APOL1 risk genotype in FSGS and other nephropathies

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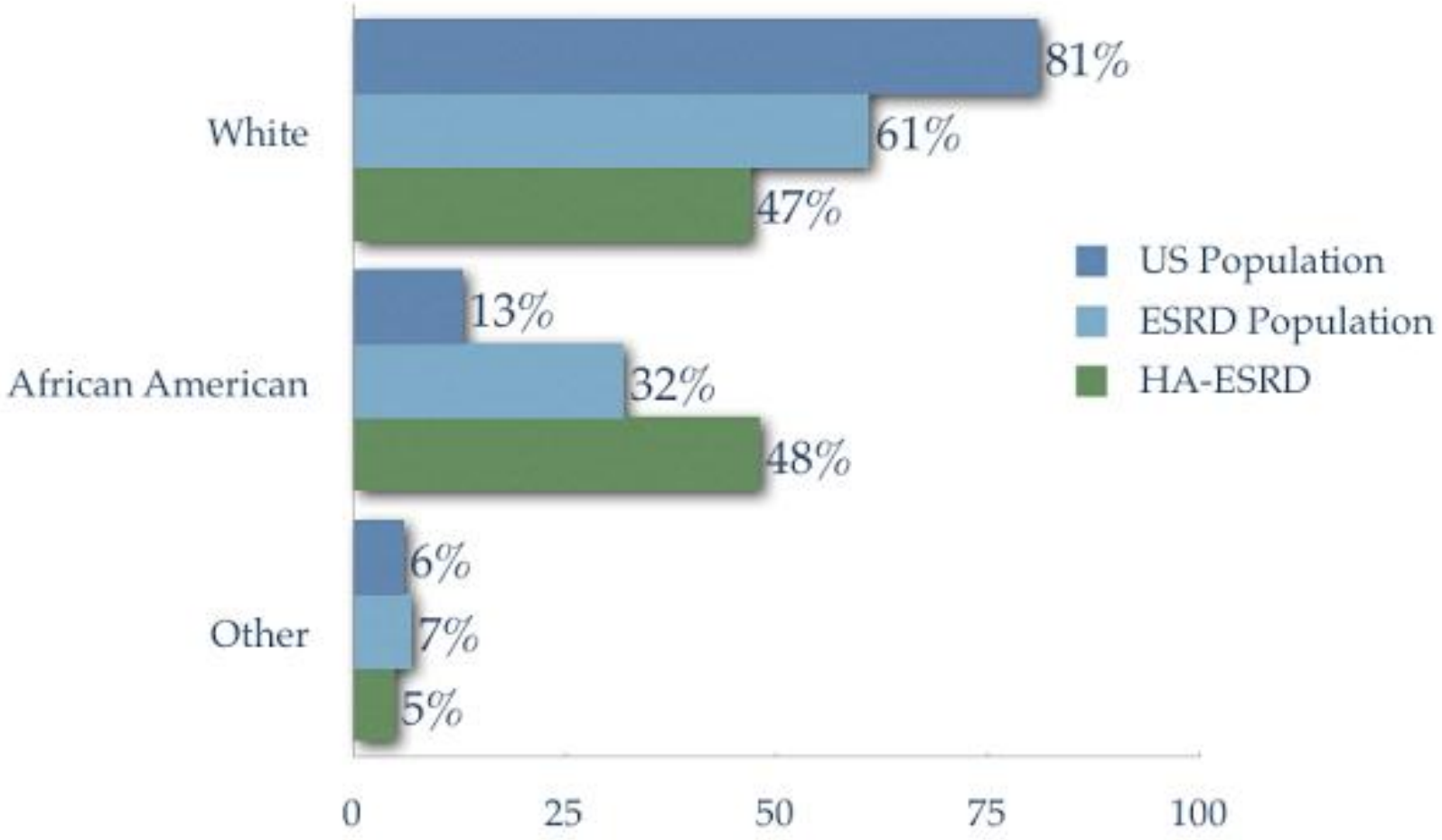
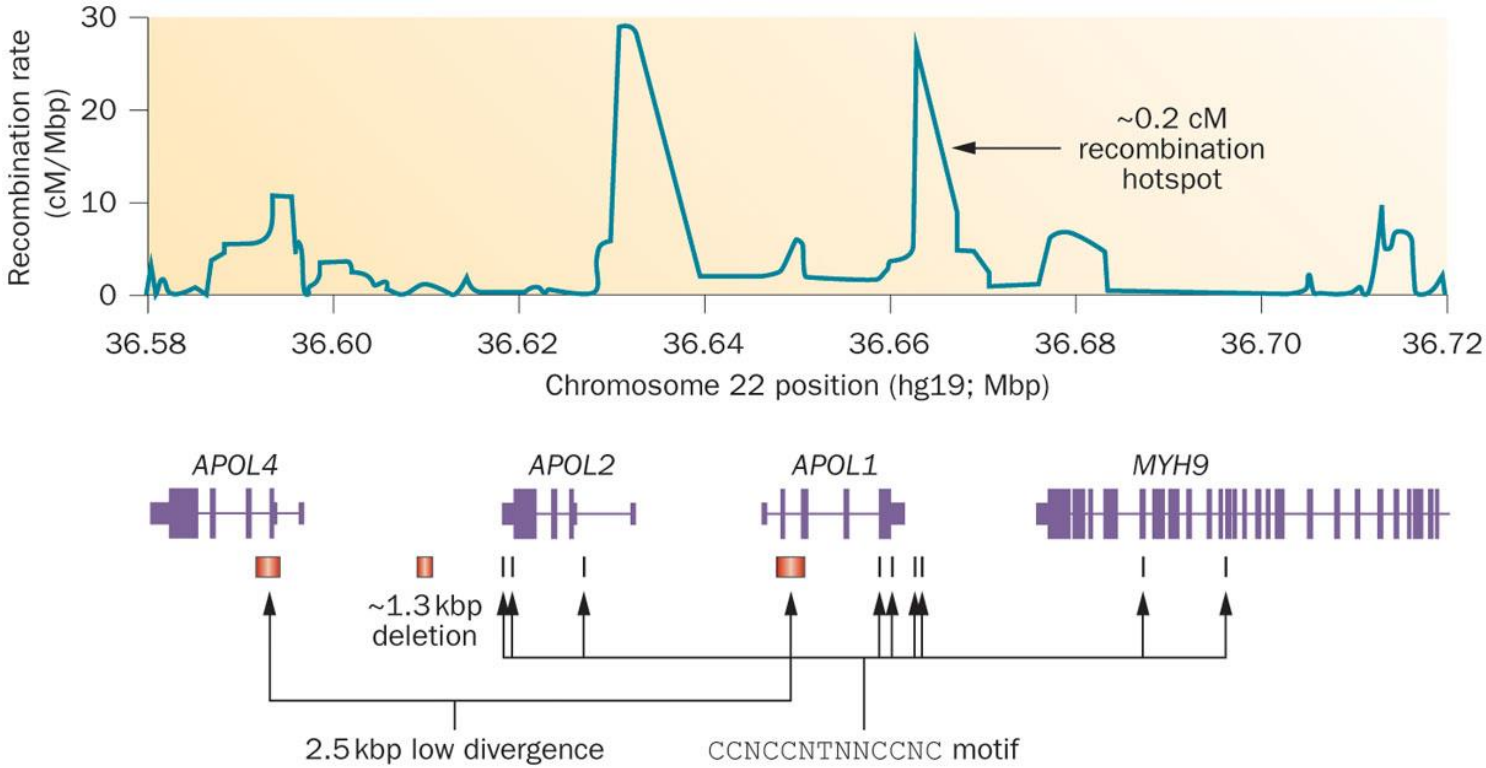
Black and White desequilibrium in USA

