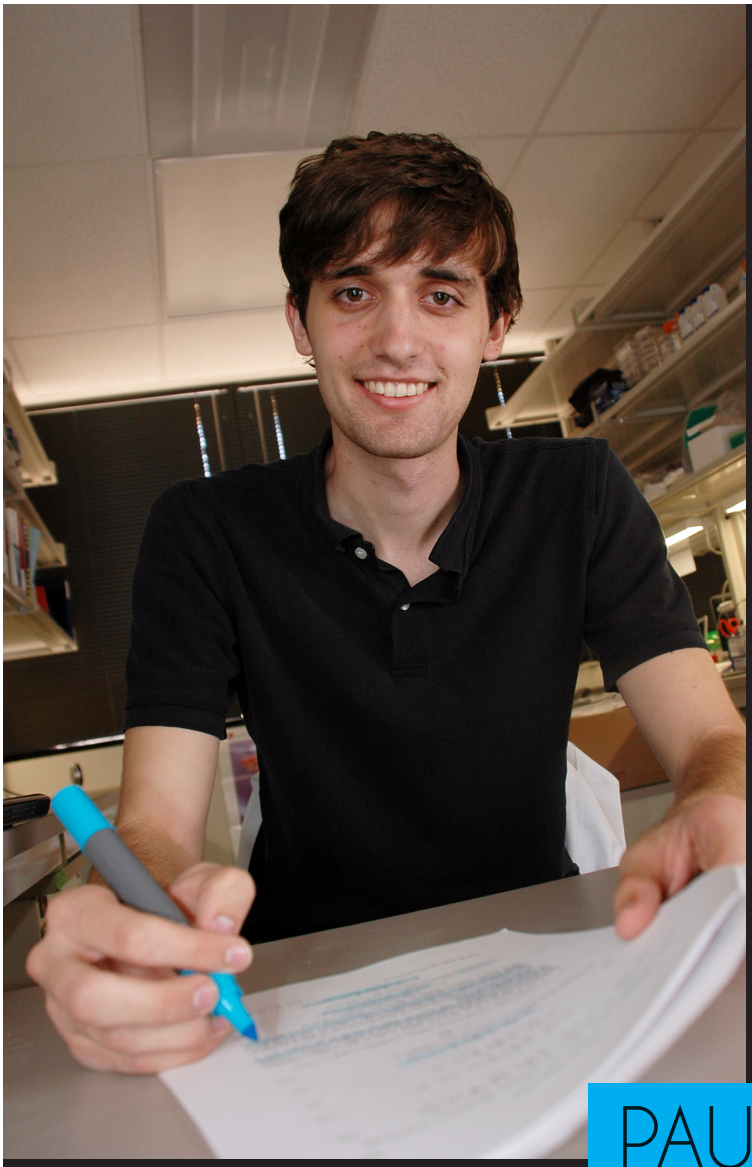

# 2010

## OGE ENERGY CORPORATION SCHOLAR

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FINAL RESEARCH MANUSCRIPTS

OMRF

# Assessing the Familial Correlations of Systemic Lupus Erythematosus Patients

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*ABSTRACT*

*Systemic lupus erythematosus (SLE) is a debilitating autoimmune disease in which the immune system begins to attack the individual. Former studies have shown that SLE is heritable and linked to certain viral infections. More specifically, all lupus patients produce autoantibodies to peptides that closely mimic structures of Epstein Barr Virus (EBV). This study examined individual familial correlations of these viral structures and peptide autoantibodies with each other and clinical manifestations in 557 African American (AA) SLE patients. We sought to establish patterns that may give clues to the development of SLE.*

*The viral data included the following quantitative measures: antibodies against EBV viral capsid antigen (EBV-VCA), EBV nuclear antigen 1 and 58 (EBNA1 and EBNA58). Anti-peptide autoantibodies for Anti-SmB/B' and anti 60kD Ro (PPPGMRPP, PPPGRRP, and amino acids 169-180 'Ro169') were also included, along with a total of 48 clinical variables, most representing the American College of Rhuematology classification criteria. The strength of the self and family correlations were assessed using FCOR (S.A.G.E. software suite) and R for statistical computing. All analyses were adjusted for age and sex. Box-Cox and logarithmic transitions were done when necessary.*

