Disparities in Lupus Outcomes: The Role of Environment and Genetics

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Disclosures

• Ashira Blazer: None
SLE is a Major Cause of Morbidity and Mortality Especially in Minority Women

(Yen and Singh 2018)
Phenome Wide Association Study: African American SLE Patients Exhibit Increased Burden of Comorbidities

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>African American (n=270)</th>
<th>Caucasian (n=715)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current age ± SD</td>
<td>44 ± 17</td>
<td>53 ± 17</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Age at Diagnosis ± SD</td>
<td>35 ± 16</td>
<td>43 ± 17</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

(Barnado, Caroll, Crofford)
NYU SLE: Black and Hispanic Patients Exhibit Higher SLE SLICC Damage Index Within the First 5 Years of Diagnosis

- A “non-zero” Damage index is independently associated with all cause mortality in SLE (Chambers, Allen et al. 2009)
- Renal and cardiovascular outcomes are among the strongest predictors of mortality (Danila, Pons-Estel et al. 2009)
- Compared to White or Asian race, Black and Hispanic SLE patients were more likely to have a “Non-Zero” Damage Index (HR 8.9) within the first 5 years of diagnosis
- Early Cardiovascular damage accrued in minority patients

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR  P Value</td>
<td>HR  P Value</td>
</tr>
<tr>
<td>Black or Hispanic Race</td>
<td>7.0 0.006</td>
<td>8.9 0.006</td>
</tr>
<tr>
<td>Age at SLICC</td>
<td>1.08 0.005</td>
<td>1.1 0.01</td>
</tr>
</tbody>
</table>
In a Single Academic Center, Are There Differences in Neighborhood Stress by Race and Ethnicity

- SLE patients seen at 3 NYU hospital centers were recruited (n=221)
- Addresses were Geocoded by census track
- Publically available data (NYC open data, NYC.gov) were accessed
  - Violent Crimes
  - Income
  - Poverty
  - Unemployment
  - Average commute to work
  - Childhood educational attainment
  - Pharmacies
  - Greenspace
African American and Hispanic Neighborhoods Have Significantly Higher Violent Crime, Unemployment, and Lower Income
Principle Component Analysis of Neighborhood Factors Shows Greatest Neighborhood Variation in Income, Educational Attainment and Unemployment Rates

- **Principal component 1** (57% of the variance)
  - Directly proportional to
    - Income
    - Childhood educational attainment
  - Inversely proportional to
    - Poverty
    - Unemployment

- **Principal component 2** (18% of the variance)
  - Proportional to poverty
  - Inversely proportional to Distance traveled to work
African American and Hispanic Patients Experience a Higher Degree of Neighborhood Stress

- Principal component 1
  - Directly proportional to:
    - Income
    - Childhood educational attainment
  - Inversely proportional to:
    - Poverty
    - Unemployment

- Mean AA: 0.5
- Mean Hispanic: -0.03
- Mean Asian: 0.44
- Mean White: -0.45
The Etiological Framework in SLE Health Disparities Reveals Multiple Causes

Pathophysiologicaal mechanisms

Genetics
Environmental triggers
Hormones

Risk
Disease severity
Treatment Response
Mortality

Socioeconomic mechanisms

Income
Educational attainment
Occupation

(Falasinnu T 2017)
Apolipoprotein L1 (APOL1) Gene Mutations: High Allelic Frequencies in those of Recent West African Heritage

• These mutations offer resistance to African trypanosomiasis
• Evolutionary advantage comes with the risk of progressive renal and cardiovascular disease
• Allelic frequencies are high
  • Ghana
    • Asante: G1: 40.9% G2: 12.9%
    • Bulsa: G1: 11.4% G2: 21.4%
  • African Americans
    • New York: G1: 20.9% G2: 13.4%
    • Southern USA: G1: 19.7% G2: 13.4%

Limou et. al
APOL1 Polymorphism-Ascribed Renal and Cardiovascular Risk Differs Across Medical Comorbidity

