SCAN ME

MACHINE LEARNING REVEALS COMBINATIONS OF SYSTOLIC BLOOD PRESSURE ASSOCIATED VARIANTS FOR HYPERTENSION PREDICTION

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BACKGROUND

- According to WHO, 1.28 billion adults aged 30-79 years worldwide have hypertension (HTN).
- HTN is a major cause of premature death as it is a key risk factor to several adverse health outcomes.
- Approximately 1 in 5 adults with HTN have their blood pressure (BP) under control.
- BP is a complex, polygenic heritable trait and Genome Wide Association Studies have identified >1000 SNVs associated with BP[1].

HYPOTHESIS

Figure 1: Diagrammatic representation of hypothesis

We hypothesized that an individual's susceptibility towards HTN and the response to certain drugs are influenced by the distinct biological pathways impacted by their unique combinations of BP-associated variants.

METHODS

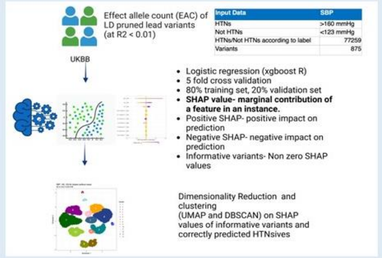


Figure 2: Flowchart explaining methodology.

RESULTS

1. Variants aid the prediction.

Table 1: Model evaluation

Features	SBP
SNPs only model	57.2 %
Clinical parameters only model	77.84 %
Clinical parameters + SNPs model	78.41 %

While including EAC of lead variants in addition to clinical parameters only marginally increases the accuracy of the prediction, a model based on the variants alone has an accuracy of 57%, indicating that these variants aid the prediction.

2. 405 SNPs contributed to HTN prediction consistently with their original direction of effect in all 5 CV subsets.

Figure 3: : Plot showing relationship between direction of effect and SHAP value for top 20 informative SNPs.

Positive effect variant
Higher EAC → Higher BP, SHAP value positive.

Negative effect variant
Higher EAC → Lower BP, SHAP value negative.

Interestingly, information on direction of effect was not supplied to the model.

3. 14 distinct systolic HTNsives clusters identified

Cluster analysis on the explanation space of a classifier could pinpoint the different reasons for belonging to a specific class[2]. 56984/ 62170 correctly predicted HTNs were assigned to clusters while 5186 were relegated as noise. To assess the effectiveness of HTNsive subtyping, we applied polygenic risk scores (PRS) to the identified clusters. PRS was based on all the LD pruned variants at R2 0.01 and normalized by the number of SNPs used in calculation.

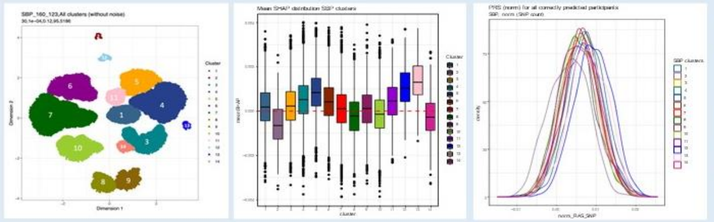
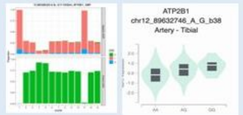


Figure 4: 14 distinct systolic HTNsive clusters. (Left to right): Scatter plot depicting 14 distinct HTN clusters, box plot illustrating the distribution of mean SHAP value of each SNP per cluster, density plots representing PRS for each cluster.

5. Cluster-specific underlying biological mechanisms pinpointed.

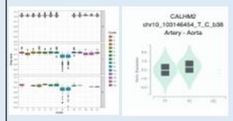
SBP1 and SBP11
- rs11105354
- EAC > 0, ~98 % individuals



Mice lacking ATP2B1 VSMCs → Increased Ca influx[3] → High BP

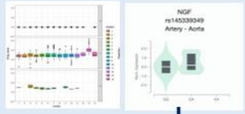
These mice had a **higher response to CCBs** for BP-lowering effects[4]

SBP8 and SBP9
- rs11191580
- EAC > 0 in all individuals



Ca influx → Vascular remodelling

SBP13
- rs145339349
- all HTNsives EAC of 1



Better prognosis post stroke[5]

SBP14
- rs12978472
- Maps to *INSR*
- all HTNsives EAC > 1

Our findings suggest downregulation of INSR in SBP14 → Insulin resistance → Hyperinsulinemia → Na absorption via RAAS[6]

CONCLUSION

Machine Learning models have demonstrated the ability to effectively identify critical variants and associated hypertensive subtypes thereby creating a pathway for implementing personalized therapeutic approaches. The identification and elucidation of biological pathways that underlie the disease subtypes can facilitate prediction of co-morbidities and alternative pharmaceutical therapies.

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