APOL1 and the NIH-APOLLO Study

Global Innovations in Patient Centered Kidney Care
George Washington School of Medicine & AAKP
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Barry I. Freedman, MD, FACP
John H. Felts III Professor
Chief, Section on Nephrology
Executive Director, Wake Forest Dialysis Program

Wake Forest™
School of Medicine

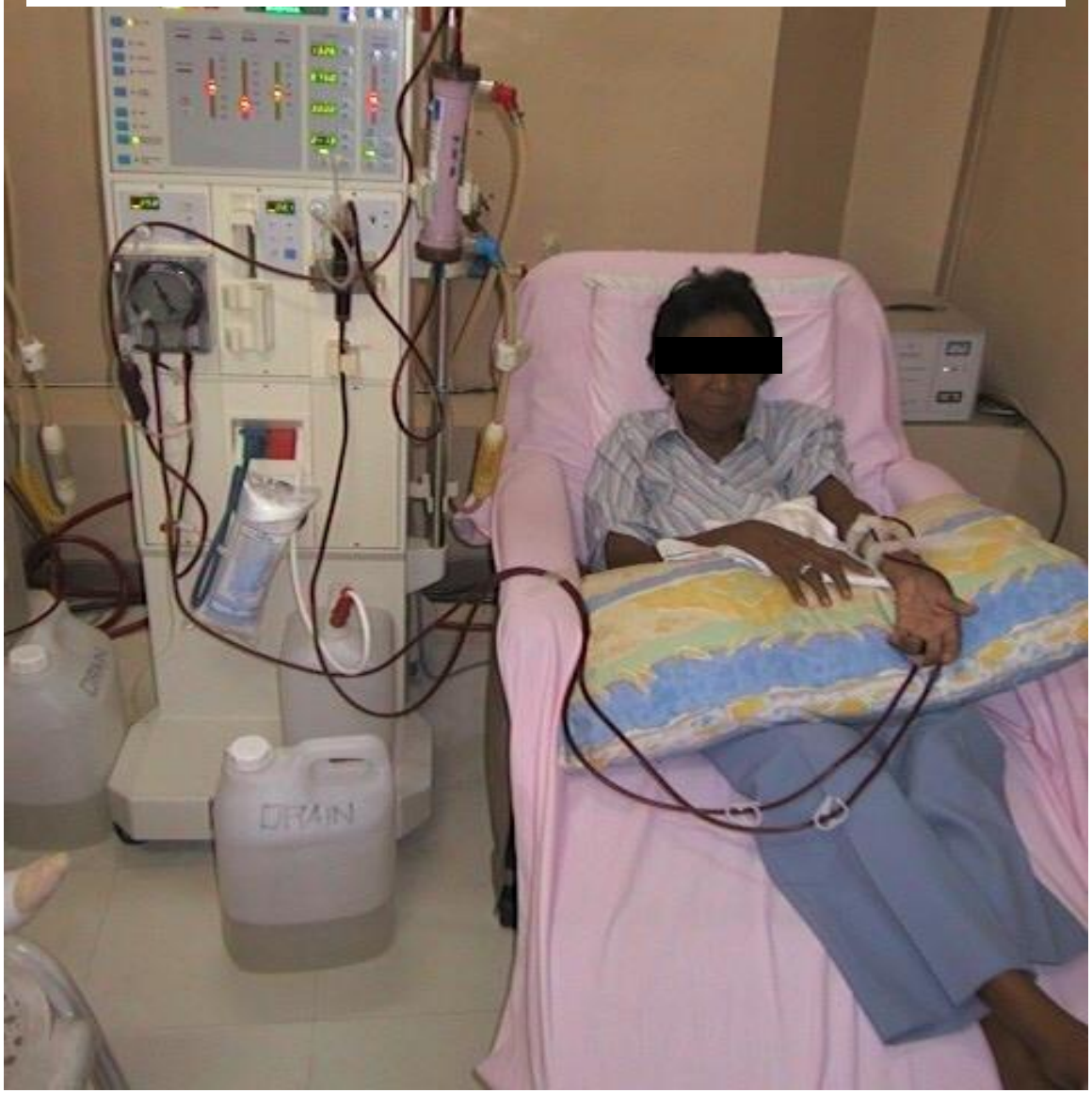
Disclosures

- Research support - NIH
- Consultant - AstraZeneca and Renalytix AI
- Wake Forest University Health Sciences and Barry Freedman have rights to a U.S. patent relating to *APOL1* gene testing

