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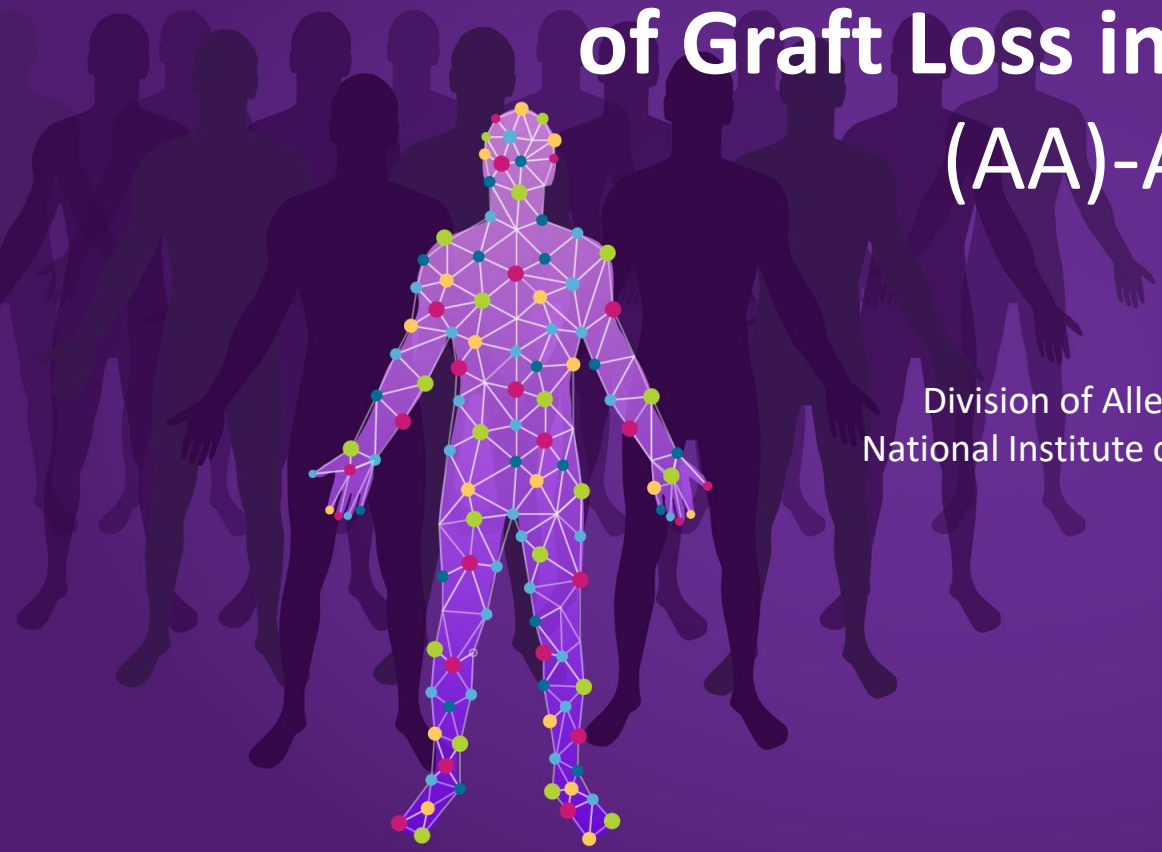
# Biological Basis for Increased Risk of Graft Loss in African American (AA)-APOL1 and Beyond



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CEOT CUTTING EDGE of TRANSPLANTATION

**TRANSPLANT SUMMIT** 2019

***NO SIZE FITS ALL:*** *Uncovering the Potential of Personalized Transplantation*

**FEBRUARY 21–23, 2019 • ARIZONA BILTMORE • PHOENIX, AZ**

## Disclosures:

**Speaker is on the APOLLO Steering Committee**

**No financial conflicts of interest**

**No other disclosures or conflicts**

**Presentation does not discuss off label use of any therapeutics or diagnostics**

**Views expressed are not from, or that of, DHHS, NIH, NIDDK, NIMHD, NIAID, DAIT, TB or the Federal government but represent views of the speaker**