Renal Disease

- Diabetes
- General
- SLE Nephritis
- Collapsing Glomerulopathy
- FSGS
- HIVAN

CVD

- SPRINT Trial
- REGARD Non-Diabetic
- Women's Health Study
- REGARD Non-Diabetic
- SLE (NYU)
Two Ancestrally African SLE Cohorts (NYC/Ghana) Were Followed Longitudinially

<table>
<thead>
<tr>
<th>Enrollment:</th>
<th>Longitudinal Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>Visit 1: Month 0</td>
</tr>
<tr>
<td></td>
<td>Visit 2: Month 6</td>
</tr>
<tr>
<td></td>
<td>Visit 3: Month 12</td>
</tr>
<tr>
<td>• Inclusion</td>
<td>• Chart Review</td>
</tr>
<tr>
<td>• Self-reported African ancestry</td>
<td>• Vital signs/SLEDAI</td>
</tr>
<tr>
<td>• 4 ACR criteria for SLE</td>
<td>• Blood Draw</td>
</tr>
<tr>
<td>• Exclusion</td>
<td>• Whole Genotyping</td>
</tr>
<tr>
<td>• Incomplete chart data</td>
<td>• Serum biomarkers</td>
</tr>
<tr>
<td>• Insignificant African admixture</td>
<td>• Serum biomarkers</td>
</tr>
<tr>
<td></td>
<td>• Vital signs/SLEDAI</td>
</tr>
<tr>
<td></td>
<td>• Serum biomarkers</td>
</tr>
</tbody>
</table>
In Both Cohorts Demographics were Similar Across Genotypes

### NYU

<table>
<thead>
<tr>
<th>Genotype</th>
<th>G0/G0 (n=36)</th>
<th>RV/G0 (n=51)</th>
<th>RV/RV (n=13)</th>
<th>P</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>43.8 ± 14.3</td>
<td>41.3 ± 14.0</td>
<td>48.1 ± 13.9</td>
<td>NS</td>
<td>43.1 ± 14.1</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>88.9</td>
<td>88.2</td>
<td>92.3</td>
<td>NS</td>
<td>90.1</td>
</tr>
<tr>
<td>Smoking History (%)</td>
<td>25.0</td>
<td>21.6</td>
<td>23.1</td>
<td>NS</td>
<td>23.0</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>5.5</td>
<td>3.9</td>
<td>7.6</td>
<td>NS</td>
<td>4.4</td>
</tr>
<tr>
<td>BMI</td>
<td>27.8 ± 8.9</td>
<td>29.6 ± 7.8</td>
<td>25.6 ± 3.6</td>
<td>NS</td>
<td>28.5 ± 7.9</td>
</tr>
<tr>
<td>A1C</td>
<td>5.2 ± 1.6</td>
<td>5.6 ± 0.6</td>
<td>6.1 ± 1.6</td>
<td>NS</td>
<td>5.6 ± 1.2</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>68.4</td>
<td>65.7</td>
<td>77.8</td>
<td>NS</td>
<td>68.3</td>
</tr>
</tbody>
</table>

Allelic Frequencies: G0: 0.62 G1: 0.21 G2: 0.17

### GH

<table>
<thead>
<tr>
<th>Genotype</th>
<th>G0/G0 (n=39)</th>
<th>RV/G0 (n=51)</th>
<th>RV/RV (n=12)</th>
<th>P</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>31.4 ± 9.2</td>
<td>32.7 ± 8.7</td>
<td>32.1 ± 8.9</td>
<td>NS</td>
<td>32.1 ± 8.9</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>NS</td>
<td>100</td>
</tr>
<tr>
<td>Smoking History (%)</td>
<td>0.00</td>
<td>2.7</td>
<td>0.00</td>
<td>NS</td>
<td>1.4</td>
</tr>
<tr>
<td>Hypertension History</td>
<td>12.0</td>
<td>14.0</td>
<td>10.0</td>
<td>NS</td>
<td>13.0</td>
</tr>
<tr>
<td>BMI</td>
<td>28.4 ± 5.8</td>
<td>27.7 ± 5.2</td>
<td>25.9 ± 5.6</td>
<td>NS</td>
<td>27.8 ± 5.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.0</td>
<td>5.0</td>
<td>0.0</td>
<td>NS</td>
<td>4.0</td>
</tr>
<tr>
<td>Past Lipid Lowering</td>
<td>20.0</td>
<td>5.4</td>
<td>0</td>
<td>NS</td>
<td>9.7</td>
</tr>
</tbody>
</table>