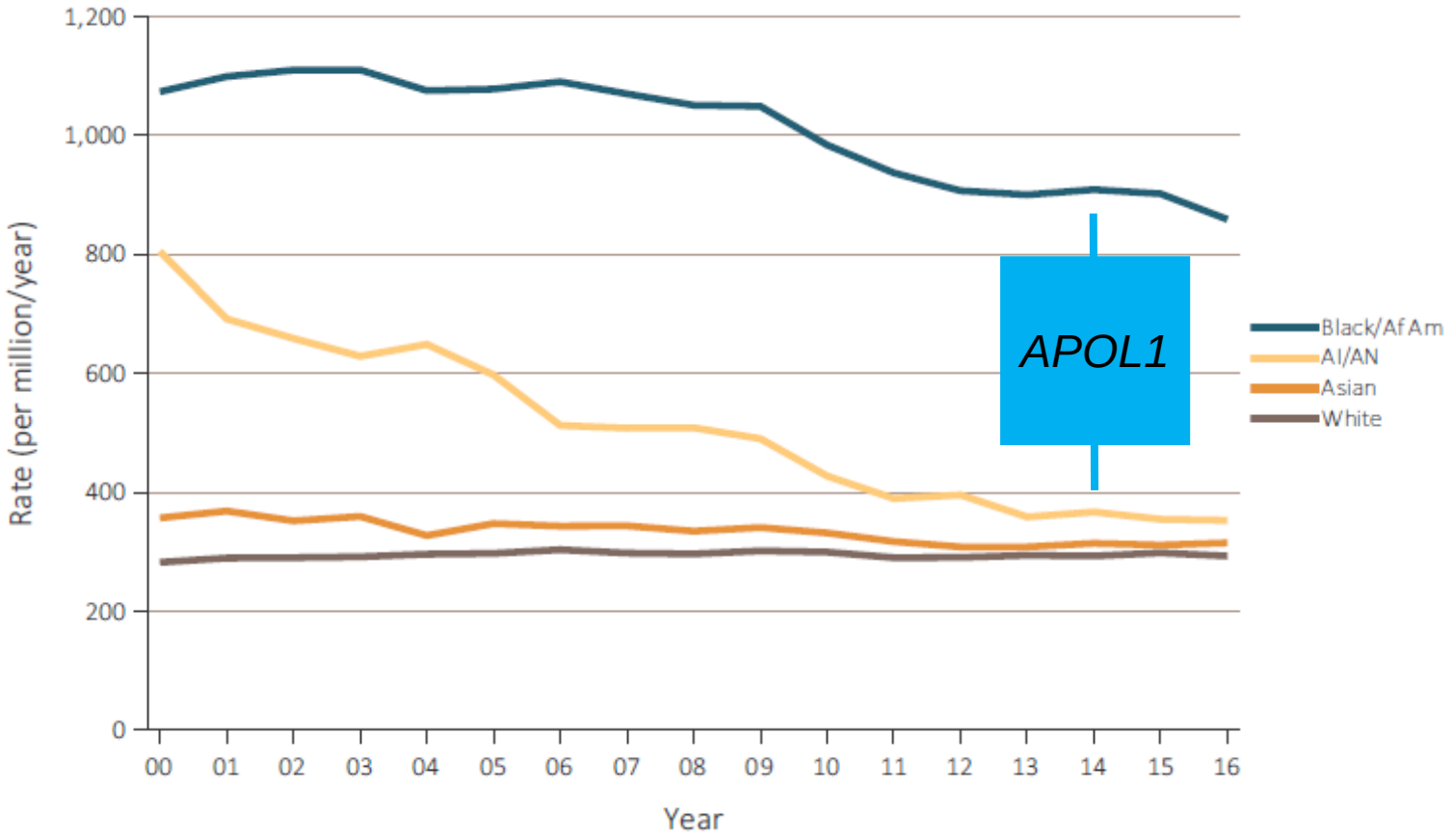
Need to Reclassify Etiologies of ESRD on the CMS 2728 Medical Evidence Report

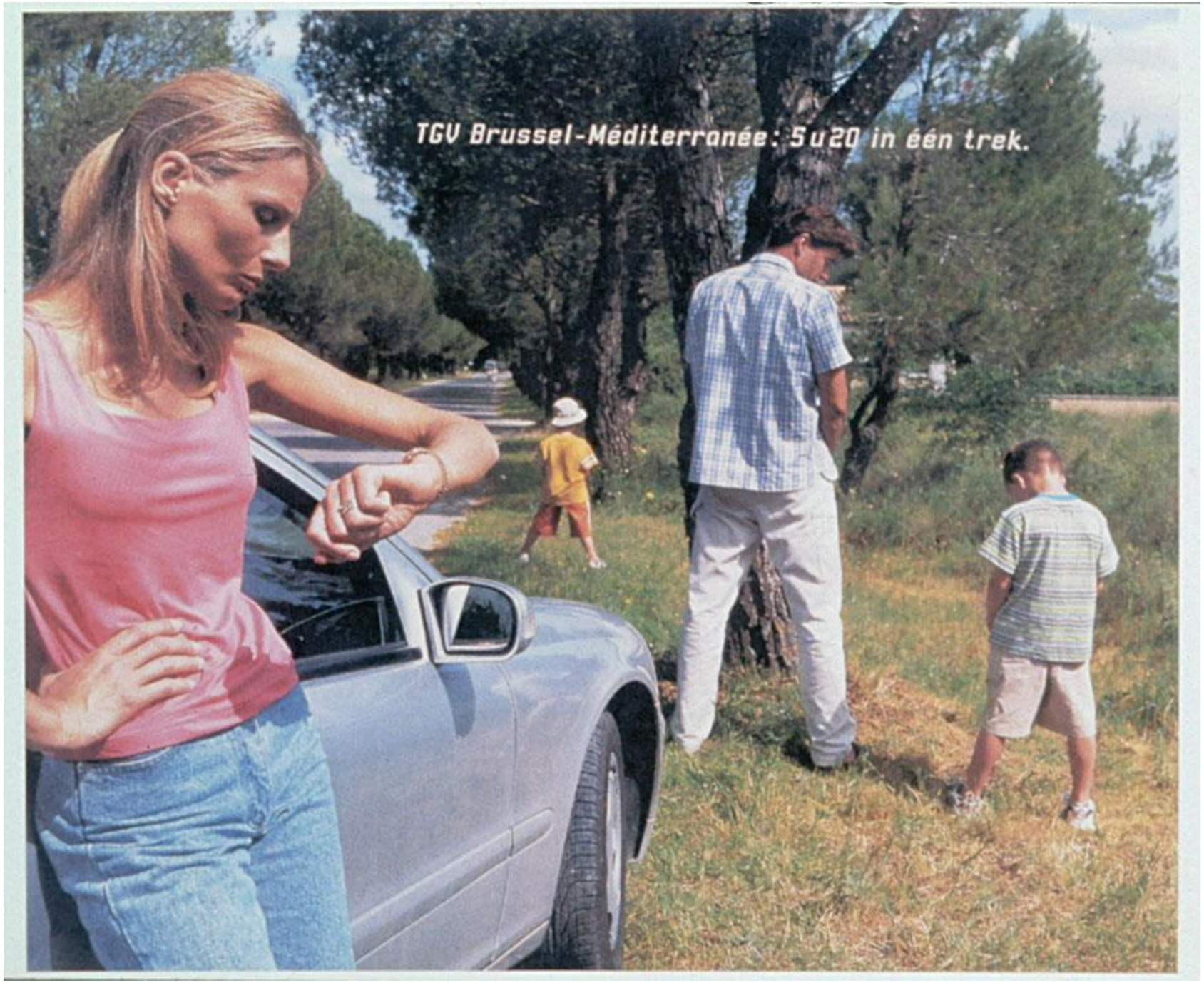
Bryan M. Tucker and Barry I. Freedman

Clin J Am Soc Nephrol 13: 477–479, 2018. doi: https://doi.org/10.2215/CJN.08310817



Annual ESRD incidence rates (USRDS 2018)




TGV Brussel-Méditerranée: 5u20 in één trek.