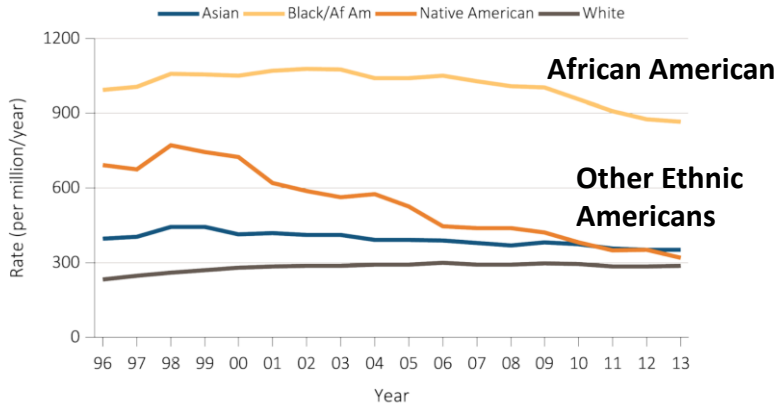
## Learning Objectives

1) **Through analysis of the biological basis for increased risk of kidney allograft loss in Americans of recent African ancestry (AA) and A*POL-1 demonstrate* an understanding of the biology and potential ethical, legal, social, and policy challenges that may accompany the translation of this new genomic knowledge into clinical transplantation and public health practice**

2) ***Prospective* Study of *APOL1* in Kidney Transplantation: NIH-supported *APOL-1* Long-term Kidney Transplantation Outcomes Network (APOLLO) national study to assess whether AA kidney donor *APOL1* genotypes predict shorter allograft survival in recipients and the post-donation health in living AA donors**

***MYH9* is associated with nondiabetic end-stage-renal disease in African Americans. 2008 Nature Genetics 40:10; 1185-1192**

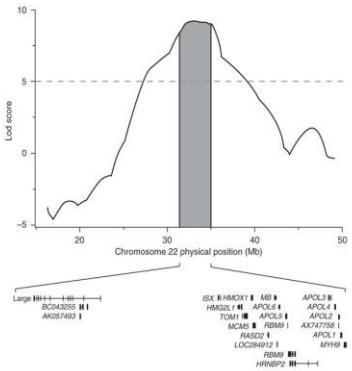
## Adjusted ESRD incidence rate, by race categories (1996–2013)



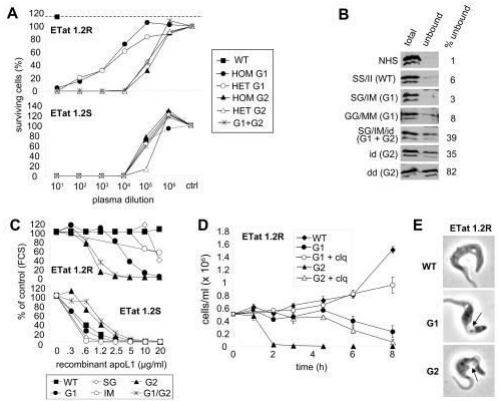

*Data Source: Special analyses, USRDS ESRD Database. *Adjusted for age and sex. The standard population was the U.S. population in 2011. Abbreviations: Af Am, African American; ESRD, end-stage renal disease.*

Figure 2 : Region of association with nondiabetic ESRD on chromosome 22.

