Genomic and Precision Medicine Forum
Duke Center for Applied Genomics & Precision Medicine

Patient-Stem Cell Derived Podocytes as Tools for Modeling APOL1-Associated Kidney Disease

Opeyemi Olabisi, MD, PhD
Assistant Professor of Medicine
Division of Nephrology

Duke Dept of Medicine
Talk Outline

- Overview of problem of APOL1 nephropathy
- Current state of APOL1 research
- Puzzle of incomplete penetrance of risk of APOL1 nephropathy
- Predicting the future: utility of human iPSC-podocyte model as predictor of APOL1 nephropathy
- Call to Action
Why is this story important to you?

1.) $40 billion

2.) 50%

3.) 35%
32 years old non-diabetic African American male with history of hypertension and biopsy-proven focal segmental glomerulosclerosis (FSGS) presents with worsening kidney function (eGFR: 35→25). He is accompanied by his 40 years old brother who is interested in donating one of his own kidneys to the patient.

They wish to know:
1) if his kidney disease is associated with APOL1 mutations.
2) likelihood of the patient developing at end stage kidney disease.
3) if it is safe for his older brother to donate a kidney to him.
Higher Rate of kidney failure in African Americans
Kidney Failure is Not a New Problem Among American Blacks
We Have Found The Enemy. It Lives on Chromosome 22

Association of Trypanolytic ApoL1 Variants with Kidney Disease in African Americans

Giulio Genovese,1,2* David J. Friedman,1,3* Michael D. Ross,4 Laurence Lecordier,5 Pierrick Uzureau,5 Barry I. Freedman,6 Donald W. Bowden,7,8 Carl D. Langefeld,8,9 Taras K. Oleksyk,10 Andrea L. Uscinski Knob,4 Andrea J. Bernhardy,1 Pamela J. Hicks,7,8 George W. Nelson,11 Benoît Vanhullebeke,5 Cheryl A. Winkler,12 Jeffrey B. Kopp,11 Etienne Pays,5† Martin R. Pollak1,13†

SCIENCE VOL 329 13 AUGUST 2010
Possessing 2 risk variants APOL1 (G1/G2) is associated with increased risk of kidney disease.

Clin Exp Nephrol; 2014; 18: 238-42
“Unintended” Consequences

Human

APOL1 (G1/G2)

Evolution

Kidney

Save the Giraffes
Allele frequencies of combined APOL1 risk variants
APOL1 genotype frequencies in African Americans

- **50-55%**: G0 / G0
- **35%**: G0 / G1, G0 / G2
- **10-15%**: G1 / G1, G2 / G2, G1 / G2

- Sleeping sickness: protective genotypes
- Kidney disease: high-risk genotypes
APOL1 Background

- 42kDa protein
- Absent in experimental animals
- Ubiquitously expressed in many tissue
- Expressed in kidney by podocytes and endothelial cells
- Liver is the primary source of circulating APOL1
- APOL1 in circulation is bound to HDL₃ particle (trypanolytic complex)
- Cellular localization: cytoplasmic and membrane associated.
- Physiologic function: innate immunity and ??
Current Tools of APOL1 Research

Population genetics

Current Strategies for Investigating APOL1 Nephropathy

Transgenic mammalian cell culture

Transgenic animals: zebrafish, mouse, frog oocytes

Lipid bilayer

Clinical Research
Proposed Mechanisms of Podocytopathy in APOL1-Associated Kidney

Currently, there is no unifying mechanism of APOL1 cytotoxicity

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Allele</th>
<th>Experimental System</th>
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<tbody>
<tr>
<td>Channel or pore</td>
<td>G1, G2</td>
<td>Cell culture</td>
</tr>
<tr>
<td>Mitochondrial dysfunction</td>
<td>G1, G2</td>
<td>Cell culture</td>
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<tr>
<td>Endolysosomal dysfunction</td>
<td>G1, G2</td>
<td>Cell culture, transgenic mice</td>
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<td>NLRP3 inflammasome activation</td>
<td>G2</td>
<td>Cell culture, transgenic mice</td>
</tr>
<tr>
<td>Protein kinase R activation</td>
<td>G1, G2</td>
<td>Cell culture, transgenic mice</td>
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<tr>
<td>αvβ3 integrin activation</td>
<td>G1, G2</td>
<td>Cell culture, transgenic mice</td>
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Question 1):