African American pedigrees (black boxes = ESRD cases)

Disparate causes of ESRD seen in these families - but not other ancestral populations

Suggested an over-arching single gene cause of ESRD

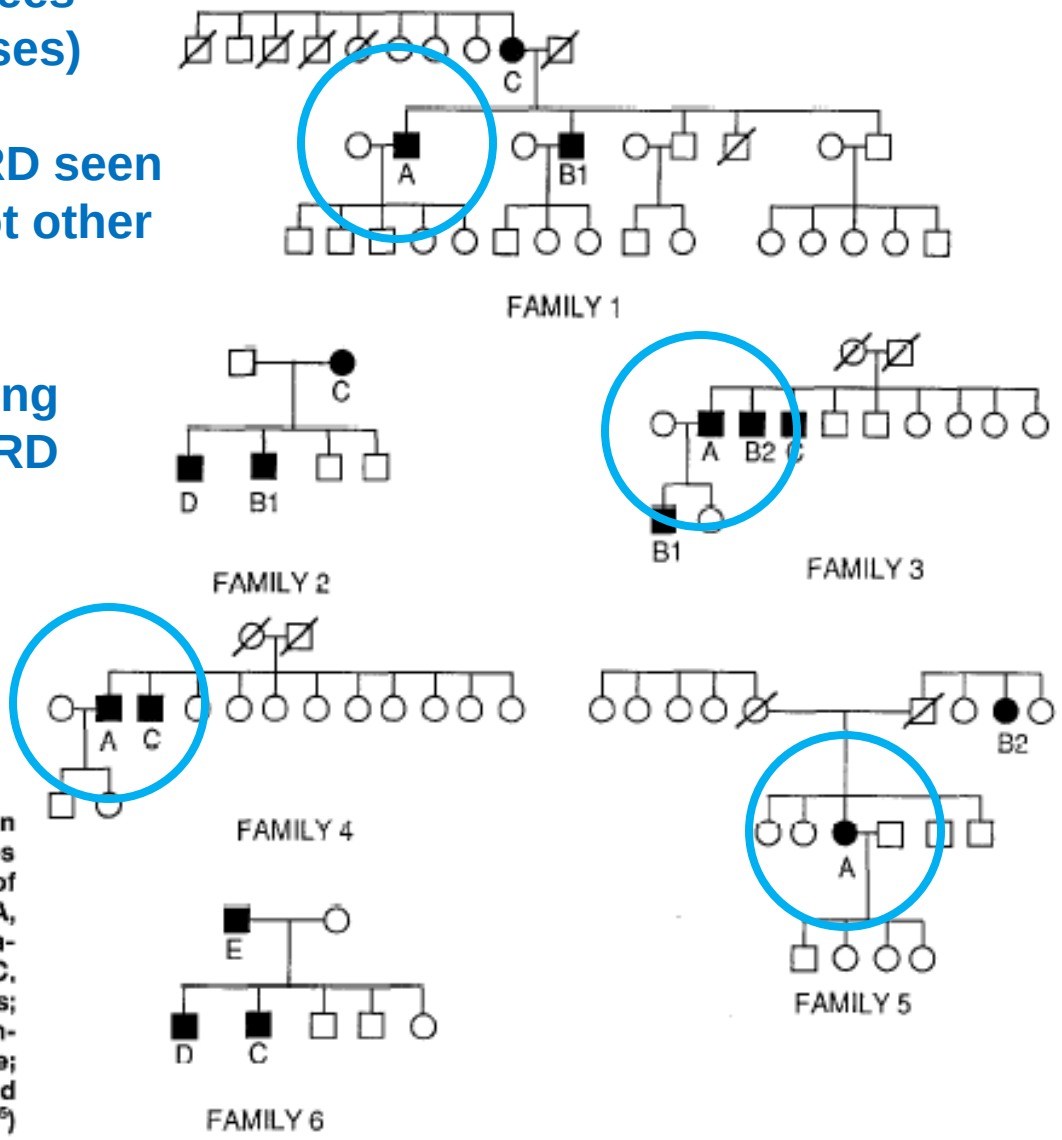


Fig 1. African-American multiplex ESRD families with disparate etiologies of ESRD. Cause of ESRD: A, hypertension; B1, type I diabetes; B2, type II diabetes; C, chronic glomerulonephritis; D, HIV nephropathy; E, unknown. □, male; ○, female; ⊘, deceased. (Modified and reprinted with permission.[75])

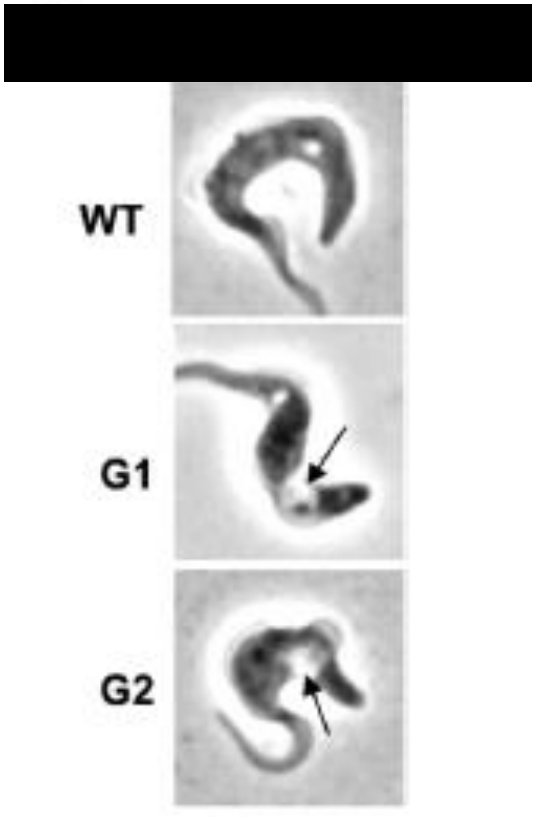
Freedman BI et al AJKD: 21;387-393, 1993