From: MYH9 is associated with nondiabetic end-stage renal disease in African Americans

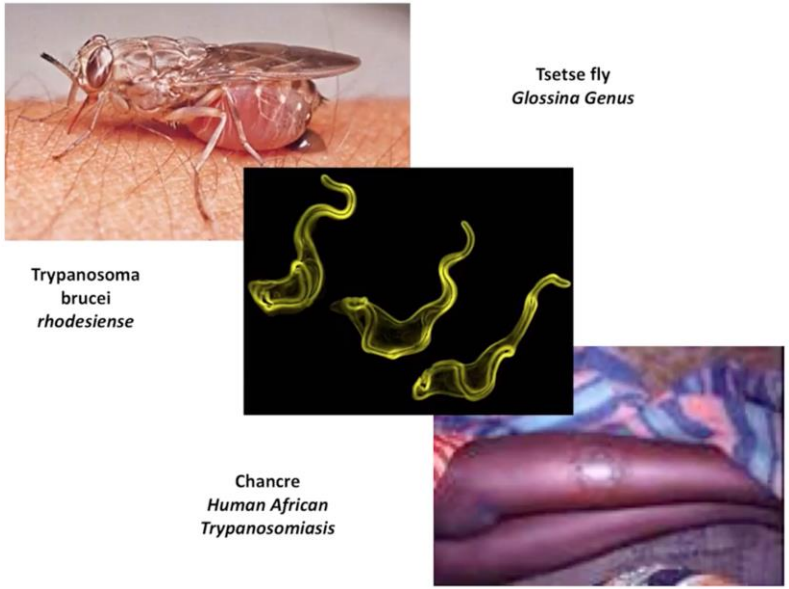


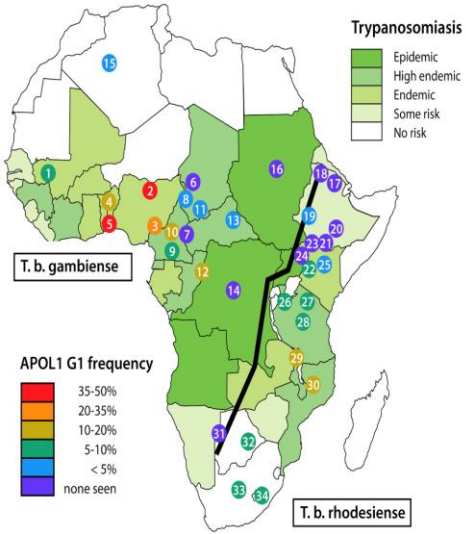

The peak lod score was 9.31, and the 95% CI spanned from 31.388650 to 35.039798 Mb, covering 22 genes. We considered a lod score for association at a particular locus of >5 as approximately genome-wide significant.

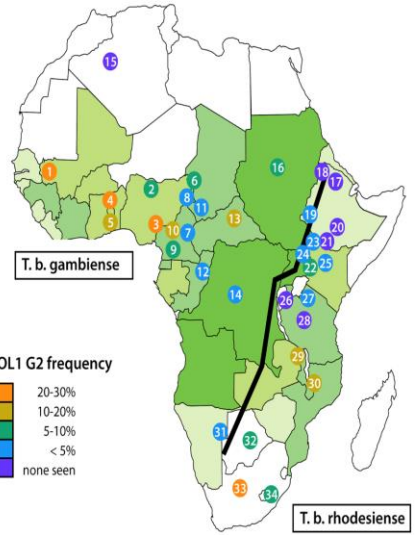



**Association of Trypanolytic ApoL1 Variants with Kidney Disease in African Americans *Science* 2010: 329:5993;841-845**

# Two high-risk variants in the *APOL1* gene (G1 and G2) have increased high frequency in Africa because they confer protection from *Trypanosoma brucei rhodesiense* infection (sleeping sickness)



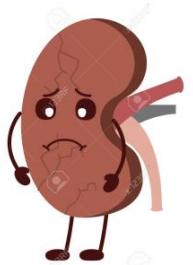



# Opportunity for deeper understanding of disease mechanism (s) and personalized renal transplantation

2 high-risk renal alleles/variants (G1, G2)

0 or 1 high-risk allele/variant (G0)

# The presence of 2 high risk renal variants in AA kidney provides the mechanistic tapestry for earlier progression to non-diabetic end stage renal disease in AA