Is the patient’s FSGS associated with APOL1 mutations?
Clinical and histopathologic Findings Associated with APOL1-Kidney Diseases

- Interferon-associated FSGS
- Lupus nephritis
- Sickle cell nephropathy
- Diabetic nephropathy
- HIVAN
- ESRD
- FSGS
## Table 1. Clinical findings in patients with collapsing PGSs after treatment with IFN

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<tr>
<th>Parameter</th>
<th>1</th>
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<th>3</th>
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<th>6</th>
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<td>56</td>
<td>41</td>
<td>64</td>
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<td>23</td>
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<td>Yes</td>
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<td>Diabetes</td>
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<td>No</td>
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<td>No</td>
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<td>Yes</td>
<td>Yes</td>
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<td>Medical history</td>
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<td>Previous IVDA</td>
<td>Previous</td>
<td>Previous</td>
<td>IVDA</td>
<td>None</td>
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<td>None</td>
<td>Obesity</td>
<td>None</td>
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<td>HCV</td>
<td>HCV</td>
<td>HCV</td>
<td>HCV</td>
<td>HCV</td>
<td>Melanoma</td>
<td>MS</td>
<td>MS</td>
<td>MS</td>
<td>IPF</td>
<td>IPF</td>
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<td>Duration of IFN therapy (months)</td>
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<td>3</td>
<td>2</td>
<td>3</td>
<td>5</td>
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<td>36</td>
<td>48</td>
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<td>4</td>
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<td>α</td>
<td>α</td>
<td>α</td>
<td>β-1A</td>
<td>β-1B</td>
<td>β-1A</td>
<td>γ</td>
<td>γ</td>
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<td>SCr (mg/dl)</td>
<td>3.2</td>
<td>9.6</td>
<td>1.3</td>
<td>1.5</td>
<td>6.9</td>
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<td>0.7</td>
<td>2.6</td>
<td>2.5</td>
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<td>24-Hour Uprot (g/d)</td>
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<td>23.7</td>
<td>4.5</td>
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<td>2.4</td>
<td>4.0</td>
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<td>Serum albumin (g/dl)</td>
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<td>1.5</td>
<td>1.3</td>
<td>2.3</td>
<td>1.6</td>
<td>0.6</td>
<td>3.3</td>
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<td>3.1</td>
<td>2.0</td>
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<td>No</td>
<td>Yes</td>
<td>No</td>
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<td>Urine sediment</td>
<td>RBCs</td>
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<td>RBCs</td>
<td>Bland</td>
<td>Bland</td>
<td>Bland</td>
<td>RBCs</td>
<td>Bland</td>
<td>WBCs</td>
<td>Bland</td>
<td>RBCs</td>
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<td>Follow-up duration (months)</td>
<td>6</td>
<td>4</td>
<td>18</td>
<td>53</td>
<td>7</td>
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<td>NA</td>
<td>54</td>
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<td>Pulse only</td>
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<td>Yes</td>
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<td>No</td>
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<td>additional immunosuppression</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Cytosan</td>
<td>No</td>
<td>No</td>
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<tr>
<td>discontinue IFN</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>final SCR (mg/dl)</td>
<td>1.2</td>
<td>1.7</td>
<td>1.0</td>
<td>5.6</td>
<td>1.0</td>
<td>1.7</td>
<td>1.2</td>
<td>2.1</td>
<td>1.5</td>
<td>1.4</td>
<td>0.65</td>
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<tr>
<td>final 24-hour Uprot (g/dl)</td>
<td>3.6</td>
<td>10.0</td>
<td>Negative</td>
<td>NA</td>
<td>4.5</td>
<td>0.5</td>
<td>1.4</td>
<td>0.65</td>
<td>NA</td>
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</table>

HD-dep, hemodialysis dependent; IPF, idiopathic pulmonary fibrosis; IVDA, intravenous drug use; MS, multiple sclerosis; NA, not available; RA, rheumatoid arthritis; RBCs, red blood cells; SCR, serum creatinine; Uprot, urinary protein; WBCs, white blood cells.
High-risk APOL1 frequency is highest among blacks with kidney disease