No diabetes, low level proteinuria

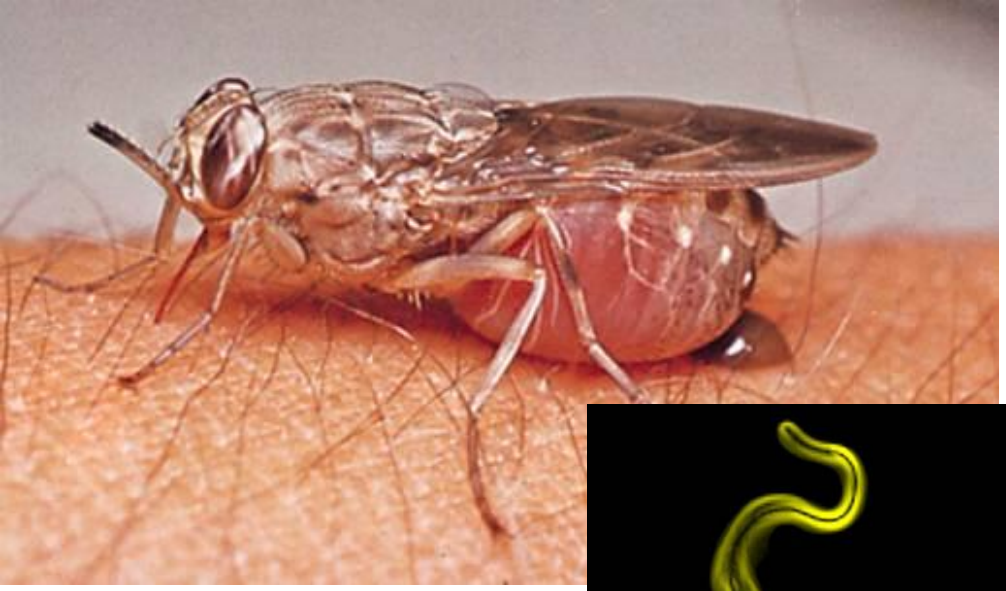
Association of trypanolytic apoL1 variants with kidney disease in African Americans

Giulio Genovese*, David J. Friedman*, Michael D. Ross, Laurence Lecordier, Pierrick Uzureau, Barry I. Freedman, Donald W. Bowden, Carl D. Langefeld, Taras K. Oleksyk, Andrea L. Uscinski Knob, Andrea J. Bernhardy, Pamela J. Hicks, George W. Nelson, Benoit Vanhollebeke, Cheryl A. Winkler, Jeffrey B. Kopp, Etienne Pays, Martin R. Pollak

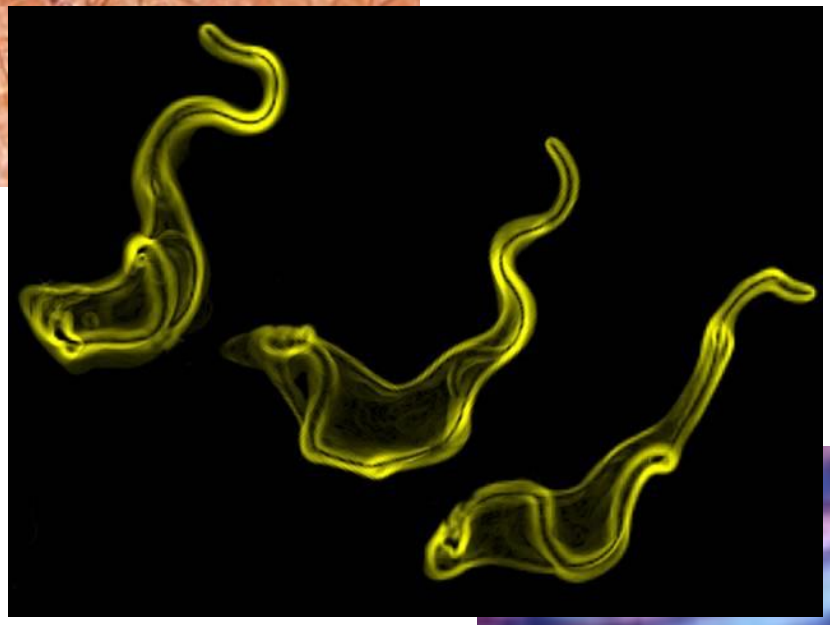
***Science* 329: 841 – 845, 2010**



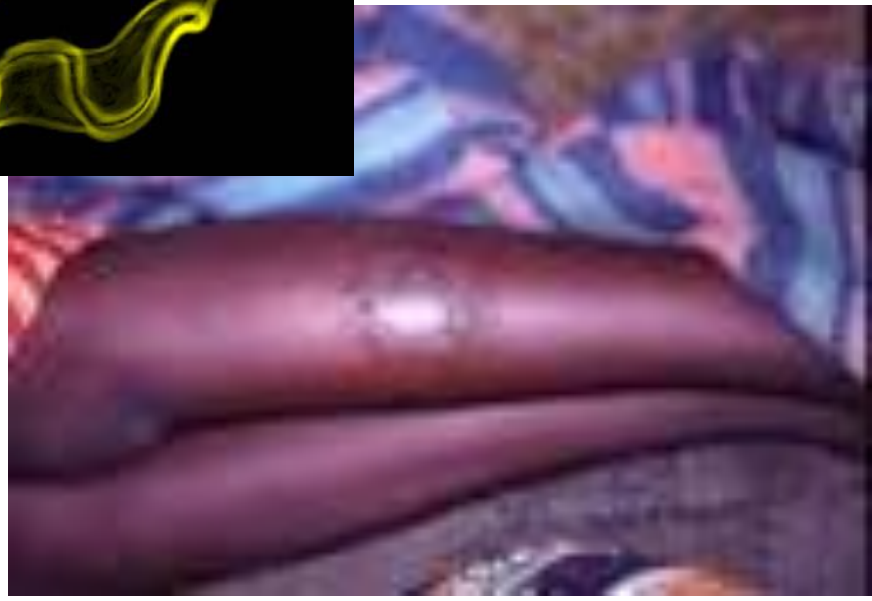
Two risk variants (G1G1, G2G2, G1G2) cause CKD: autosomal recessive



