc.	Etc.

Boosted random forest framework effectively classifies IAV, SARS2 and VHF screens



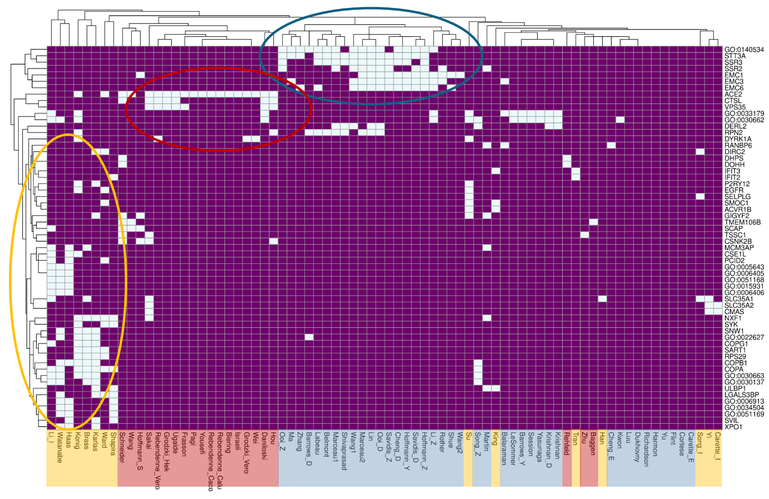
Reference

Prediction	IAV	SARS2	VHF
IAV	8	0	1
SARS2	1	19	0
VHF	6	1	39

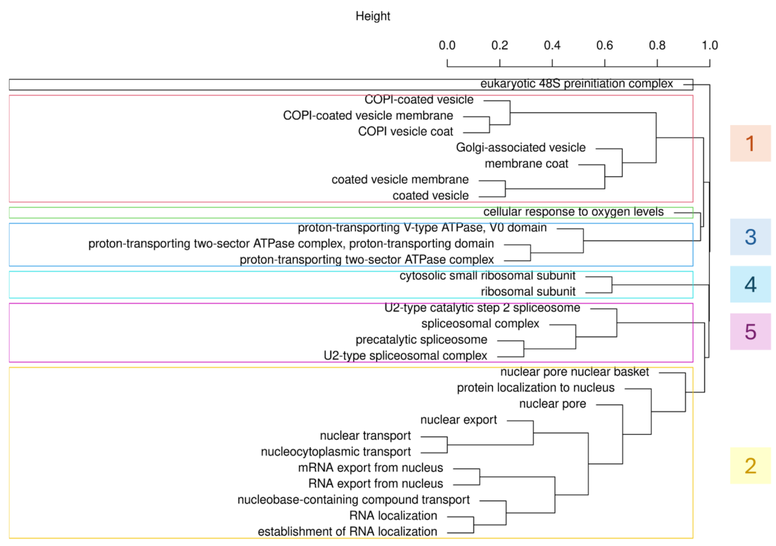
The model achieved a balanced accuracy of 0.88, with class-specific accuracies of 0.76 for IAV, 0.97 for SARS2, and 0.89 for VHF.

Weighted hierarchical clustering of high-impact features reveals virus-specific similarities

The SARS-CoV-2 cluster is primarily characterized by the presence of ACE2. The VHF cluster distincts by its overlap in genes involved in the ER protein-containing complex and the corresponding enriched gene set. Interestingly, the IAV cluster is predominantly defined by diverse gene sets.

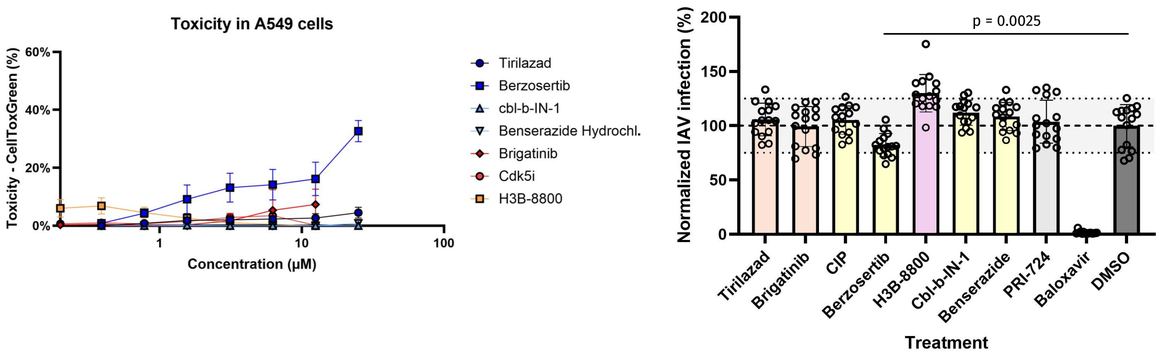


IAV-related gene sets cluster by transport, translation, and splicing processes



Hierarchical clustering of gene sets (Jaccard similarity) revealed seven functional clusters spanning nuclear/vesicle transport (COPI-coated), ATP synthesis/pH regulation, RNA splicing, and ribosomal processes. Drugs were selected targeting proteins in these clusters and prioritized via network-based drug repurposing (Cheng et al., 2018).

Network-predicted berzosertib reduced viral load in IAV-infected A549 cells



Discussion

Host dependency factor screening data show high variability at the gene level, while consistency improves when focusing on significantly enriched gene sets. A boosted random forest model distinguished VHF viruses, SARS-CoV-2, and IAV with 88% balanced accuracy. Feature-based clustering revealed an IAV-specific group characterized by COPI-coated vesicle transport, nuclear trafficking, proton transport, ribosomal function, and splicing. Recovery of known HDFs (e.g., ACE2, STT3A, XPO1) supports the validity of the approach and highlights virus-specific host dependencies. Finally, a network-based drug repurposing pipeline prioritized candidate compounds, and berzosertib significantly reduced viral load in IAV-infected A549 cells, demonstrating the translational potential of this strategy.

References

- Cheng et al.; Nat Commun. 2018; 9(1):2691.
- Edinger et al.; J. Gen. Virol. 2014; 95: 26.
- Logiudice, Jacopo et al.; Pathogens 2025; 14,(1)63.
- Wagoner et al., Microbiol Spectr. 2022; 10:e0333122

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