African Americans

- FSGS/HIVAN: 72%
- HTN-ESRD: 40%

There is a 7/10 chances that the patient (FSGS) has high risk APOL1 genotype
Question 2):

What is the likelihood that this patient’s FSGS will progress to end stage kidney disease?
High Risk APOL1 Genotype is Associated with Rapid Progression to ESRD

Rapid CKD Progression

Delta eGFR: -2.2/year

Delta eGFR: -1.5/year

Early age of starting dialysis

Mean Age at Dialysis Initiation

# of ApoL1 Risk variants

Modified from:
Kanji Z, Powe CE, Powe NR, Pollak MR, Thadhani R et., al. JASN 2011; 22(11) 2091-7

AASK
NEJM 2013;369:2183-96
Question 3:
If his brother is a carrier of high risk APOL1 genotype,
i) will he also develop FSGS in the future?

ii) Will you advice him to become a kidney donor?
The Risk of ESRD is higher among black donors

High Risk APOL1 genotype is associated with low pre- and post-donation renal function

**APOL1 Genotype and Renal Function of Black Living Donors**

Mona D. Doshi,¹ Mariella Ortigosa-Goggins,² Amit X. Garg,³ Lihua Li,³ Emilio D. Poggio,⁴ Cheryl A. Winkler,⁵ and Jeffrey B. Kopp⁶

A

![Graph showing eGFR (mL/min/1.73 m²) before and after donation for low-risk and high-risk APOL1 genotypes.](image)

- Pre-donation
- Post-donation

JASN, 2018
Limitation of APOL1 genotyping: it does not distinguish HR carriers who will develop APOL1 nephropathy from those that will remain healthy.

All African Americans

APOL1 Genotyping

Low Risk APOL1 genotype carriers (will be free from AAKD, 80%)

High Risk Carriers (6.3 million people)

- High Risk APOL1 genotype carriers (will develop AAKD, 20%)
- Low Risk APOL1 genotype carriers
There is Need for a Risk Stratification Tool

APOL1 Genotyping

High Risk Carriers
(6.3 million people)

Low Risk Carriers

Unlikely to develop APOL1 nephropathy
(80%, 5 million people)

Highly likely to develop APOL1 nephropathy
(20%, 1.3 million people)

What is Currently Possible

The future
Podocyte Injury is central to ApoL1-induced kidney Disease

A common feature of APOL1 associated nephropathy:
1) Histologic evidence of podocyte injury
2) Proteinuria (may precede GFR decline)
Lack of disease-relevant podocyte model is a major obstacle to progress in APOL1 research.
Two-hit model of APOL1-podocytopathy/nephropathy

- High-risk ApoL1 genotype (1st hit)
- Environmental factors such as IFNγ or HIV) (2nd hit)

Podocyte injury/ApoL1-nephropathy

However, only 50% of African Americans carriers of high-risk ApoL1 genotype develop HIVAN in the setting of uncontrolled HIV infection
Three-hit Model of APOL1-podocytopathy/nephropathy

High-risk ApoL1 genotype (1st hit)

Environmental factors—such as IFNγ or HIV) (2nd hit)

Podocyte-specific modifier (3rd hit)

Gene expression

• Genetic
• Epigenetic
• Transcriptional product: Protein/LncRNA/miRNA
• Post-translational modification

APOL1-podocytopathy/nephropathy
Patient-Derived Podocytes (iPods) as Tool for studying APOL1 Nephropathy

Biomarkers discovery

Discovery of mechanism of APOL1-podocytopathy

Personalized drug discovery

IPSC-podocyte retains genetic and reestablishes epigenetic identity of the donor’s native podocyte
Enrollment Criteria

**General Exclusion Criteria:**
1) Diagnosis of Diabetes Mellitus
2) Diagnosis of HIV infection
3) Recent blood transfusion
4) Exposure to alkylating chemotherapy

**FSGS Cases**
- Biopsy-proven, non-diabetic FSGS (n=17)
- Excluded due to DM (n=1)
- Enrolled as Cases (n=16)
- APOL1 Genotype:
  - 2 risk alleles (11/16; 68.7%)
  - 1 risk allele (3/16; 18.7%)
  - 0 risk allele (2/16; 12.5%)