Tsetse fly
Glossina Genus



Trypanosoma brucei *rhodesiense*

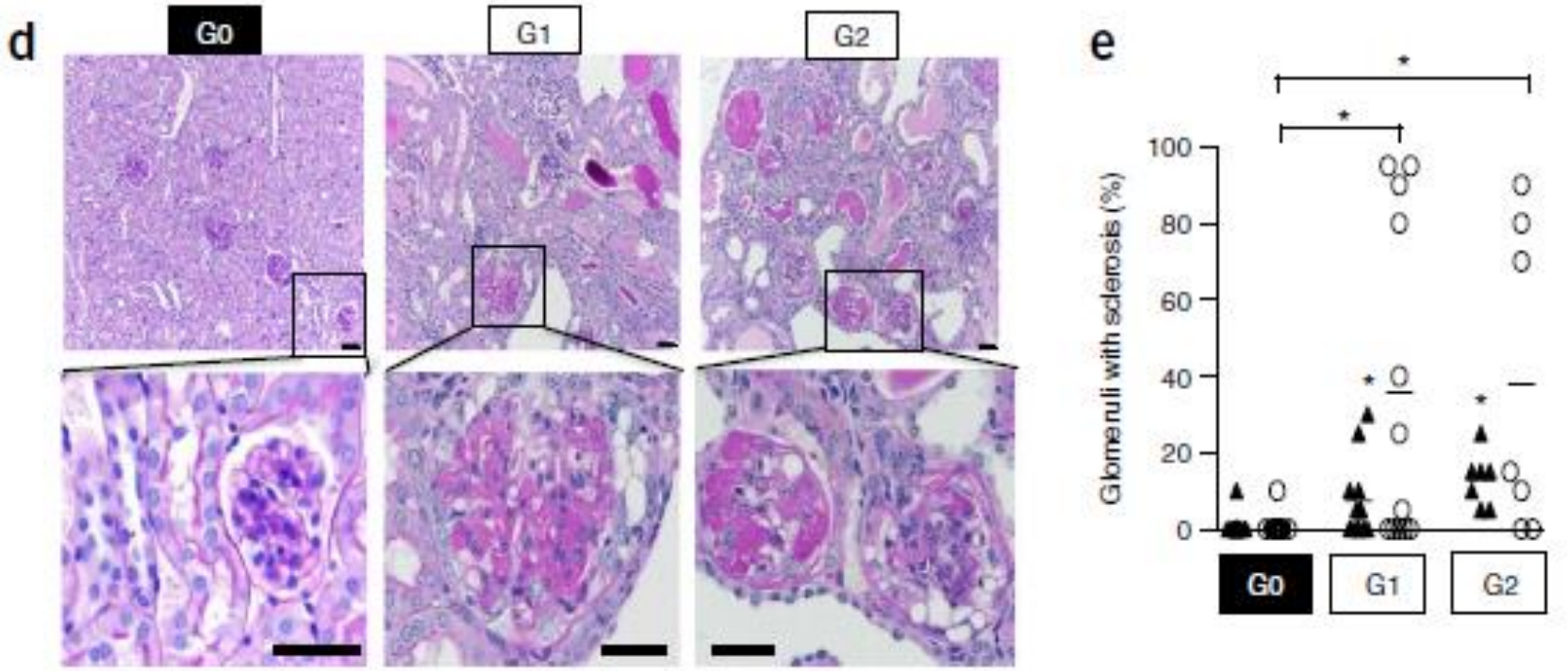


Chancre
Human African Trypanosomiasis

Transgenic expression of human *APOL1* risk variants in podocytes induces kidney disease in mice

Pazit Beckerman[1,13], Jing Bi-Karchin[1,13], Ae Seo Deok Park[1], Chengxiang Qiu[1], Patrick D Dummer[2], Irfana Soomro[3], Carine M Boustany-Kari[4], Steven S Pullen[4], Jeffrey H Miner[5], Chien-An A Hu[6], Tibor Rohacs[7], Kazunori Inoue[8], Shuta Ishibe[8], Moin A Saleem[9], Matthew B Palmer[10], Ana Maria Cuervo[11], Jeffrey B Kopp[2] & Katalin Susztak[1,12]

APOL1 variants are the cause of kidney disease



published online 20 February 2017; doi:10.1038/nm.4287

nature medicine

APOL1 - strongest genetic association in complex human disease

Frequency of renal-risk variants in African Americans:

13% two copies = RISK [5.33 million people]

39% one copy = CARRIER

48% no copies

- **Risk variants virtually absent in European, Asian and Hispanic populations**
- **Population attributable risk in FSGS & HIVAN is 70%**
- ***APOL1* only found in humans, gorillas and baboons**

Sickle cell variants are present in ~8% of the African American population

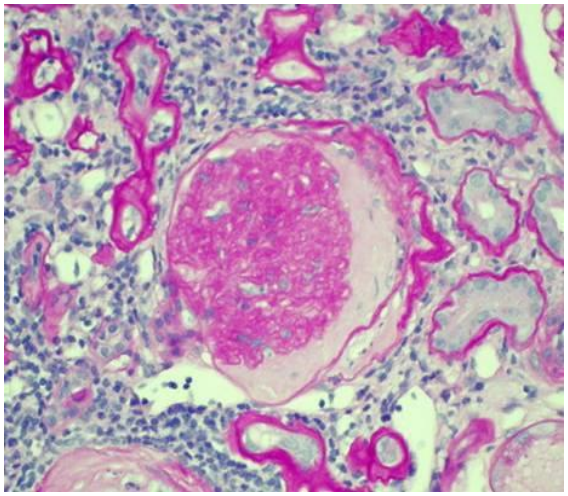
Spectrum of *APOL1*-associated nephropathy

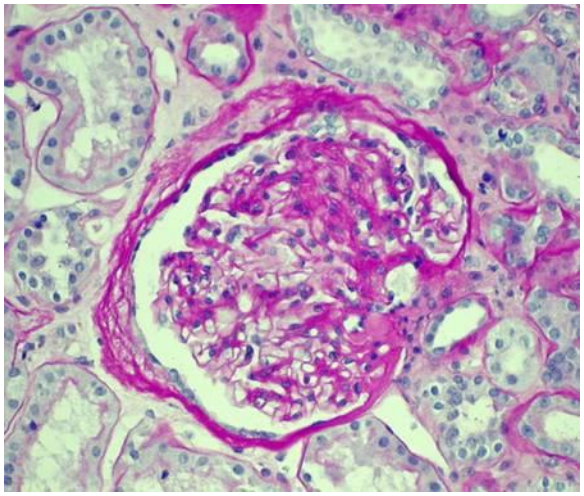
Solidified Glomerulosclerosis

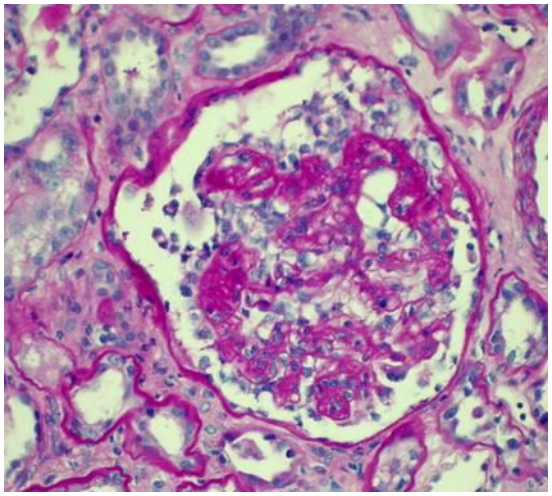
~~Hypertensive nephrosclerosis~~

Focal Segmental Glomerulosclerosis

Collapsing FSGS (HIVAN)







