



Abstract Type : Oral presentation

Abstract Submission No.: A-0241

Abstract Topic : Basic Research

Cross-reactive gut microbial proteins in Lupus Nephritis

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Objectives : Lupus nephritis (LN) is a severe manifestation of systemic lupus erythematosus (SLE) and a major cause of morbidity and mortality in affected individuals. Recent research has demonstrated that gut microbes may contribute to LN pathogenesis by harboring cross-reactive epitopes capable of inducing host immune responses and promoting autoantibody production. This study aimed to identify gut microbial antigens that mimic human autoantigens in patients with LN, employing an immunoinformatics pipeline and novel screening approaches.

Methods : Fecal samples were collected from LN patients at baseline and after treatment. The gut microbiome was analyzed by next-generation sequencing, followed by an immunoinformatics approach using the CRESSP pipeline to predict structurally based cross-reactive epitopes. Serum autoantibodies were then profiled using phage immunoprecipitation sequencing (PhIP-Seq) to validate the predicted epitopes.

Results : A total of eight LN patients were enrolled, with a median interval of 2.7 years between baseline and follow-up. Using CRESSP, 1,156 potential cross-reactive B-cell epitope candidates were identified. PhIP-Seq analysis revealed that 1,013 autoantibodies decreased after treatment, with 153 of these overlapping with CRESSP predictions. These included known lupus-related autoantibodies such as TRIM21 (Ro52), SSB (Ro60), XRCC5, and SNRPA, as well as novel targets (NNT, DDX50, ALAS1, NONO, NRXN3) that showed high BLOSUM62 scores (≥ 2) and significant structural similarity.

Conclusions : Our study shows that the gut microbiome of LN patients harbors bacterial antigens with strong structural similarity to human autoantigen targets, and that these cross-reactive epitopes can be identified through informatics-based approaches. These findings offer new perspectives on LN pathophysiology and may aid the design of future therapeutic strategies.