Allelic Frequencies: G0: 0.63 G1: 0.24 G2: 0.13
NYU Cohort: APOL1 Variant Carriers Exhibited Accelerated Renal Disease, CVD, and Damage Accrual

Risk Factor | Odds Ratio | P value
---|---|---
1 or 2 APOL1 Allele Copies | 7.9 | 0.006
ESRD | 1.2 | 0.8
Smoking | 5.3 | 0.008
12 Month Average Prednisone Dose >10mg | 0.98 | 0.4
Body Mass Index | 0.96 | 0.4
Hypertension | 3.9 | 0.02

Multivariate Analysis: APOL1 Associates With CVD
NYU Cohort: Variant Carriers Developed Atherosclerotic Disease at Earlier Ages

A. Time To Event Analysis

B. Number at Risk by Decade

<table>
<thead>
<tr>
<th>Decade</th>
<th>G0/G0</th>
<th>RV/G0</th>
<th>RV/RV</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>35</td>
<td>56</td>
<td>14</td>
</tr>
<tr>
<td>30</td>
<td>28</td>
<td>42</td>
<td>12</td>
</tr>
<tr>
<td>40</td>
<td>19</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>50</td>
<td>13</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>60</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

A) Time-to-event analysis for symptomatic atherosclerotic CVD as represented by Kaplan Meier Curves. The Y axis represents proportion of individuals free of the outcome, and the X axis represents subject age.

B) The number of individuals present at each decade time point.

Hazard Ratios:
G0/G0 vs RV/G0: 4.2 p=0.003
G0/G0 vs RV/RV: 4.6 p=0.006
Ghanaian Cohort: APOL1 Variants Associate with Higher SLICC Damage Indexes

**G0/G0**
- Cataract: 0
- Optic Atrophy: 0
- Cognitive Impairment: 0
- Seizures: 0
- CVA: 0
- Pulm HTN: 0
- Pulm Fibrosis: 0
- Pulm infarction: 0
- Angina: 0
- Cardiomyopathy: 0
- Valve: 0
- Pericarditis: 0
- Claudication: 0
- Pulp loss: 0
- Sign significant tissue loss: 0
- Venous thrombosis: 0
- GI infarction: 0
- Mesenteric Insufficiency: 0
- Chronic peritonitis: 0
- GI Stricture: 0
- Muscular Atrophy: 0
- erosive arthritis: 0
- Osteomyelitis: 0
- Scarring alopecia: 0
- Other scarring: 0
- Skin ulceration: 0
- Gonadal failure: 0
- Diabetes: 0
- Malignancy: 0
- Total SLICC: 0

**G1/G0**
- Cataract: 6
- Optic Atrophy: 2
- Cognitive Impairment: 4
- Seizures: 6
- CVA: 1
- Pulm HTN: 2
- Pulm Fibrosis: 0
- Pulm infarction: 4
- Angina: 12
- Cardiomyopathy: 0
- Valve: 0
- Pericarditis: 0
- Claudication: 17
- Pulp loss: 0
- Sign significant tissue loss: 8
- Venous thrombosis: 0
- GI infarction: 0
- Mesenteric Insufficiency: 8
- Chronic peritonitis: 0
- GI Stricture: 8
- Muscular Atrophy: 0
- erosive arthritis: 8
- Osteomyelitis: 0
- Scarring alopecia: 8
- Other scarring: 0
- Skin ulceration: 0
- Gonadal failure: 0
- Diabetes: 0
- Malignancy: 0
- Total SLICC: 27