Odds Ratio=7.3

OR=17

OR>29

Proteinuria & nephropathy progression rate

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

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

APOL1 causes ~30-35% of ESRD in African Americans and contributes to:

- **Excess risk of non-diabetic CKD in African Americans, relative to European Americans**
- **Poorer outcome in lupus nephritis among African American patients**
- **Shorter renal allograft survival in kidneys transplanted from African American donors**

APOL1 genotyping could revolutionize kidney transplantation

- Now employed by many transplant programs to assess potential living kidney donors
- The NIH APOLLO Consortium is assessing *APOL1* in deceased & living donor kidney transplantation
- *APOL1* genotyping may:
  - Better define donor quality (change organ allocation)
  - Improve donor-recipient match with longer graft fxn
  - Reduce the discard rate of kidneys
  - Lead to more kidney transplantations
  - Improve safety in living kidney donation

American Journal of Transplantation 2002; 2: 68–75
Munksgaard International Publishers

ISSN 1600-6135

Effect of Donor Factors on Early Graft Survival in Adult Cadaveric Renal Transplantation

S. John Swanson[a,e], Iman O. Hypolite[b], Lawrence Y. C. Agodoa[c], D. Scott Batty Jr[a,e], Paul B. Hshieh[d], David Cruess[d], Allan D. Kirk[e], Thomas G. Peters[a,f] and Kevin C. Abbott[g,*,**]

Key words: African American donor, body mass index, cadaveric renal transplantation, donor death, donor/recipient weight ratio, graft survival

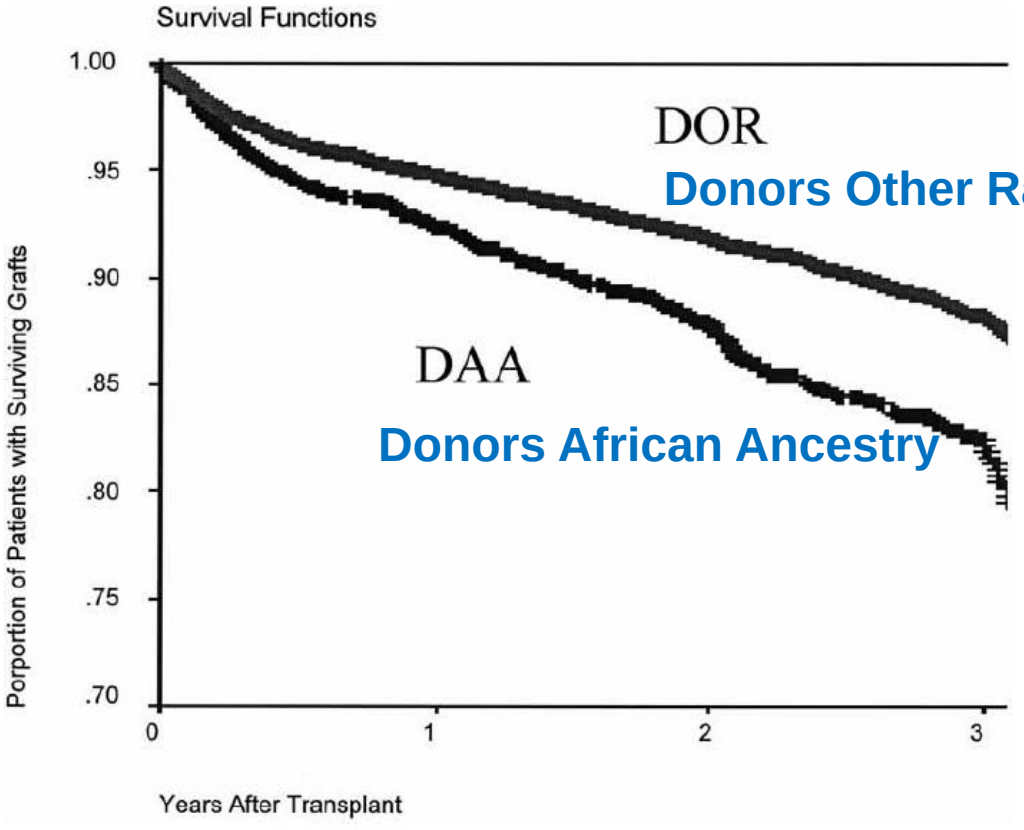
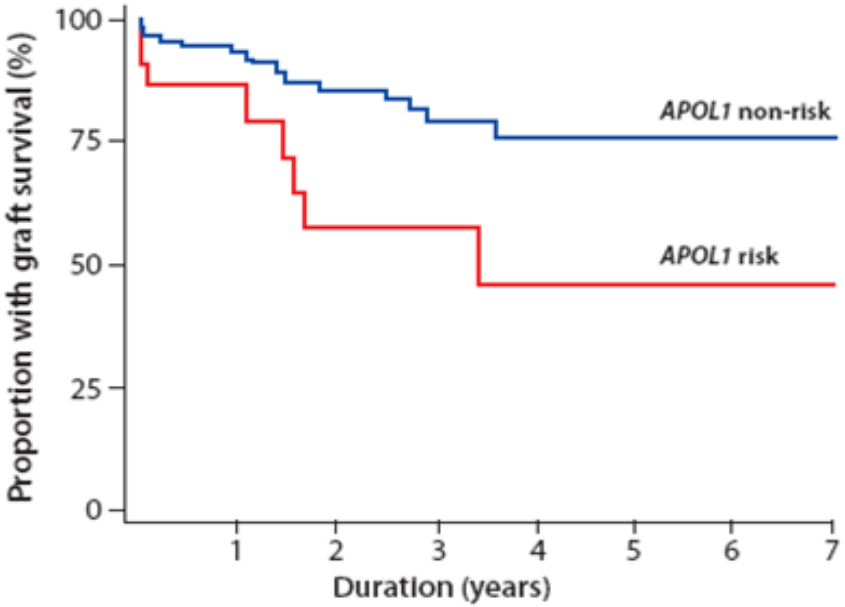


Figure 2: Kaplan-Meier plot of death-censored graft survival, US cadaveric renal transplant recipients, 1 July 1994–30 June 1998. DAA = Donor African American, DOR = Donor other race.