**Healthy Controls**
- Healthy Volunteer with no known kidney disease (n=22)
- Excluded due to DM, eGFR < 60, or UTP/Cr >0.15 (n=2)
- Enrolled as Controls (n=20)
- APOL1 Genotype:
  - 2 risk alleles (2/20; 10%)
  - 1 risk allele (10/20; 50%)
  - 0 risk allele (8/20; 40%)
## Summary of Clinical Characteristics of Enrolled Participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Biopsy-proven FSGS Cases (n=16)</th>
<th>Healthy Controls (n=20)</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>11 (68.7%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Women</td>
<td>5 (31.3%)</td>
<td>12 (60%)</td>
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<tr>
<td><strong>APOL1 Genotype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 risk alleles</td>
<td>11 (68.7%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>1 risk allele</td>
<td>3 (18.7%)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>0 risk allele</td>
<td>2 (12.5%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td><strong>Mean age at enrollment (SD)</strong></td>
<td>45 (10.5)</td>
<td>51.5 (8.9)</td>
</tr>
<tr>
<td><strong>eGFR (ml/min/1.73m^2)</strong></td>
<td>34 (0-102)</td>
<td>98.9 (63-130)</td>
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<tr>
<td><strong>UTP/Cr (SD)</strong></td>
<td>3.6 (3.4)</td>
<td>0.08 (0.03)</td>
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<tr>
<td><strong>FSGS with collapsing features</strong></td>
<td>6 (37.5%)</td>
<td>Not applicable</td>
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</table>
Characterization of Patients–derived iPSCs

Histochemical Confirmation of stem cell markers

Confirmation of Trilineage Differentiation Potential (Pluritest)

Confirmation of Genomic integrity (Karyotyping)
Reprograming stem cells into podocytes

Mature induced-pluripotent-stem-cell-derived human podocytes reconstitute kidney glomerular-capillary-wall function on a chip

Samira Musah¹²³, Akiko Mammoto⁴, Thomas C. Ferrante¹, Sauveur S. F. Jeanty¹, Mariko Hirano-Kobayashi¹⁴, Tadanori Mammoto⁴, Kristen Roberts¹, Seyoon Chung¹, Richard Novak¹, Miles Ingram¹, Tohid Fatanat-Didar¹, Sandeep Koshy¹, James C. Weaver¹, George M. Church¹²³ and Donald E. Ingber¹³⁴⁵*
iPSC-Podocyte Whole Genome Transcriptome Analysis by RNA – Seq

<table>
<thead>
<tr>
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<th>HR Case (N = 7)</th>
<th>HR Control (N = 2)</th>
<th>LR Control (N = 2)</th>
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<tbody>
<tr>
<td>Untreated</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>+ IFNγ</td>
<td>D</td>
<td>E</td>
<td>F</td>
</tr>
</tbody>
</table>

HR Case: High risk genotype, with FSGS
HR Control: High risk genotype, no FSGS
LR Control: Low risk genotype, no FSGS
Human iPSCs-derived podocytes express markers of podocytes

O. Olabisi et. al. pre publication
**IFNγ Induces Unique DEGs in iPSC-Podocytes of FSGS patients with HR genotypes**

### Table

<table>
<thead>
<tr>
<th></th>
<th>HR Case (N = 7)</th>
<th>HR Control (N = 2)</th>
<th>LR Control (N = 2)</th>
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<tr>
<td>Untreated</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>+ IFNγ</td>
<td>D</td>
<td>E</td>
<td>F</td>
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<tr>
<td>DEG: log fold change &gt; 1, FDR &lt; 0.05</td>
<td>~15,000 DEG</td>
<td>O. Olabisi et. al. pre publication</td>
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IFNγ-Induced Genes in HR Cases

Table:

<table>
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<th>HR Case (N = 7)</th>
<th>HR Control (N = 2)</th>
<th>LR Control (N = 2)</th>
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<tbody>
<tr>
<td>Untreated</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>+ IFNγ</td>
<td>D</td>
<td>E</td>
<td>F</td>
</tr>
</tbody>
</table>