*First, we confirmed the relationship between EBV and anti-peptide autoantibodies (EBNA58 and PPPGMRPP, EBNA1 and PPPGRRP, and Ro169 with both EBNA1 and EBNA58). Fifteen clinical variables were correlated with EBV. EBNA1 was most significantly correlated with ACLIgG (p=.0017), EBNA58 with Renal disorders (p=.0159), and EBV-VCA with AGLIgM (p=.0014). Previous studies have shown ACLIgG to be associated with renal manifestations in AA. Thirty-two significant clinical correlations were observed for the three anti-peptide autoantibodies, two of which were significant at p<.0001 (Anti-RNP with PPPGMRPP, and Anti-Sm with PPPGRRP). Among siblings, ssDNA was significantly correlated with both EBNA1 (p=.0015) and PPPGMRPP (p=.0005). These results support both a heritable and environmental component to SLE.*

## INTRODUCTION

Systemic Lupus erythematosus is a debilitating autoimmune disorder in which the immune system begins to create autoantibodies that attack the individual. Although recognition and treatment of lupus have gotten better with recent medical advances, SLE is still debilitating or even fatal in some cases. Therefore it is important to understand the mechanisms that are causing this disease so we can further improve treatment with the final goal of prevention or finding a cure. SLE is a very broad and complex disease because it can affect almost any organ in the body; therefore, it is often misdiagnosed. The American College of Rheumatology states that for a person to be diagnosed with SLE, they must satisfy 4 of 11 criteria.1,2

It is well known that lupus has a genetic component to it due to the large increase of risk for those with family members that already have lupus. However, it can be difficult to differentiate genetic and environmental risk factors due to families sharing not only the same genes, but usually the same environment as well. Familial correlation can help find genetic links as well as establish some things which may be environmentally linked.

## METHODS AND MATERIALS

This study involved 557 African American (AA) individuals affected with SLE. The clinical features used in this study are shown in figure 1 as are the viral data and anti-peptide autoantibodies. Anti-peptide autoantibodies for Anti-SmB' and anti 60kD Ro (PPPGMRPP, PPPGRRP, and amino acids 169-180 'Ro169') were also included.

The original data comes from the information gathered by the Lupus Family Registry and Repository as well as Dr. Montgomery's Early Lupus Autoimmunity Study which were funded by a contract from the National Center of Research Resources and a grant from the Rheumatic Disease Research Clinical Center, respectively. The continuous data was transformed using a Box-Cox or log base e transformations programmed in the statistical program R. Age and sex adjustments were also made utilizing R.

After all adjustments were made, the data was submitted to FCOR (S.A.G.E. software suite) to find familial associations between the viral structures, clinical data, and peptide structures in each individual and between the 69 siblings. This analysis also included the standard error to see which values were significantly correlated. All the data was then analyzed in Microsoft Excel.

It was important to ensure independence of the individuals because our data included family members who share the same or similar genes. In order to fix this, we re-ran the correlations on the data in which all but one person from each family had been deleted to ensure data was not biased. (Note: Anywhere a group of individuals is denoted "Single" implies a single person from each family.) Doing this "single" analysis in addition to the family correlations can help differentiate whether symptoms or viral/auto-antibodies levels are caused by genetic background, environment of the patient, or both of these factors.

Results: A total of 146 significant correlations were found between the viral structures, peptides, and clinical data. All correlations had a significance $p < .05$ and