Afro-american have a fourfold increased risk of ESRD



- Identification of a locus on chromosome 22 associated with FSGS, HIVAN, non diabetic ESRD and hypertensive ESRD
- Identification of *APOL1*, encoding for ApoL1



Kao et al, Nat Genet, 2008
Genovese et al, Science, 2010
Kopp et al, JASN, 2011

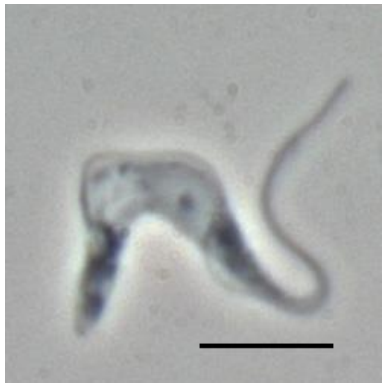
FSGS and hypertensive nephropathies

- FSGS and hypertension attributed ESRD associated with 2 risk alleles of *APOL1*
  - G1, 2 missense variants (S342G et I384M)
  - G2, 6 base pair deletion (N388del:Y389del)
  - G1 and G2 are exclusive, never occurring on the same chromosome
- Association at the homozygous or compound heterozygous state
  - Recessive pattern of inheritance

Genovese et al, Science, 2010

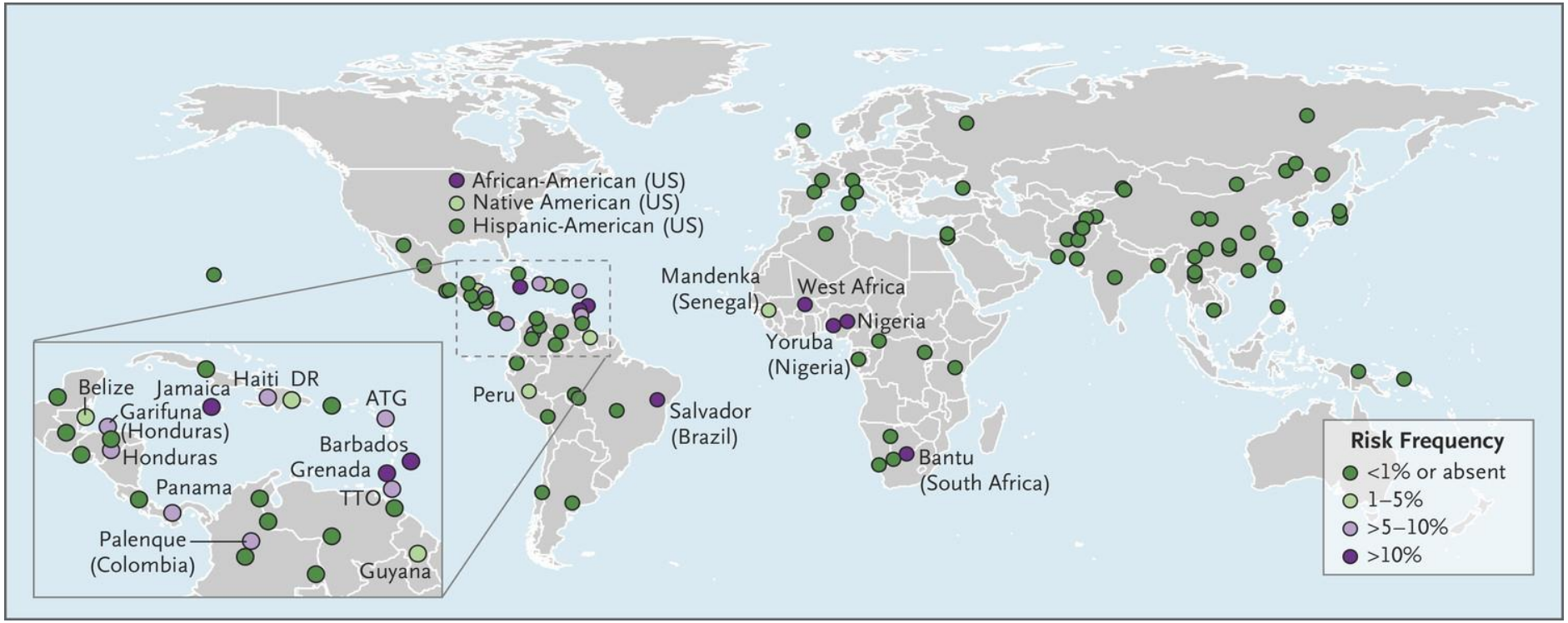
ApoL1, trypanolytic factor

- ApoL1 is the human trypanolytic factor which confers a resistance to *Trypanosoma brucei brucei*, one of the causes of sleeping sickness
  - *In vitro* only the kidney disease-associated ApoL1 variants lyse *Trypanosoma brucei rhodesiense*
  - *APOL1* gene may have undergone natural selective pressure in Western Africa