**G1/G1**
- Cataract: 2
- Optic Atrophy: 0
- Cognitive Impairment: 2
- Seizures: 2
- CVA: 0
- Pulm HTN: 4
- Pulm Fibrosis: 0
- Pulm infarction: 2
- Angina: 0
- Cardiomyopathy: 0
- Valve: 0
- Pericarditis: 0
- Claudication: 8
- Pulp loss: 0
- Sign significant tissue loss: 8
- Venous thrombosis: 0
- GI infarction: 0
- Mesenteric Insufficiency: 8
- Chronic peritonitis: 0
- GI Stricture: 8
- Muscular Atrophy: 0
- erosive arthritis: 8
- Osteomyelitis: 0
- Scarring alopecia: 8
- Other scarring: 0
- Skin ulceration: 0
- Gonadal failure: 0
- Diabetes: 0
- Malignancy: 0
- Total SLICC: 27

**Additive (RCN)**
- Cataract: 6
- Optic Atrophy: 2
- Cognitive Impairment: 4
- Seizures: 6
- CVA: 1
- Pulm HTN: 2
- Pulm Fibrosis: 0
- Pulm infarction: 4
- Angina: 12
- Cardiomyopathy: 0
- Valve: 0
- Pericarditis: 0
- Claudication: 17
- Pulp loss: 0
- Sign significant tissue loss: 8
- Venous thrombosis: 0
- GI infarction: 0
- Mesenteric Insufficiency: 8
- Chronic peritonitis: 0
- GI Stricture: 8
- Muscular Atrophy: 0
- erosive arthritis: 8
- Osteomyelitis: 0
- Scarring alopecia: 8
- Other scarring: 0
- Skin ulceration: 0
- Gonadal failure: 0
- Diabetes: 0
- Malignancy: 0
- Total SLICC: 27

**P-values**
- Total SLICC: P=0.1
- Renal: P=0.05
- Cardiac: P=0.04
APOL1 Variants Associate with Higher Urine Protein, Creatinine, and Blood Pressure

### Urine Protein by Dipstick Over Time

<table>
<thead>
<tr>
<th>Time</th>
<th>G0/G0</th>
<th>RV/G0</th>
<th>RV/RV</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>0.9</td>
<td>1.06</td>
<td>2.49</td>
<td>0.03</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>107 ± 11</td>
<td>109 ± 18</td>
<td>121 ± 20</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>72 ± 10</td>
<td>72 ± 11</td>
<td>83 ± 18</td>
<td>0.003</td>
</tr>
</tbody>
</table>
The SLE Case Fatality Rate Was Significantly Higher in APOL1 Variant Homozygous Patients

<table>
<thead>
<tr>
<th>Causes of Death</th>
<th>G0/G0</th>
<th>RV/G0</th>
<th>RV/RV</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0/G0</td>
<td></td>
<td></td>
<td>• ESRD</td>
</tr>
<tr>
<td>RV/G0</td>
<td>• Sepsis during pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV/RV</td>
<td>• Heart Failure/Pulm edema</td>
<td>• ESRD</td>
<td>• Unknown (renal failure at death)</td>
</tr>
</tbody>
</table>

P = 0.003
APOL1-Associated Damage Accrual: Increased Inflammation or Decreased Tissue Resistance?

- Increased SLE Inflammation?
- Decreased tissue resistance to inflammation?
### NYU Cohort: Variant Homozygotes Progressed to ESRD Despite More Reassuring Biopsies

#### Distribution of Biopsy Class by APOL1 Genotype

<table>
<thead>
<tr>
<th>Biopsy Class</th>
<th>G0/G0</th>
<th>RV/G0</th>
<th>RV/RV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class II</td>
<td>5/24</td>
<td>6/24</td>
<td>1/24</td>
</tr>
<tr>
<td>Class III</td>
<td>3/12</td>
<td>2/12</td>
<td>1/12</td>
</tr>
<tr>
<td>Class III+V</td>
<td>3/12</td>
<td>2/12</td>
<td>1/12</td>
</tr>
</tbody>
</table>