Survival of transplanted kidneys from African American donors



Similar to European Donor kidney outcomes

***APOL1* non-risk**								
No. at risk	114	82	52	35	18	7	6	3
No. with graft loss (%)	–	7 (6%)	13(11%)	16 (14%)	17 (15%)	17 (15%)	17 (15%)	17 (15%)
No. censored	–	25	49	63	79	90	91	94
***APOL1* risk**								
No. at risk	22	12	8	5	2	1	1	0
No. with graft loss (%)	–	3 (14%)	7 (32%)	7 (32%)	8 (36%)	8 (36%)	8 (36%)	8 (36%)
No. censored	–	7	7	10	12	13	13	14

Figure 1: Renal allograft survival according to APOL1 genotype.

Kaplan-Meier renal allograft survival curve for recipients of donor kidneys with (red line) and without (blue line) two APOL1 risk variant alleles.

The majority of failed allografts from 2 risk-variant donors had *APOL1*-associated lesions
Recipient *APOL1* genotypes do not impact outcomes (not a circulating factor)

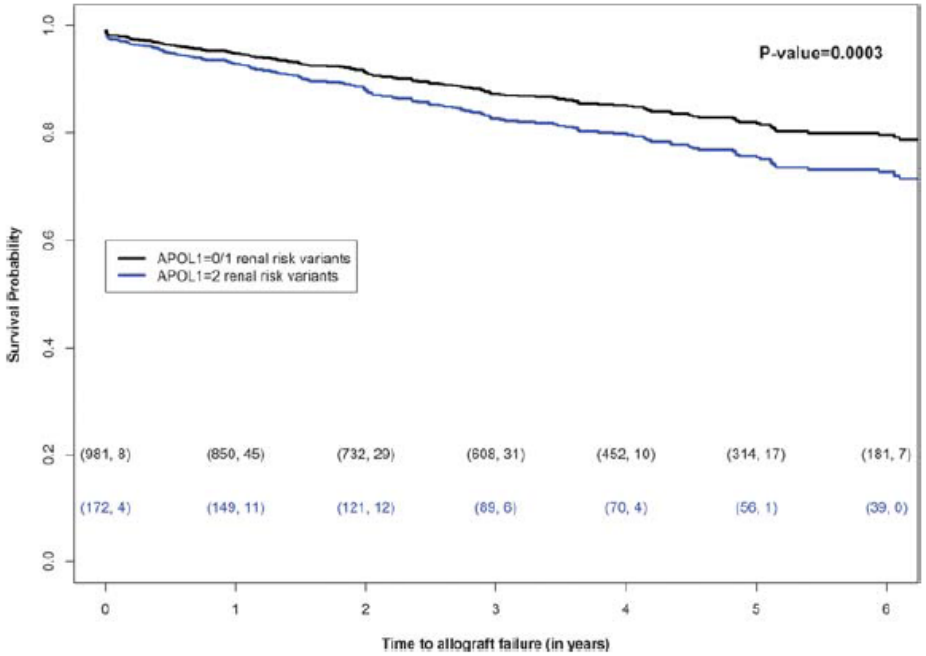
Reeves-Daniel & Freedman *Am J Transplant* 2011

Original Clinical Science

Transplantation ■ Month 2015 ■ Volume 00 ■ Number 00 DOI: 10.1097/TP.0000000000000969

APOL1 Genotype and Kidney Transplantation Outcomes From Deceased African American Donors

Barry I. Freedman, MD,[1,2] Stephen O. Pastan, MD,[3] Ajay K. Israni, MD, MS,[4,5] David Schladt, MS,[5] Bruce A. Julian, MD,[6] Michael D. Gautreaux, PhD,[7] Vera Hauptfeld, PhD,[8] Robert A. Bray, PhD,[9] Howard M. Gebel, PhD,[9] Allan D. Kirk, MD, PhD,[10] Robert S. Gaston, MD,[3] Jeffrey Rogers, MD,[11] Alan C. Farney, MD,[11] Giuseppe Orlando, MD, PhD,[11] Robert J. Stratta, MD,[11] Sumit Mohan, MD, MPH,[12,13] Lijun Ma, MD, PhD,[1] Carl D. Langefeld, PhD,[14] Donald W. Bowden, PhD,[2] Pamela J. Hicks, BS,[2] Nicholette D. Palmer, PhD,[2] Amudha Palanisamy, MD,[1] Amber M. Reeves-Daniel, DO,[1] W. Mark Brown, MA,[14] and Jasmin Divers, PhD[14]



1153 DDKT transplants
…. 624 unique donors
113 transplant centers

FIGURE 1. Adjusted Kaplan-Meier survival plots (full model) in 1153 deceased-donor kidney transplantations from African American donors based on donor *APOL1* genotypes. Plots compare survival of kidneys from donors with 2 renal-risk variants versus that for kidneys from donors with fewer than 2 renal-risk variants. The numbers within the parentheses below the curves reflect (number of functioning allografts at the start of each year, number of allograft failures within that year).

TABLE 2.

Multivariate association results for time to renal allograft failure, based on *APOL1* genotype (recessive model) in the full model (excluding recipient diabetes mellitus, BMI, dialysis vintage and induction immunosuppression)

Data set	Variable	Hazard Ratio	95% CI	*P*
Full data set: Emory University, DeKAF Genomics, Wake Forest + University of Alabama at Birmingham (N = 1153) 881 in analysis 178 graft failures	*APOL1* (recessive model)	2.05	(1.39-3.02)	0.0003
	Increasing donor age	1.18	(1.00-1.40)	0.05
	Maximum panel-reactive antibodies	1.00	(1.00-1.01)	0.45
	Increasing recipient age	0.70	(0.56-0.87)	0.001
	No. HLA mismatches	0.94	(0.85-1.04)	0.25
	Cold ischemia time	1.00	(0.99-1.02)	0.58
	Standard-criteria donor (yes)	0.70	(0.43-1.12)	0.13
	Recipient sex (female)	0.97	(0.70-1.35)	0.87
	Source/recipient ethnicity (ref WFU/other)		Overall interaction, $P = 0.06$	

Freedman BI, et al. Transplantation 2016

ALLOCATION OF KIDNEYS

Goal of new KDRI allocation system: eliminate unrealized allograft years by improving matching of kidneys and recipients using estimates of organ quality and recipient longevity

10 factors in deceased kidney donors contribute to 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

American Journal of Transplantation 2017; 17: 1543–1549
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[3,8]

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.