Genovese et al, Science, 2010

APOL1 G1 and G2 Risk Alleles in 111 Populations



Nadkarni et al. N Engl J Med 2018

Spectrum of *APOL1* nephropathies

Study	Disease	N patients	Cases (%)	Controls (%)	OR
Friedman (2011)		1776	NA	13	NA
Genovese (2010)	**FSGS**	205	66	12.5	10.5
Kopp (2011)	**FSGS**	217	72	13	16.9
Kopp (2015)	**FSGS**	32	72	NA	NA
Kopp (2011)	**HIVAN**	54	72	8	29.2
Genovese (2010)	**Hypertensive ESRD**	1030	46.5	12	7.3
Lipkowitz (2013)	**Hypertensive CKD**	675 (AASK)			2.57
Tzur (2010)	**ESRD**	430	18	3	6.7
Ashley-Koch (2011)	**Sickle cells disease**	140			PU, eGFR (MYH9)
Kormann (2017)	**Sickle cells disease**	152	7		ESRD, DFG
Freedman (2014)	**Lupus ESRD**	855	25	12	2.7
Larsen (2013)	**Lupus –collapsing GN**	546 lupus GN 26 collapsing	17, 50% of collapsing		5.4

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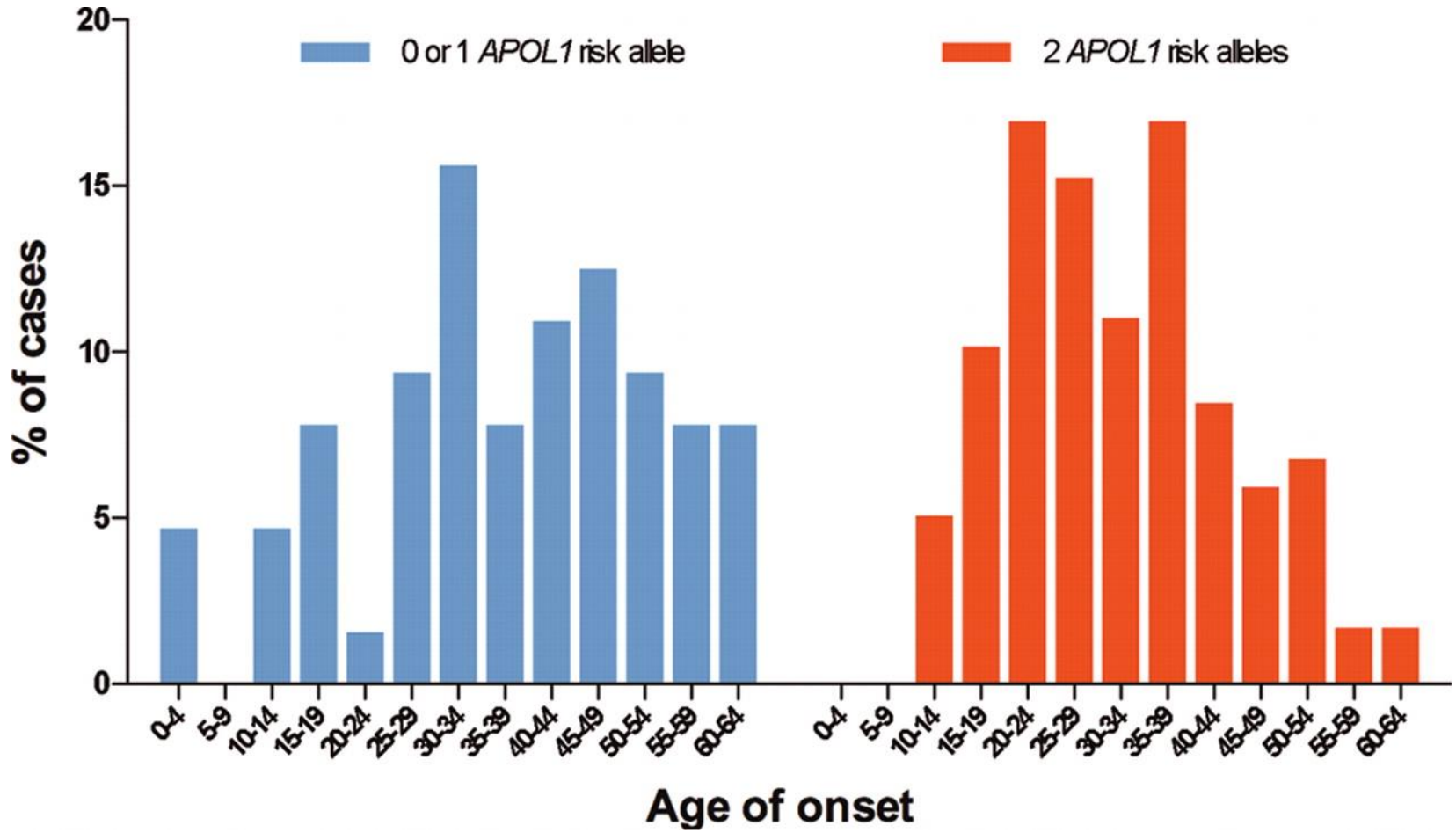
Age at onset



APOL1-associated FSGS tends to present at a younger age and at a narrower onset age range, with 70% of cases presenting between 15 and 39 years (P = 0.0009)

Kopp et al. JASN, 2011

APOL1 and FSGS in France

- 152 patients (139 families) FSGS/SRNS
- HR genotype 43.1% (66/152)
  - vs 18.9% (106/562) in a control population of African origin ($p<0.0001$)
  - HR genotype 60% (45/75) of patients from French West Indies
  - 27.3% (21/77) of patients originating from Africa ($p<0.0001$)