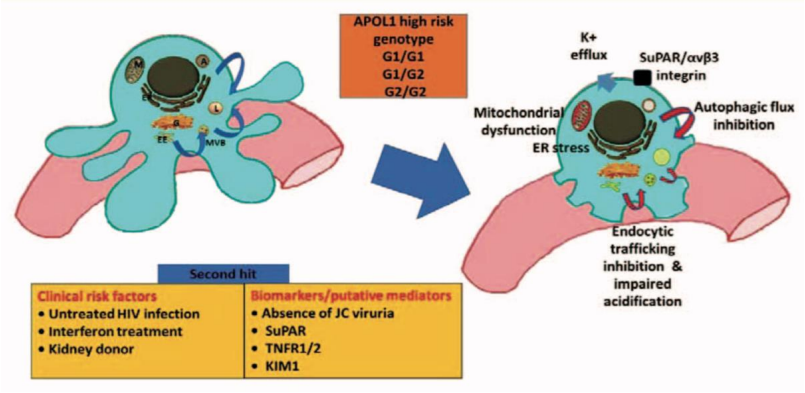


**2 high-risk renal alleles (G1, G2)**
**vs.**
**0 or 1 high risk allele**

**Deceased donor kidney transplantation**

**Living donor kidney transplantation**

**Biological mechanism**




**NIH supported: APOL1 Long-term kidney transplantation outcomes network (APOLLO)**

# Kidneys from deceased AA donors with 2 *APOL1* high risk alleles are associated with increased risk of allograft failure and reduced function

| | Daniel (AJT) 2011 | Freedman (AJT) 2015 | Freedman (AJT) 2016 |
|---|---|---|---|
| Transplant center | WF | WF, UNC, UAB | WF, UNC, UAB Emory, DeKAF |
| Transplant subjects (renal) | 136 | 675 | 1153 |
| 0 or 1 high risk *APOL1* variants | 114 (84%) | 576 (85%) | 981 (85%) |
| 2 high risk *APOL1* variants | 22 (16%) | 99 (15%) | 172 (15%) |
| Follow-up (m) | 28 | 24 | 36 |
| Adjust hazard ratio for allograft failure with 2 vs. 0/1 high risk variants | 3.84 (no 95% CI) | 2.26 (95% CI: 1.37-3.74) | 2.05 (95% CI: 1.39-3.02) |

…though most recipients of a donor graft with 2 *APOL1* high-risk gene variants do not develop early allograft failure (? 2nd hit)

# The effect of adjusting the present KDRI equation by using *APOL1* genotype instead of race adds more precision to the KAS

American Journal of Transplantation 2017; 17: 1840–1848
Wiley Periodicals Inc.



doi: 10.1111/ajt.14113

## Effect of Replacing Race With Apolipoprotein L1 Genotype in Calculation of Kidney Donor Risk Index

B. A. Julian[1,*], R. S. Gaston[1], W. M. Brown[2], A. M. Reeves-Daniel[3], A. K. Israni[4,5], D. P. Schladt[5], S. O. Pastan[6], S. Mohan[7], B. I. Freedman[3,8] and J. Divers[2,8]

genotype in KDRI better defines risk associated with kidneys transplanted from deceased African American donors, substantially improves KDRI score for 85–90% of kidneys offered, and enhances the link between donor quality and recipient need.

**The goal of the KDRI allocation system is to eliminate unrealized allograft years by improving matching of kidneys and recipients using estimates of organ quality and recipient longevity**

**Ten factors in the kidney donor are used to compute the KDRI:**

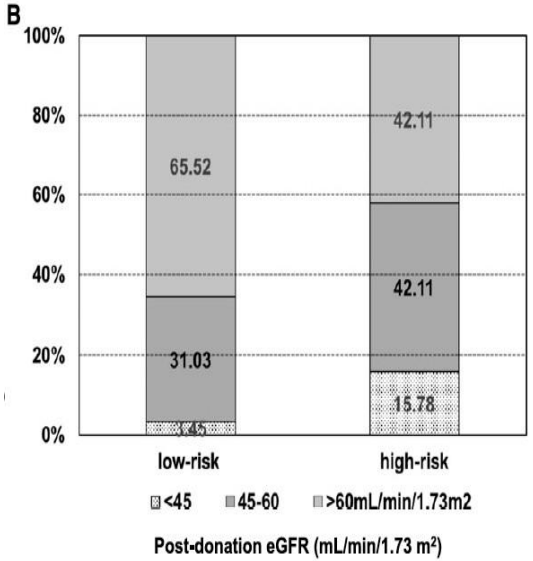
Age, height, weight, ethnicity (African American vs non-African American), history of hypertension, history of diabetes, cause of death – stroke, serum creatinine, hepatitis C status, donation after circulatory death