Figure 1.png

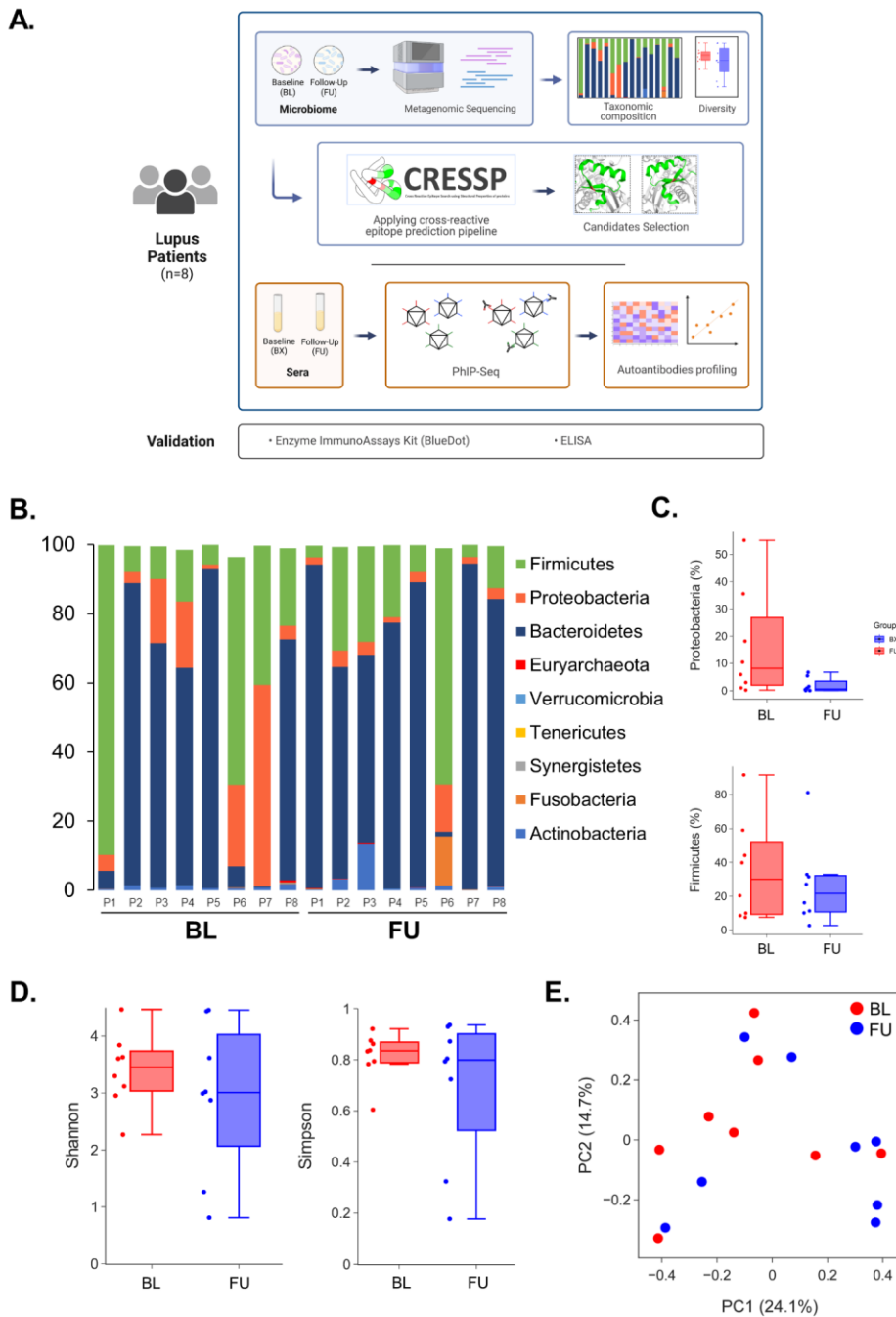
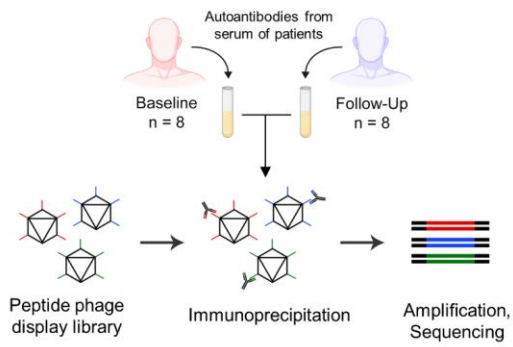
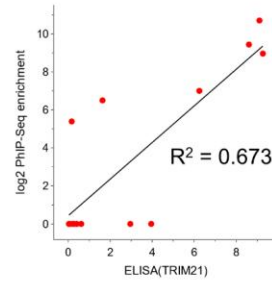


Figure 1.png

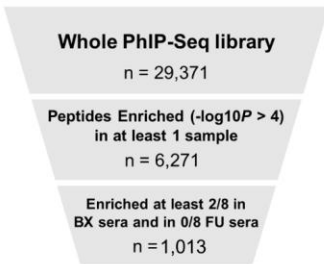
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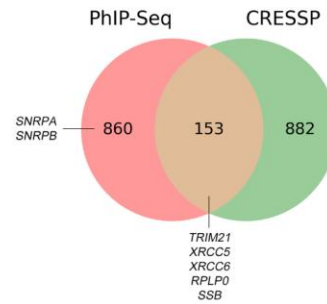
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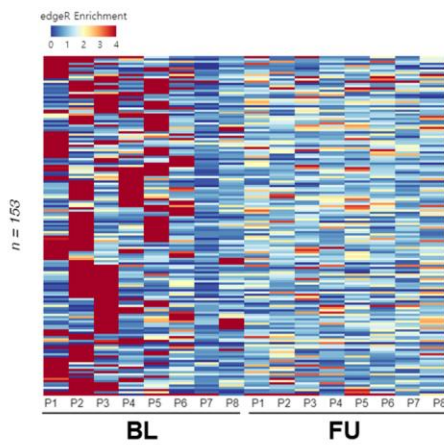
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