Gribouval et al, NDT, 2018

Mutations in known monogenic SRNS genes

- Mutations were found in 17 patients, 11.2%, in 15 families (10.8%)
  - Only 1 patient in the HR group
    - presenting with congenital nephrotic syndrome
    - compound heterozygous for 2 *NPHS1* mutations
  - In the LR group, 16 individuals in 14 families had causative mutations
    - 10 autosomal recessive mutations
    - 6 autosomal dominant mutations (sporadic cases)

Gribouval et al, NDT, 2018

Clinical presentation

	Total	*APOL1* LR group		*APOL1* HR group		p
		Mutation	No mutation	Mutation	No mutation	
N patients (families)	152 (139*)	86 (82)		66 (59)		
		16 (14)	70 (68)	1 (1)	65 (58)	
Familial	41 (26.8%)	5 (31.2%)	**8 (11.4%)**	1	**27 (41.5%)**	< 0.0001[1]
Age at onset (yrs)	17.1 (14.0)	6.9 (9.2)	14.7 (14.1)	0	22.5 (12.8)	<0.0001[1] <0.0001[2] 0.007 [3]
Age at onset>18 yrs	57 (37.5%)	3 (18.7%)	19 (27.1%)	0	35 (53.8%)	0.0026[1] 0.01[2]
Proteinuria (g/d)	7.4 (7.2)	7.4 (5.2)	7.6 (8.5)	2.5	7.6 (7.5)	NS
Albuminemia g/L	19.4 (10.4)	23.7 (11.9)	18.4 (13.7)	NA	19.2 (7.8)	NS
eGFR	88.6 (37.9)	82.0 (31.6)	98.8 (32.7)	100	78.9 (43.2)	0.02[1]

Gribouval et al, NDT, 2018

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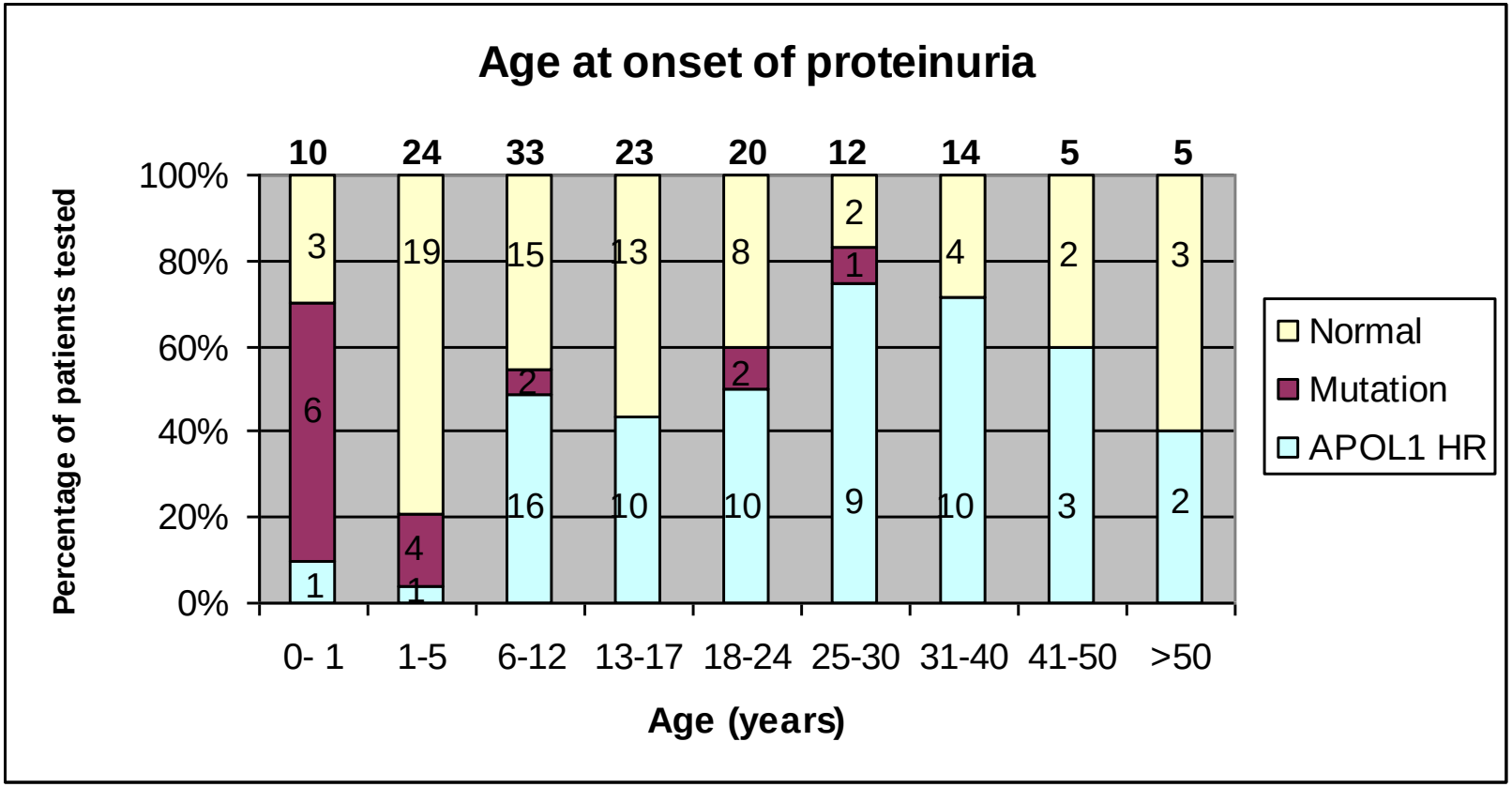
Gribouval et al, NDT, 2018

Age at onset of proteinuria according to *APOL1*



Gribouval et al, NDT, 2018

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Gribouval et al, NDT, 2018

Treatment

- Sensibility to glucocorticoids in African American:
  - 29% (12/42) if 2 *APOL1* risk-alleles
  - 33% (5/15) if 0 or 1 *APOL1* risk-allele (P = 0.5)