**Table 2:** Comparison of KDRIs and KDPIs, grouped by number of *APOL1* renal-risk variants

| | 0 or 1 *APOL1* variant | | 2 *APOL1* variants | |
|---|---|---|---|---|
| KDRI equation | Current | Revised | Current | Revised |
| Race | AA | AA | AA | AA |
| Coefficient β | | | | |
| Race | 0.179 | NA | 0.179 | NA |
| *APOL1* genotype | NA | 0.000 | NA | 0.411 |
| Hazard ratio | | | | |
| Race | 1.196 | NA | 1.196 | NA |
| *APOL1* genotype | NA | 1.000 | NA | 1.508* |
| KDRI | 1.4972 | 1.2518 | 1.4689 | 1.8527** |
| Scaling factor (for 2014) | 1.2218 | 1.2218 | 1.2218 | 1.2218 |
| KDRI scaled | 1.2254 | 1.0246 | 1.2023 | 1.5164 |
| KDPI | 71% | 53% | 69% | 88% |

Julian BA et al. AJT 2017

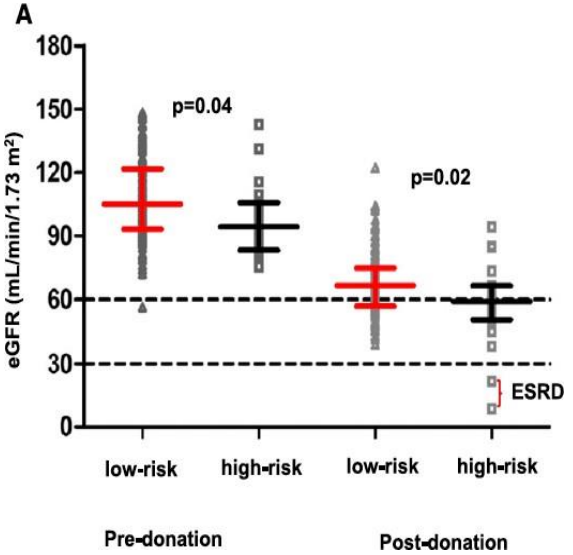
# *APOL1* and living donor outcomes




**Post-Donation: Greater proportion have CKD 3 or lower**

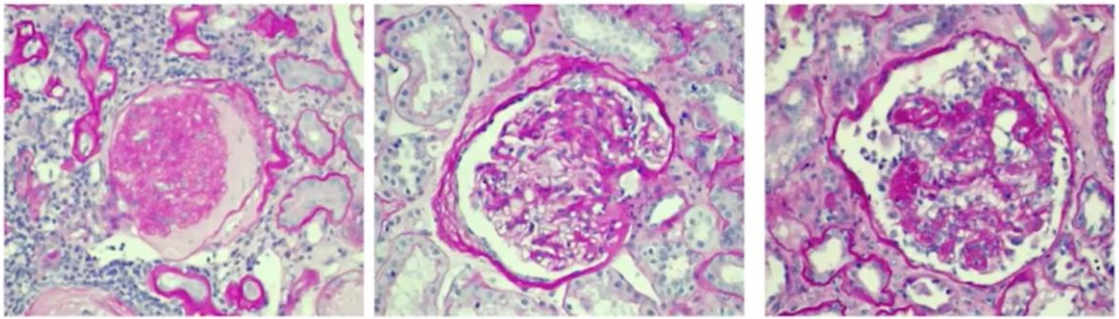
Doshi et al JASN 2018

## Lower eGFR with 2 *APOL1* risk alleles



# Spectrum of *APOL1*-associated nephropathy

| Focal Global Glomerulosclerosis | Focal Segmental Glomerulosclerosis | Collapsing FSGS (HIVAN) |
|---|---|---|
| "Hypertensive nephrosclerosis" | | |