| | Categorical | Binary | Quantitative |
|---|---|---|---|
| Clinical Data: | | | |
| | Malar Rash | ANA Positive or Negative | double stranded DNA titer |
| | Discoid Rash | Anti-ENASm | single stranded DNA Normalized |
| | Photosensitivity | Anti ENAnRNP | Complement CH50 normalized |
| | Oral Ulcer | Anti ENARo | ACLIgA |
| | Arthritis | Anti ENALa | double stranded DNA titer nonzero |
| | Serositis | Anti ENAP | single stranded DNA titer raw |
| | Pericarditis | Anti ENAJo | single stranded DNA titer normalized |
| | Pleuritis | Anti ENA1UIL | ACLIgG |
| | Renal Disorder | Anti ENA greater than 1UIL | ACLIgM |
| | Proteinuria | | Complement CH50 Raw |
| | Cellular Masts | | Complement CH50 Normalized |
| | LE Cells | | ANA titer logarithmic transformation |
| | Neurological Disorder | | |
| | Seizures | | |
| | Psychosis | | |
| | Hematology | | |
| | Hemolytic Medical Record | | |
| | Leukopenia | | |
| | Lymphopenia | | |
| | Thrombosis | | |
| | Immunologic disorder | | |
| | LECellMedRecord | | |
| | Anti-DNA | | |
| | Anti-DNA(OMRF) | | |
| | Anti-Sm | | |
| | Anti Sm(OMRF) | | |
| | Antiphospholipid AB | | |
| | False Positive Medical Record | | |
| | Lupus Anticoagulant | | |
| | Anticardiolipin | | |
| | Anticardiolipin(OMRF) | | |
| | Antinuclear antibodies(ANA) | | |
| | Antinuclear antibodies(OMRF) | | |
| Viral Data: | | | |
| | | | Epstein Barr Nuclear Antigen 58 |
| | | | Epestein Barr Nuclear Antigen 1 (Mosaic) |
| | | | Herpes Simplex Virus 1 |
| | | | Herpes Simplex Virus 2 |
| | | | Cytomeglavirus |
| Anti-peptide autoantibodies: | | | |
| | | | PPPGMRPP |
| | | | PPPGRRP |
| | | | Ro169 |

**Table 1. Categories of data received.**

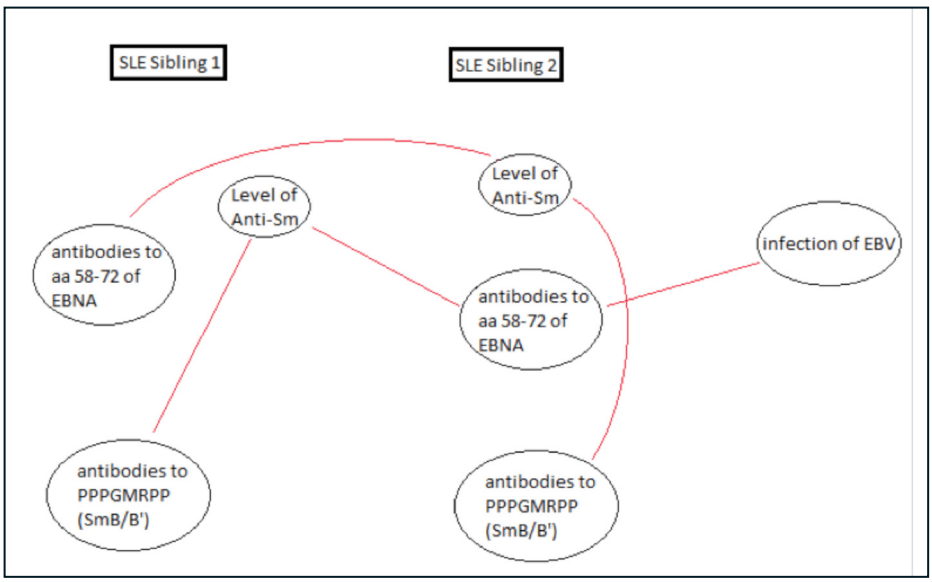


**Figure 1 shows the relationship between two SLE siblings regarding certain factors pertinent to lupus.**

a correlation > .1 or < -.1. Many of these correlations support previous work such as PPPGMRPP having a correlation with EBNA1 and EBNA58.3 The attached supplement shows all of the specific correlations and p-values associated with in correlation in this study. Some of the most interesting correlations found were the relationship in the sibling data between Anti-Sm and EBNA58, but no relationship in the self data. Another interesting point is that in HSV2 and the three peptide structures are all significantly correlated between the siblings but not with the self data.

## DISCUSSION

Figure 2 shows the correlations between levels of Anti-Sm, EBNA58 antibodies and antibodies to PPPGMRPP in two siblings. The correlation between Anti-Sm and PPPGMRPP makes sense because Anti-Sm is a subset of PPPGMRPP. However, it is interesting to note that levels of EBNA58 correlate with levels of Anti-Sm in the other sibling, but not within the individual. Although it is clear that genes regulate the production of both of these autoantibodies, it appears that environmental factors are causing this relationship. A possible explanation for this would be that the age at infection in which case the immune system would be more/less developed which may cause a different response to the virus. More research must be done to confirm or reject this hypothesis.

## REFERENCES

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