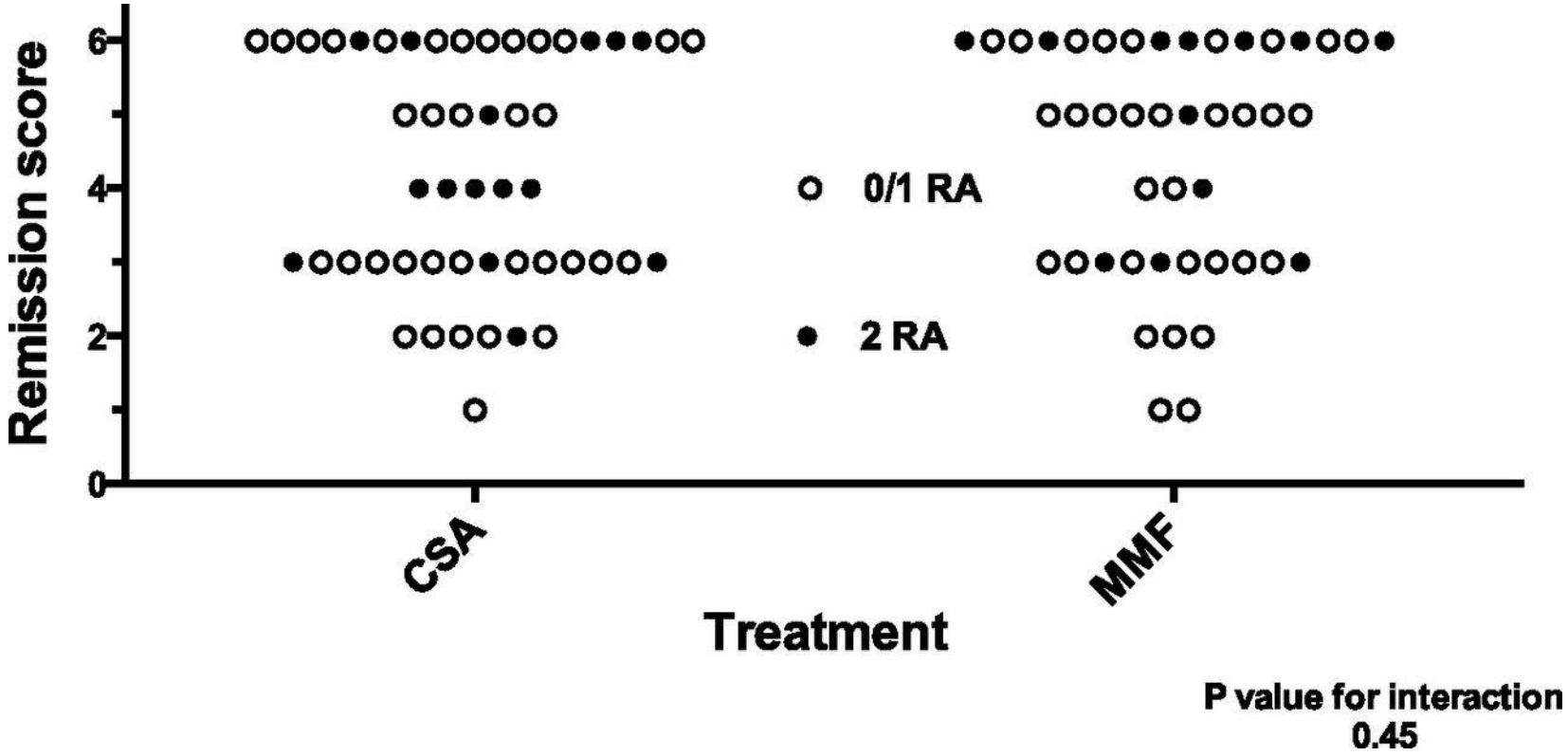
Kopp et al, JASN, 2011

Treatment and evolution

		APOL1 LR group		*APOL1* HR group		p
		Mutation	**No mutation**	**Muta-tion**	**No mutation**	
Glucocorticoid treatment	101 (66.4%)	4 (25.0%)	52 (74.3%)	1	44 (67.7%)	0.003[2] 0.0004[3]
Steroid resistant	95 (94.0%)	4 (100%)	**46 (88.5%)**	1	**44 (100%)**	0.03 [1]
Follow up	6.2 (9.2)	5.3 (8.2)	7.5 (11.1)		5.2 (7.1)	NS
eGFR	97.5 (62.9)	103.2 (99.1)	107.9 (58.2)		85.1 (62.5)	0.02 [1]
ESRD	45 (29.6%)	7 (43.7%)	17 (24.3%)		21 (32.3%)	NS
Age at ESRD	22.2 (14.1)	13.4 (8.8)	17.9 (13.4)		27.9 (13.8)	0.03 [1] 0.01[2]

