Background Belimumab has a therapeutic benefit in active SLE, especially in patients with high titers of anti-dsDNA antibodies. The current study was designed to address whether the profound loss of naïve B cells in belimumab treated patients is accompanied by a shift in the immunoglobulin repertoire of either mature B cells or plasma cells.

Methods 15 SLE patients who had been continuously treated with belimumab 10 mg/kg monthly for >5 years were matched with 17 SLE controls. 5 SLE patients newly starting with belimumab treatment were studied before and 6 months after drug initiation. B cell phenotyping was performed using flow cytometry. Mature B cells and plasmablasts were sort purified, VH libraries were generated using barcoded primers (iRepertoire) and pooled libraries were sequenced using miSeq. Analyses of unmutated and mutated IgM sequences from mature B cells and all plasmablasts were performed using customized Perl and R scripts.

Results Phenotyping – novel findings:
1. BAFF regulates the transitional B cell checkpoint with conservation of transitional type 1 cells and ~90% loss of transitional type 3 and naïve B cells after chronic belimumab treatment.
2. Neither ‘naïve activated’ B cells nor CD21hi B cells subset are preferentially depleted by belimumab.
3. The early increase in CD27+ class switch cells after belimumab treatment is due to an increase in memory B cells rather than B1 cells.
4. After >5 years of treatment, class switched memory B cells, B1 B cells and plasmablasts are also substantially depleted.

Next Generation Sequencing of VH genes:
1. There was no redistribution of V, D or J family usage among unmutated IgM sequences.
2. There was no effect of belimumab on the frequency of the autoreactive VH4–34 gene or on CDR3 length or composition in unmutated IgM sequences.
3. There was a significantly greater loss of VH4–34 among mutated IgM sequences and plasmablast sequences compared with unmutated sequences in subjects treated with chronic belimumab than in lupus controls.

Conclusions Although BAFF highly regulates survival of naïve B cells past the T1 stage in humans, we were unable to identify an effect of belimumab on VH distribution or CDR3 composition of naïve B cells, suggesting a minimal effect on selection of the naïve B cell repertoire. By contrast belimumab may promote negative selection of autoreactive activated naïve B cells and plasmablasts.
helper function. The strong and specific positive correlation between Tph cell and CD21low B cell frequencies suggests that these cells may act coordinately in the pathologic autoimmune response in SLE.

Acknowledgements We acknowledge the Accelerating Medicines Partnership RA/SLE Network and its members.

Auto Antibodies

**AA-01** PHENOME-WIDE ASSOCIATION STUDIES UNCOVER HIERARCHY OF AUTOANTIBODIES IN SYSTEMIC LUPUS ERYTHEMATOSUS

April Barnado*, Robert J Carroll, Carolyn Casey, Joshua C Denny, Leslie J Crofford. Department of Medicine, Vanderbilt University Medical Center, USA; Department of Biomedical Informatics, Vanderbilt University Medical Center, USA; Department of Medicine, Lehigh Valley Health Network, USA

Background Systemic lupus erythematosus (SLE) is a heterogeneous disease with diverse presentations. dsDNA antibodies associate with renal disease. Less is known about comorbidities in SLE patients without dsDNA antibodies. Using a large electronic health record (EHR) cohort, we sought to identify comorbidities that associate with dsDNA status. We used a technique that scans across EHR billing codes called phenome-wide association study (PheWAS) to compare SLE patients with and without dsDNA antibodies. We also evaluated the relative importance of SLE specific autoantibodies on SLE criteria.

Methods We used our validated SLE algorithm of ≥4 counts of the SLE ICD-9 code and ANA positive ≥1:160 while excluding dermatomyositis and systemic sclerosis ICD-9 codes with a positive predictive value of 94% and a sensitivity of 86%. We identified SLE cases in a de-identified EHR that contains over 2.8 million subjects. Autoantibody status was defined as ever positive for dsDNA, RNP, Smith, SSA, and SSB. PheWAS was performed in dsDNA positive vs negative SLE patients using logistic regression adjusting for current age and race. For multiple testing, a false discovery rate (FDR) p of 0.05 was used. We also performed logistic regression to assess the impact of autoantibodies, age, sex, and race on SLE criteria. Results We identified 1097 SLE subjects. As expected, dsDNA positive subjects, compared to dsDNA negative, were more likely to have renal codes including nephritis (OR=4.60, FDR p=2.33 × 10⁻⁹), renal failure (OR=2.30, FDR p=1.85 × 10⁻⁵), and end stage renal disease (OR=2.63, FDR p=0.01). After adjusting for sex, age, and other autoantibodies, dsDNA was independently associated with nephritis (p=1.98 × 10⁻⁶) and chronic kidney disease (p=0.001) and also associated, along with SSB, with serositis (p=0.01) and hematologic criteria (p=0.001) (figure 1). dsDNA negative subjects were more likely to have codes for sleep, pain, and mood disorders.

Conclusion Using PheWAS, we uncovered a hierarchy within SLE specific autoantibodies where dsDNA, compared to other autoantibodies, was a powerful predictor of major organ involvement in SLE.