#### Activity Index
- **G0/G0**: 5/24
- **RV/G0**: 6/24
- **RV/RV**: 1/24

#### Chronicity Index
- **G0/G0**: 3/12
- **RV/G0**: 2/12
- **RV/RV**: 1/12

#### % Sclerotic Glomeruli
- **G0/G0**: 29%
- **RV/G0**: 14%
- **RV/RV**: 8%

<table>
<thead>
<tr>
<th>Biopsy Class</th>
<th>Creatinine</th>
<th>uPCR</th>
<th>% ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class II</td>
<td>1.2</td>
<td>2.5</td>
<td>18%</td>
</tr>
<tr>
<td>Class III</td>
<td>1.1</td>
<td>2.8</td>
<td>15%</td>
</tr>
<tr>
<td>Class III+V</td>
<td>2.2</td>
<td>4.1</td>
<td>43%</td>
</tr>
</tbody>
</table>

| P value | 0.04 | 0.01 | 0.06 |

| P value | 0.01 | 0.04 | OR: 5.7 P=0.05 |
APOL1 Homozygotes Exhibit Less Serologic Activity
APOL1-Associated Damage Accrual: Increased Inflammation or Decreased Tissue Resistance?

- Increased SLE Inflammation?

- Decreased Tissue resistance to inflammation?
APOL1 Variant Genes Encode Amino Acid Changes Which Reduce Protein Structural Stability

- APOL1: One member of a 6 gene family on chromosome 22.13
  - Ancestral G0 allelic frequency: 0.65
  - Variant G1: Two non-synonymous substitutions at position 342 and 384 allelic frequency: 0.22
  - Variant G2: Two amino acid deletion at position 388 allelic frequency: 0.13

- Amino acid changes decrease APOL1 variant interaction efficiency with other proteins

(Grams, Rebholz et al. 2016)(Sharma, Friedman et al. 2016)
Toxicity Model: APOL1 Variants May Upset the Autophagy/Pore Formation Balance (Literature Summation Transfection Models)

- Inflammatory and hypoxic stress induces APOL1 expression.
- At moderate levels APOL1 competes with Beclin1 to bind anti-death BCL2 family proteins, therefore propagating autophagy.
- Over-expression leads to free APOL1 which can form pores in the membranes of acidic organelles (Lysosomes/Mitochondria).
- Variant APOL1 binds poorly to BCL2 lowering the pore formation threshold.
Study Rationale: SLE Inflammatory Pathways Increase APOL1 Expression and Burden of Toxic Protein in Variant Carrying Endothelium

- Toll Like Receptor 4/7 Ligation
  - Down stream TLR4 effectors bind the APOL1 Promoter
  - Interferon Regulatory Factor, enhances both interferon and APOL1 transcription

- Inflammatory Cytokines
  - Types I and II Interferons
  - TNF-α

(Nichols et al. 2015) (Blazer et al. 2017)
Conceptual Model: SLE-Related Stimuli Increase Intracellular APOL1 Expression Causing Injury in Variant Carrying Cells

Inflammatory Stimulus:
- TLR Ligand
- IFN Gamma

↑APOL1 Expression

Reference Allele Cell
- Autophagy/Cell maintenance
- Normal Metabolism

Risk Variant Cell
- Autophagy initiation
- Pore formation
- Lysosome:
  - ↓ Autophagic flux
  - ↓ Mitophagy
  - Mitochondria respiration defects

Risk Variant Cell
- Functional Consequences?

Atherosclerosis Risk
APOL1 is Expressed in Vascular-Relevant Cell Types: Endothelial Cells and Mononuclear Cells. How Might Variants Influence Their Behavior?
Study Question:
What are the functional consequences of IFN-induced APOL1 over expression in human umbilical vein endothelial cells (HUVECs)?

Approach:
• Establish HUVEC cell cultures representing each genotype
• Confirm APOL1 expression response with cytokine treatment using qPCR and immunoblot
• Functional read outs:
  • Lysosome integrity
  • Autophagosome accumulation
  • Mitochondrial morphology

NYU Langone Health
SLE- Relevant Inflammatory Stimuli Increase Endothelial Cell APOL1 Expression Across Genotypes

APOL1 Messenger RNA: qPCR

<table>
<thead>
<tr>
<th>Cytokine Treatment</th>
<th>Expression Normalized to GAPDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Trt</td>
<td>0</td>
</tr>
<tr>
<td>IFN α</td>
<td>10</td>
</tr>
<tr>
<td>IFN γ</td>
<td>20</td>
</tr>
<tr>
<td>TNF α</td>
<td>10</td>
</tr>
</tbody>
</table>