Gribouval et al, NDT, 2018

APOL1 genotype and immunosuppressive drugs

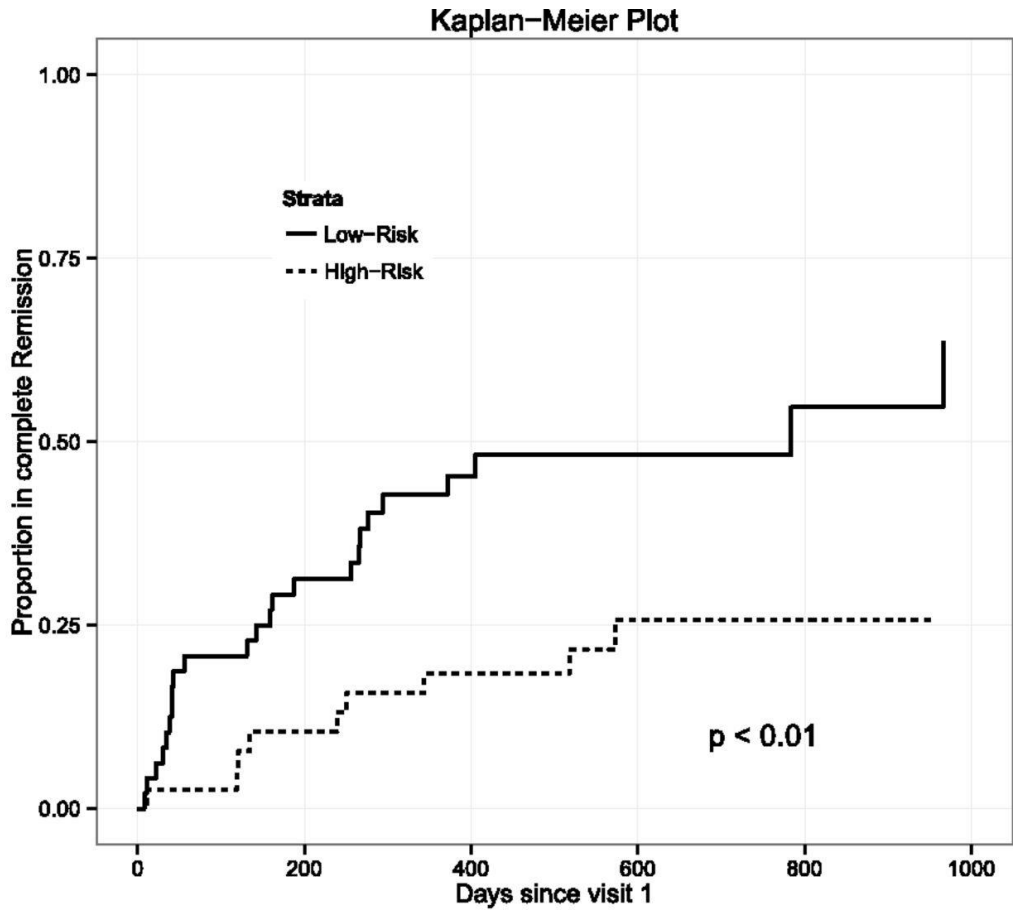


FSGS clinical trial: remission score after immunosuppressive treatment not modified by *APOL1* genotype

Kopp et al. JASN, 2015

Remissions according to *APOL1*: NEPTUNE

APOL1 high-risk genotype was significantly associated with a 70% reduction in the probability of complete remission at any time, independent of histologic diagnosis



High−Risk	39	34	30	17	11	7
Low−Risk	51	32	20	11	7	4

Numbers at risk

Sampson et al. JASN, 2016

APOL1 in cortico-sensitive nephrotic syndrome

- 115 African American children
  - 65 cortico-sensitive
  - 50 cortico-resistant
- HR *APOL1* allele not associated to cortico-sensitve nephrotic syndrome ($P = 0.5$)
- Significant association to cortico-resistant nephrotic syndrome ($P = 1.04 \times 10^{-7}$; OR, 4.17)

Adeyemo et al, AJKD, 2018

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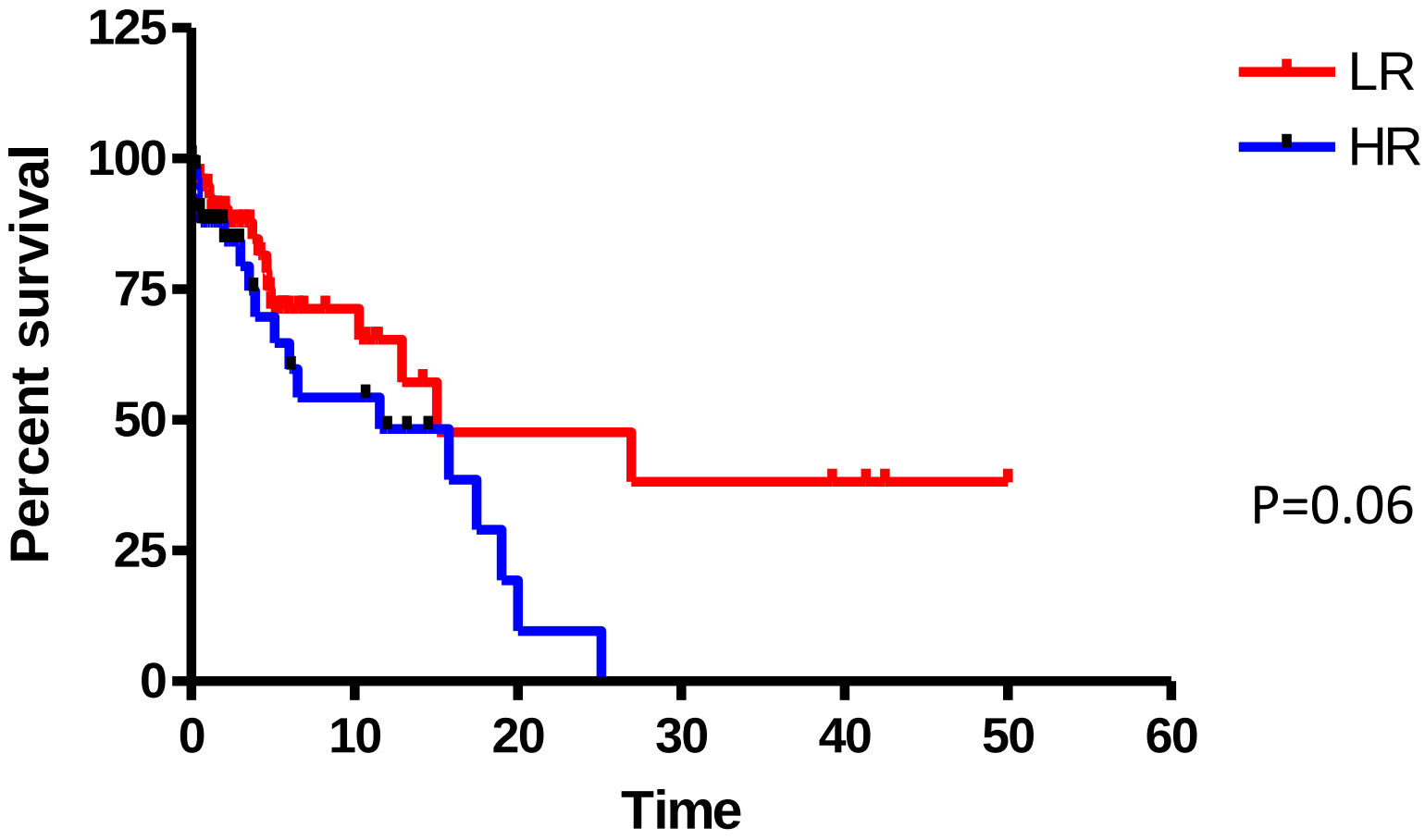
Gribouval et al, NDT, 2018