| Odds Ratio=7.3 | OR=17 | OR=29 |
|---|---|---|

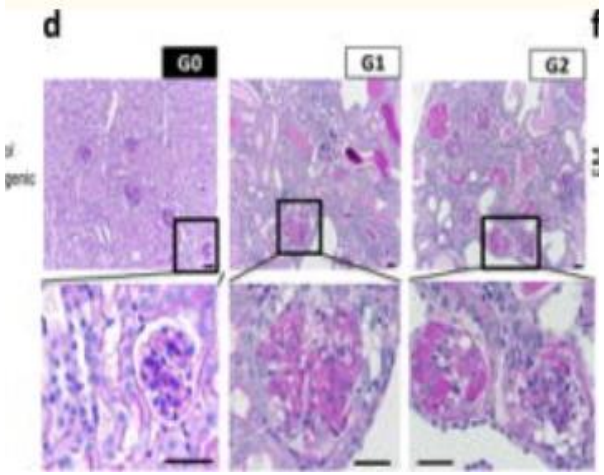
**Proteinuria & nephropathy progression rate**

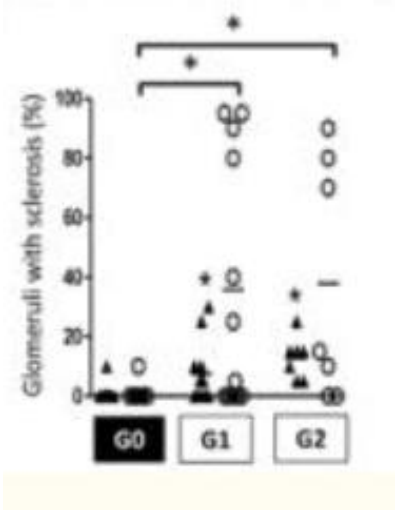
Freedman, Bowden & Rich. *Brenner and Rector's The Kidney* 9th Edition 2011

+ sickle cell nephropathy
+ severe lupus nephritis
+ donor allograft failure

**Direct evidence linking APOL1 gene to pathogenesis was challenging since this gene is only present in some primates and humans**