Significance level

Higher Expression in HR Cases at baseline

Higher Expression in HR Cases + IFNγ

O. Olabisi et. al. pre publication
IFNγ-Induced Genes in HR Controls

Higher Expression in HR Controls at baseline

- Higher Expression in HR Controls + IFNγ

O. Olabisi et. al. pre publication
IFNγ induces higher levels of chemotaxic chemokines in iPSC-Podocytes of HR Cases

O. Olabisi et. al. pre publication
Integrative Genomics Identifies Novel Associations with APOL1 Risk Genotypes in Black NEPTUNE Subjects

Matthew G. Sampson,* Catherine C. Robertson,* Sebastian Martini,† Laura H. Mariani,† Kevin V. Lemley,‡ Christopher E. Gillies,* Edgar A. Otto,* Jeffrey B. Kopp,§ Anne Randolph,† Virginia Vega-Warner,* Felix Eichinger,† Viji Nair,† Debbie S. Gipson,* Daniel C. Cattran,‖ Duncan B. Johnstone,¶ John F. O’Toole,** Serena M. Bagnasco,†† Peter X. Song,‡‡ Laura Barisoni,§§ Jonathan P. Troost,* Matthias Kretzler,††† John R. Sedor,**‖ and the Nephrotic Syndrome Study Network


Table 5. Differentially expressed genes in glomerulus

<table>
<thead>
<tr>
<th>Gene</th>
<th>Fold Change</th>
<th>SAM Score</th>
<th>q Value</th>
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<tr>
<td>CXCL9</td>
<td>4.1</td>
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<td>CXCL11</td>
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<td>UBD</td>
<td>3.0</td>
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</table>
Expression of CXCL9-11 is regulated by JAK-STAT

IRGs:
CXCL9
CXCL10
CXCL11
JAK-STAT1 Pathway is Upregulated in iPSC-Podocytes of HR Case

Ingenuity Pathway Analysis

Canonical Pathways

- Dendritic Cell Maturation
- T Cell Exhaustion Signaling Pathway
- Death Receptor Signaling
- Pattern Recognition Receptors of Bacteria and Viruses
- Th1 Pathway
- Retinoic acid Mediated Apoptosis Signaling
- Neuroinflammation Signaling Pathway
- Interferon Signaling
- Huntington's Disease Signaling
- Activation of IRF by Cytosolic Pattern Recognition Receptors
- Role of RIG1-like Receptors in Antiviral Innate Immunity
- TREM1 Signaling
- Osteoarthritis Pathway
- Th17 Activation Pathway
- Sphingosine-1-phosphate Signaling
- Endothelin-1 Signaling
- Salvage Pathways of Pyrimidine Ribonucleotides
- Inflammasome pathway
- Tec Kinase Signaling
- iNOS Signaling
- Type I Diabetes Mellitus Signaling
- Acute Phase Response Signaling
- Th2 Pathway
- Prolactin Signaling
- JAK/Stat Signaling

O. Olabisi et. al. pre publication
JAK-STAT1 Pathway is Upregulated in iPSC-Podocytes of HR Case

O. Olabisi et. al. pre publication
JAK-STAT signaling is activated in the kidney and peripheral blood cells of patients with focal segmental glomerulosclerosis

Jianling Tao\textsuperscript{1,3}, Laura Mariani\textsuperscript{2,3}, Sean Eddy\textsuperscript{2}, Holden Maecker\textsuperscript{1}, Neeraja Kambham\textsuperscript{1}, Kshama Mehta\textsuperscript{1}, John Hartman\textsuperscript{2}, Weiqi Wang\textsuperscript{1}, Matthias Kretzler\textsuperscript{2,4} and Richard A. Lafayette\textsuperscript{1,4}

Upregulation of Interferon Regulated Genes in iPSC-Podocytes of HR Case

But not all Interferon Regulated Genes are upregulated in iPSC-Podocytes of HR Case
Summary: JAK-STAT Pathway and IRGs are potentiated in iPSC-podocyte of Blacks with APOL1 Nephropathy

IRGs:
- CXCL9
- CXCL10
- CXCL11
Potential Application of iPSC-Podocyte Risk Stratification Tool

All African Americans

APOL1 Genotyping

High Risk Carriers (6.3 million people)