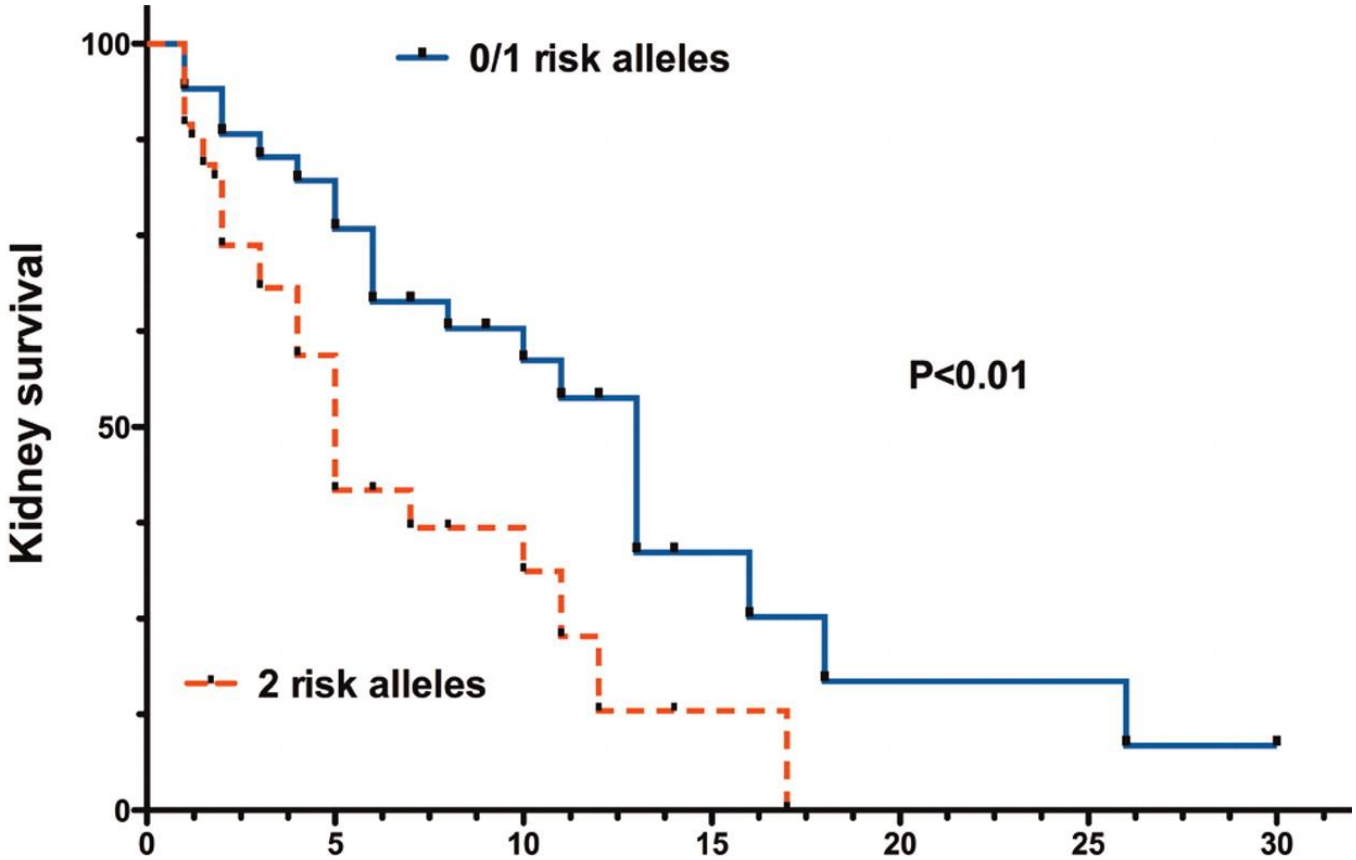
Renal survival



Patients at risk									
APOL1 LR	58	21	13	7	6	6	5	3	1
APOL1 HR	55	15	11	6	3	1	0	0	0