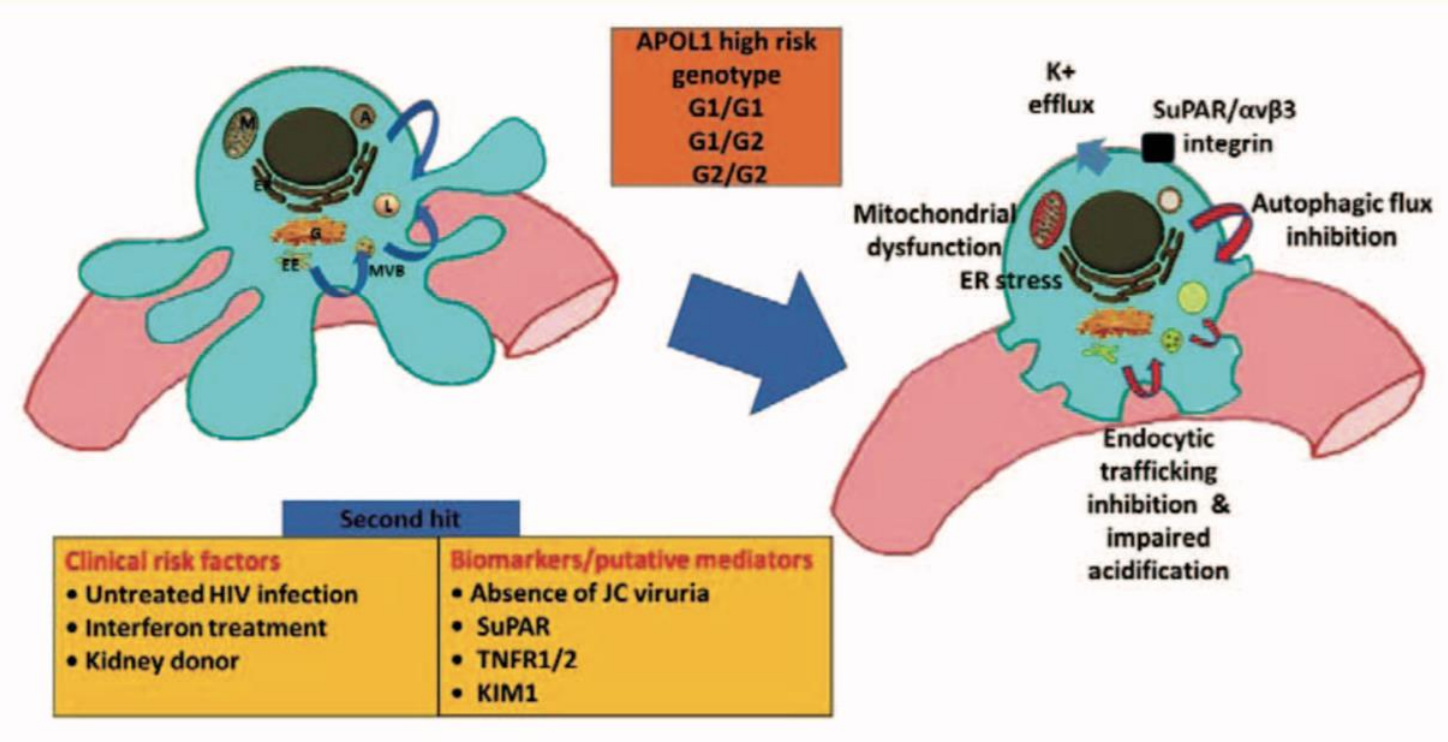
# Transgenic expression of human *APOL1* risk variants in podocytes induces kidney disease in mice. Beckerman P: Nature Medicine (2017) 23:4;429-438




Generation of a mouse model with cell-type-specific inducible expression of APOL1 variants

Evidence *APOL1* variants cause kidney disease – not simply disease association


APOL1 high risk genotype
G1/G1
G1/G2
G2/G2
M
A
E
L
G
EE
MVB
K+ efflux
SuPAR/αvβ3 integrin
Mitochondrial dysfunction
ER stress
Autophagic flux inhibition
Endocytic trafficking inhibition & impaired acidification
Second hit
Clinical risk factors
• Untreated HIV infection
• Interferon treatment
• Kidney donor
Biomarkers/putative mediators
• Absence of JC viruria
• SuPAR
• TNFR1/2
• KIM1

# *APOL1* and kidney transplantation

## 2 vs. (0-1)*APOL1* high-risk renal variants in donor

1. Increased risk of graft failure in the recipient
2. Recipient *APOL1* alleles – no impact on graft outcomes (donor genotype drives outcome phenotype)
3. BUT, 4 – 5 subjects with high-risk kidney variants do not develop early graft failure (? requires 2nd trigger or hit)
4. Increased risk of CKD in AA living donors

# Quo vadis…mandatory *APOL1* genetic testing?

## *APOL1* Long-term kidney transplantation outcomes network

**(…prospectively assess whether AA kidney donor high-risk renal *APOL1* variants predict shorter allograft survival in recipients and post-donation health in living donors**

# Acknowledgements

**Patients and human research subjects**
**Wake Forest Scientific and Data Research Center**
**APOLLO Network Investigators**
**United Network Organ Sharing (UNOS)**
**Scientific Registry of Transplant Recipients (SRTR)**
**Association of Organ Procurement Organizations (AOPO)**
**American Society of Histocompatibility and Immunogenetics (ASHI)**
**Cutting Edge of Transplantation (CEOT)**

**www.TheApolloNetwork.org**

**QUESTIONS ?**