Low Risk Carriers

What is Currently Possible

Highly Likely to Become Possible as Result of the Proposed Studies

Highly likely to develop AAKD (20%, 1.3 million people)

Unlikely to develop AAKD 80%, 5 million people

iPSC-Podocyte

Transcriptome-based Biomarkers analysis

IFNγ
Future Direction funded by DP2 Award

Validation Cohorts

Duke APOL1 Nephropathy Biorepository (DARB)

H3Africa

**Cases:** Black non-diabetic patients with biopsy-proven FSGS

**Controls:** Black patients (>50 years old) with normal kidney function

*Geriatrics with normal kidney function*
If you see eligible cases/controls, call or email us

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Cases: Black non-diabetic patients with biopsy-proven FSGS
Controls: Black patients (>50 years old) with normal kidney function
*Geriatrics with normal kidney function
Summary

1. Individuals of recent African ancestry have excess risk of developing end stage kidney disease.

2. Variants in APOL1 gene explain much of this excess risk.

3. Only some carriers of 2 risk alleles of APOL1 gene develop APOL1-nephropathy.

4. Human Stem Cell-derived podocytes are promising tools for screening and discovering therapy for APOL1 nephropathy.

5. Potentiated Inflammatory Pathways may be important modifiers of APOL1 nephropathy
Acknowledgement

- Members of Olabisi Laboratory
- Duke Department of Medicine (Kathleen Cooney)
- Division of Nephrology (Myles Wolf)
- Duke Molecular Physiology Institute

Collaborators: Colleagues, patient participants, H3Africa.

Funding Sources:
- Robert Wood Johnson Foundation (Harold Amos Faculty Development Program)
- NIH Director’s New Innovator Award 1DP2-DK124891
Patient-Stem Cell Derived Podocytes as Tools for Modeling APOL1-Associated Kidney Disease

Opeyemi Olabisi, MD, PhD
Assistant Professor of Medicine
Division of Nephrology
# Lifetime Risk of APOL1 Nephropathies

<table>
<thead>
<tr>
<th>AA population genotype frequencies:</th>
<th>Low-Risk Genotypes</th>
<th>High-Risk Genotype</th>
<th>High-Risk Genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Risk Alleles ~42%</td>
<td>1 Risk Alleles ~45%</td>
<td>2 Risk Alleles ~13%</td>
<td>Explained variance</td>
</tr>
<tr>
<td>1 Risk Alleles ~45%</td>
<td></td>
<td></td>
<td>Population-attributed Risk</td>
</tr>
<tr>
<td>2 Risk Alleles ~13%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIVAN</th>
<th>2.5% (1:40)</th>
<th>4% (1:25)</th>
<th>50% (1:2)</th>
<th>37%</th>
<th>68%</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSGS</td>
<td>0.2% (1:500)</td>
<td>0.3% (1:333)</td>
<td>4.25% (1:24)</td>
<td>18%</td>
<td>68%</td>
</tr>
<tr>
<td>HTN-attributed ESRD</td>
<td>1.5% (1:65)</td>
<td></td>
<td>11% (1:9)</td>
<td></td>
<td>52%</td>
</tr>
</tbody>
</table>

Modified from Seminars in Nephrology, 2015; 35:222-236
Kidneys with APOL1 Risk Variants Show Increased Allograft Failure

Risk of APOL1 Nephropathy travels with the kidney

American Journal of Transplantation 2011; 11: 1025-1030
IFNγ Induces Significant Transcriptional Changes in iPSC-Podocytes
Sub-Saharan Africans have highest frequency of risk variants ApoL1

Fig. 1. Map of West Africa with the known population frequencies of APOL1 two-risk allele carriers.

Ulasi et al., Nephron Clin Pract 2013; 123:123-8
iPSC-Podocytes of HR Cases Have Higher Steady State APOL1 Protein levels

**mRNA**

![Graph showing mRNA expression](image)

**Protein**

![Graph showing protein expression](image)

O. Olabisi et. al. pre publication
Proposed Model of APOL1-Induced Podocytopathy

Legend:
2nd hit
A Model of G1 or G2 APOL1-Induced Cytotoxicity in HEK cells

Olabisi et al., PNAS (2016); 113:830-7