Changes in allocation based on *APOL1*

0/1 *APOL1* RRVs

KDRI

Current

1.4972

KDPI

Current

71%

2 *APOL1* RRVs

KDRI

Current

1.4689

KDPI

Current

69%

Julian, Freedman, Divers 2016 AJT

Changes in allocation based on *APOL1*

0/1 *APOL1* RRVs

KDRI

Current	Revised
1.4972	**1.2518**

KDPI

Current	Revised
71%	**53%**

85% frequency

2 *APOL1* RRVs

KDRI

Current	Revised
1.4689	**1.8527**

KDPI

Current	Revised
69%	**88%**

15% frequency

Julian, Freedman, Divers 2016 AJT

P value 2.2×10^{-16}

CLINICAL RESEARCH www.jasn.org

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. Kopp[6]

[1]Division of Nephrology, University of Michigan, Ann Arbor, Michigan; [2]Division of Nephrology, Miami Transplant Institute, University of Miami, Miami, Florida; [3]Division of Nephrology, Western University, London, Ontario, Canada; [4]Department of Nephrology and Hypertension, Cleveland Clinic, Cleveland, Ohio; and [5]Basic Research Laboratory, National Cancer Institute, Leidos Biomedical Research, Frederick Laboratory for Cancer Research, Frederick, Maryland and [6]Kidney Disease Branch of National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

12 year follow-up of 136 African American living kidney donors

J Am Soc Nephrol 29: ●●●–●●●, 2018. doi: https://doi.org/10.1681/ASN.2017060658

Table 1. Predonation characteristics of live kidney donors on the basis of *APOL1* renal risk genotype

Predonation Characteristics	High-Risk Genotype, *n*=19	Low-Risk Genotype, *n*=117	*P* Value
Age, yr	37±9	37±9	0.84
Women, %	61	63	0.85
Weight, kg	85±16	82±18	0.49
Body mass index, kg/m^2	30±5	29±6	0.45
Systolic BP, mm Hg	121±7	120±10	0.56
Diastolic BP, mm Hg	72±8	73±8	0.61
Serum creatinine, mg/dl	0.98±0.18	0.89±0.18	0.06
eGFR, ml/min per 1.73 m^2	98±17	108±20	0.03
Fasting blood sugar, mg/dl	92±12	91±12	0.62
Education, %			0.09
None to 8th grade	11	1	
9th–11th Grade	6	15	
High school	40	34	
Some college	33	38	
Bachelors	11	6	
Postgraduate	0	6	
Individual income, %			0.97
<$12,000	11	13	
$12,000–$25,000	28	28	
>$25,000	61	60	
Employed, full or part time, %	83	80	0.79
Family history of hypertension, yes, %	79	71	0.48
Family history of ESRD, yes, %	89	76	0.20
Relationship to the recipient, %			0.27
Parent	11	9	
Sibling	37	38	
Child	42	28	
Spouse	5	9	
Other	5	16	

High-risk genotype is defined as carrying two *APOL1* renal risk alleles, and low-risk genotype is defined as carrying one or zero *APOL1* renal risk alleles. Data are presented as mean±SD. To convert serum creatinine from milligrams per deciliter to micromoles per liter, multiply by 88.4. Family history of hypertension and ESRD was defined as first degree relative with these conditions.

Table 2. Postdonation outcomes between live kidney donors on the basis of *APOL1* renal risk genotype

Postdonation Outcomes	High-Risk Genotype, *n*=19	Low-Risk Genotype, *n*=117	*P* Value
Time since donation, yr	11.3 [9.1–12.5]	11.6 [9.1–13.6]	0.75
Postdonation weight, kg	89±18	88±18	0.72
Change in weight since donation, kg	+4.8±17	+5.5±17	0.87
Systolic BP, mm Hg	128±12	130±19	0.70
Change in systolic BP since donation, mm Hg	+7±12	+10±19	0.48
Diastolic BP, mm Hg	82±10	83±27	0.81
Change in diastolic BP since donation, mm Hg	+10±12	+7±12	0.89
Hypertension, %	44	49	0.74
Treated for hypertension with medication, %	75	67	0.29
Serum creatinine, mg/dl	1.71±1.2	1.26±0.3	0.003
CKD-EPI eGFR, ml/min per 1.732 m^2	57±20	67±15	0.02
CKD-EPI eGFR <60 ml/min per 1.732 m^2, %	67	36	0.01
MDRD eGFR, ml/min per 1.732 m^2	58±20	68±14	0.01
MDRD eGFR <60 ml/min per 1.732 m^2, %	53	32	<0.01
ESRD, %	11	0	0.02
uACR, mg/g	8.89 [2.6–23.8]	4.99 [2.5–11.8]	0.81
Microalbuminuria, %	16	10	0.86

High-risk genotype is defined as carrying two APOL1 renal risk alleles, and low-risk genotype is defined as carrying one or zero APOL1 renal risk alleles. Data are presented as mean±SD if normally distributed or median [interquartile range] in not normally distributed. To convert serum creatinine from milligrams per deciliter to micromoles per liter, multiply by 88. ESRD was defined by receipt of dialysis or kidney transplant. Microalbuminuria was defined as uACR>30 mg/g or >3 mg/mmol. MDRD, Modification of Diet in Renal Disease.

- **There is a need to improve safety of living kidney donation in African Americans**
- ***APOL1* genotyping may reduce post-donation kidney failure in African Americans**

Wake Forest *APOL1* Collaborative Team

Nephrology
Barry I. Freedman
Lijun Ma
Mariana Murea
Center for Human Genomics
Donald W. Bowden
Nicholette D. Palmer
Pamela J. Hicks
Public Health Sciences
Carl D. Langefeld
Jasmin Divers
David M. Reboussin
Lipid Sciences
John S. Parks
Transplantation
Robert J. Stratta
Amber Reeves-Daniel

Wake Forest™
School of Medicine

NIH
Jeffrey Kopp
Cheryl Winkler
Beth Israel Deaconess
Martin Pollak
David Friedman
Technion
Karl Skorecki
Etty Kruzel-Davila
Arkana
Chris Larsen
FIND Investigators
APOLLO Investigators
AASK Investigators
SPRINT Investigators

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