

Auto-antibody discovery in primary biliary cholangitis (PBC) using phage immunoprecipitation sequencing (PhIP-Seq)

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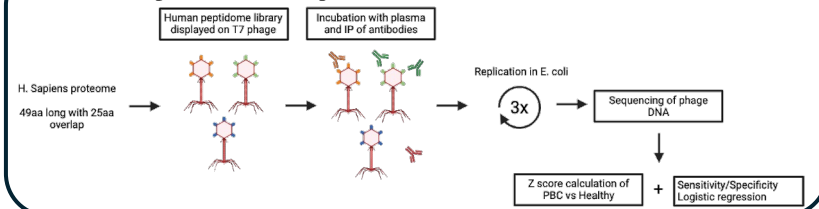
BACKGROUND: PBC is an autoimmune liver disease affecting the small bile ducts. Although bile duct damage in PBC is thought to be mediated by immune cells, immunosuppressive treatments have shown little promise. Thus, our understanding of PBC pathophysiology remains incomplete. Since current PBC diagnostic markers (ie. AMAs & ANAs) are highly sensitive, the goal of this project is not to establish new diagnostics. Instead, we focus on studying the auto-antibody landscape of PBC patients to better understand the disease mechanism.

METHODS

1. Collect blood from cohort of patients with PBC and healthy controls.

PBC: 28 Healthy: 94

2. Run samples on PhIP-seq



DISCUSSION: In addition to known PBC antibodies, new antigens were identified to be associated with PBC. TRIP12 is an E3 ubiquitin ligase which localizes to the nucleus. As ANA are diagnostic in PBC, TRIP12 antibodies may reflect epitope spread of immune response. DPEP2 is a dipeptidase which hydrolyzes leukotrienes from D4 to E4. It was identified as a PBC susceptibility locus via GWAS.¹ Antibodies against DPEP2 may interfere with catalytic activity leading to higher levels of the more potent leukotriene D4, which in turn may lead to recruitment of eosinophil and other immune cells. Further studies will be needed to validate DPEP2 and interrogate the effect of antibodies on its catalytic function.

ACKNOWLEDGEMENTS: Chan Zuckerberg Biohub/Initiative.

References:

1. Hitomi, Y. & Nakamura, M. The Genetics of Primary Biliary Cholangitis: A GWAS and Post-GWAS Update. *Genes (Basel)* **14**, 405 (2023).

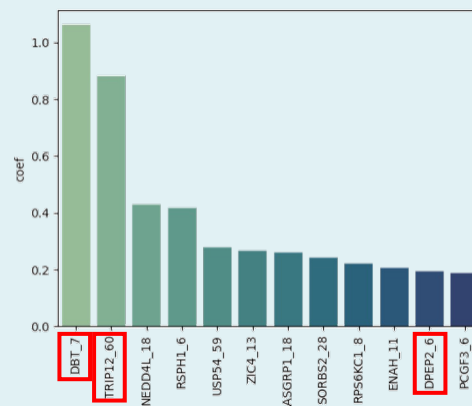
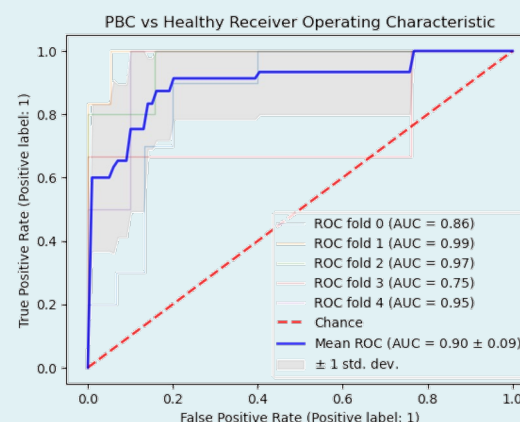
Phage immuno-precipitation identifies new auto-antibodies in primary biliary cholangitis.

UCSF

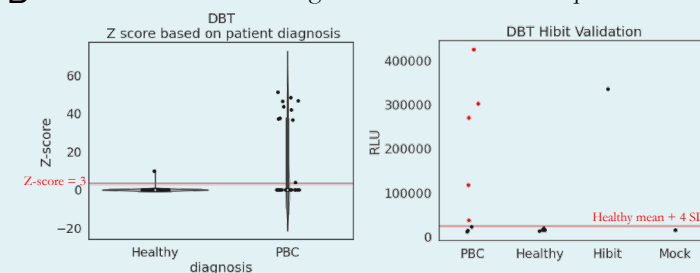
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RESULTS

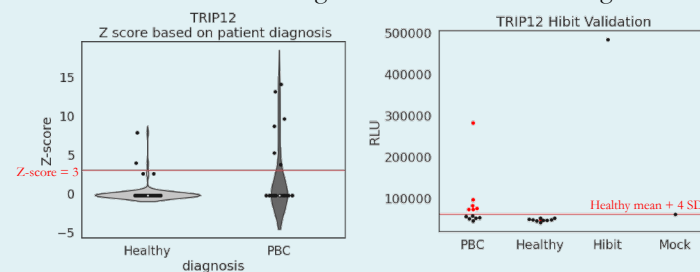
A Logistic regression using PhIP-Seq antibodies can differentiate PBC from healthy control patients.



B DBT is a known PBC antigen identified via PhIP-Seq and validated using HiBit.



C TRIP12 is a new PBC antigen found and validated using HiBit



D DPEP2 is a new PBC antigen, which correlates with advanced liver fibrosis.