IFNα, IFNγ, and TNFα induced APOL1 messenger RNA: means = 8.29, 18.2, 7.8 respectively

**IFNγ > other cytokines: (F=6.1; p=0.036)

APOL1 Protein: Immunoblot

Protein control: tubulin (red) APOL1 protein: (green)
In vivo Correlate APOL1 is Expressed in the Vascular Microenvironment

Figure 1: Axial sections of coronary arteries (explanted human hearts, magnification 1X). Sections denoted by * and ** represent samples taken from the same donor at a plaque free and plaque containing sites.
APOL1 Expression Increases with Increasing Coronary Injury

- Coronary Stenosis No Plaque
- Intimal Thickening No Plaque
- Pathological Intimal Thickening No Plaque

CD31

APOL1

Pathological Diagnosis
APOL1 Expression Increases with Increasing Coronary Injury

Cholesterol Clefts

Fibroatheromatous Plaque: Fibrous Cap, Necrotic Core, Foam Cells, and Extracellular Cholesterol

Advanced, Necrotic, Atherosclerotic Plaque

Pathological Diagnosis
APOL1 Staining Can Be Seen in Coronary Endothelial Cells and Invading Macrophages
APOL1 Variant Carrying Endothelial Cells Exhibit Decreased Lysosomal Membrane Integrity

Lysosome Intensity

Integrated Density

Genotype and Condition

G0/G0 Untrt
G0/G0 IFN
G0/G0 HCQ
RVG0 Untrt
RVG0 IFN
RVG0 HCQ
RVRV Untrt
RVRV IFN
RVRV HCQ

Lysotracker™

Blazer et. al
Variant Carrying Endothelium is Deficient in Autophagy—a Cellular Maintenance Process

**Autophagosomes: Green fluorescent Puncta**
Mitochondrial respiration profiles by genotype and treatment condition:

- White: G0/G0
- Purple: RV/G0
- Green: RV/RV
Interferon Lowers BHI More Significantly in Variant Carrying Endothelial Cells

- Bioenergetic Health Index (BHI): Validated measure of mitochondrial health
- Untreated HUVECs: No difference in BHI \((p=0.4)\)
- Interferon-treated RV/G0 and RV/RV HUVECs significantly dropped BHI \((p=0.001)\)
Healthy mitochondria must be maintain membrane potential to undergo fusion and escape mitophagy.

Healthy mitochondria escape degradation by mitophagy (analogous to autophagy), by fusing to form networks. This process requires adequate membrane potential. (Okamoto et al)
RV Homozygotes Exhibit IFN Dependent Mitochondrial Defects

Mitochondrial Area (n=1251)

Genotype and Treatment
Macrophage Read Outs
APOL1 Variant Carrying Macrophages Exhibit Impaired Mitochondrial Respiration

Mitochondrial Respiration Profiles By Genotype and Condition

- G0G0 notrt
- G0G0 IFN
- RVG0 notrt
- RVG0 IFN
- RVRV no trt
- RVRV IFN

Chronic Inflammatory Disease Activity

ATP Production

Spare Respiratory Capacity (%)
Variant-Carrying Macrophages Exhibit Less Metabolic Potential

![Graph showing metabolic phenotypes](image)
Confirmatory Immunofluorescence: Variant-Carrying Macrophages Exhibit Fewer Polarized Mitochondria as Measured by MitoProbe to MitoTracker Ratios
Confirmatory Immunofluorescence: Variant-Carrying Macrophages Exhibit Fewer Polarized Mitochondria as Measured by MitoProbe to MitoTracker Ratios
Translational implications

• Disparities in Cardiovascular outcomes—particularly in autoimmune disease—may be in part due to a genetic propensity towards endothelial injury
• APOL1 variant alleles are common in African Americans and may prime carriers for tissue injury
• The influence of APOL1 on tissue injury appears to be out of proportion to inflammatory insult
• Wider APOL1 genetic allele testing may aid in risk stratification
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Colton Center for Autoimmunity
Innate and TH17 Serum Cytokine Levels by SLEDAI and APOL1 Genotype

**African American**

- IL-1a
- IL-6
- IL-17

**Ghanaian**

- IL-1a
- IL-6
- IL-17