Gribouval et al, NDT, 2018

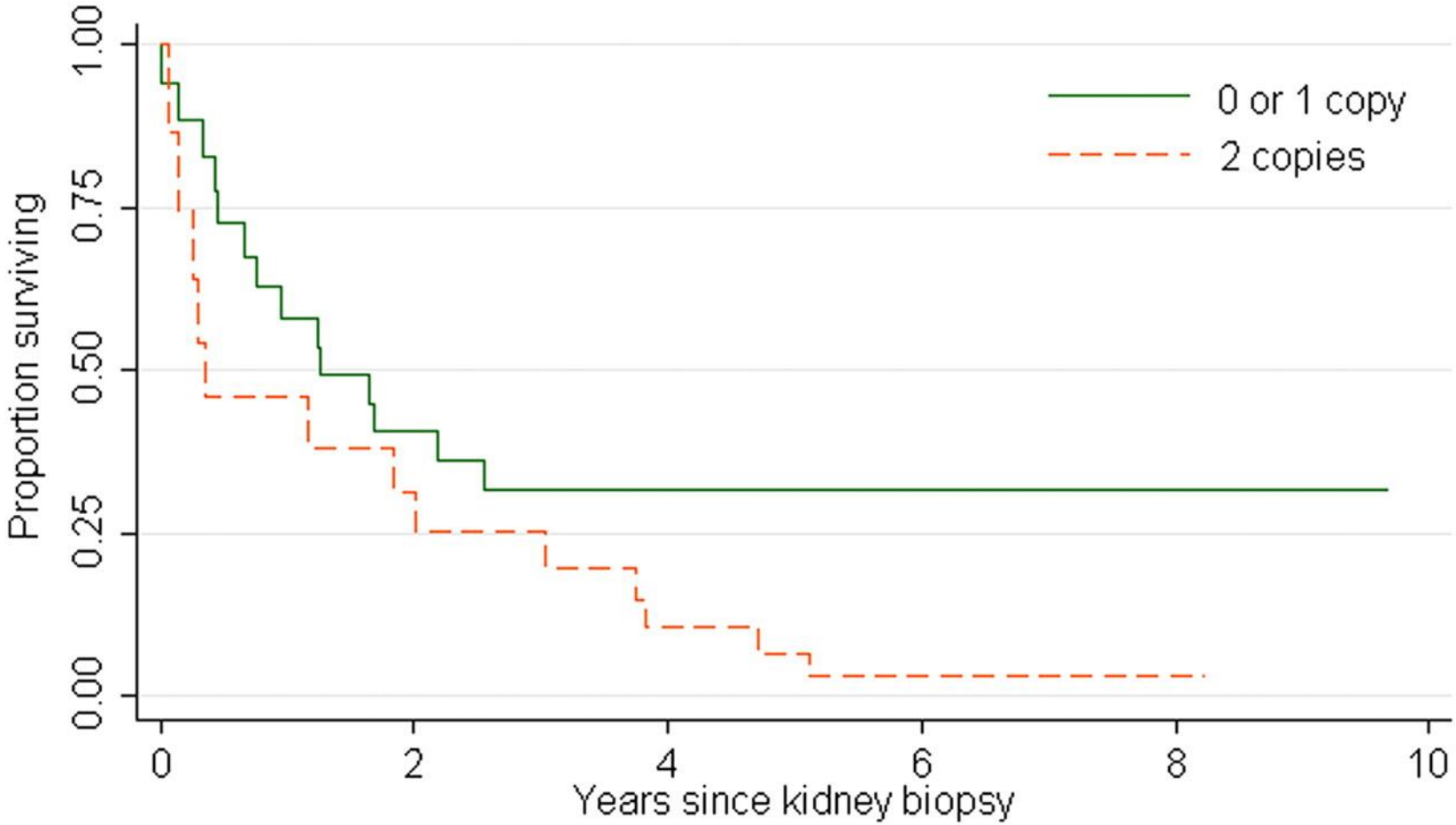
Renal survival in FSGS



0/1 alleles	34	24	12	4
2 alleles	58	19	11	1

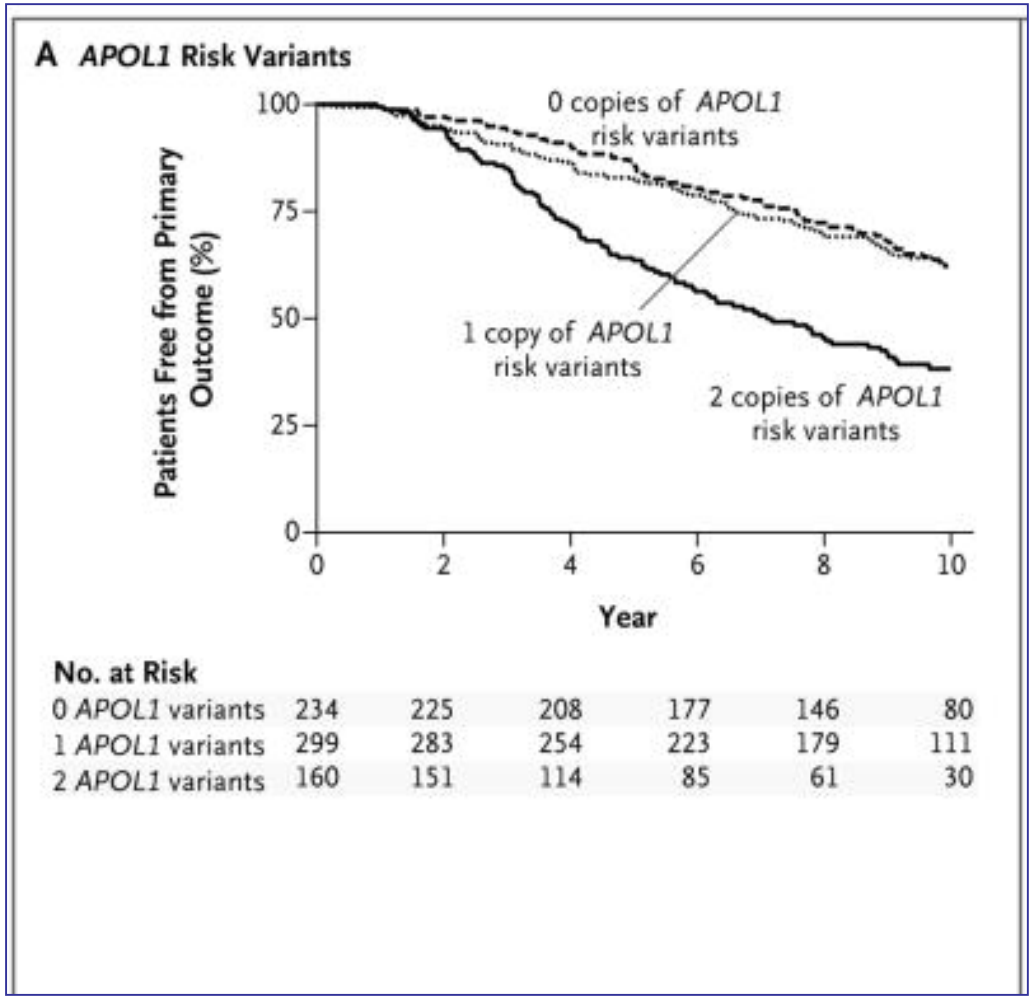
Kopp et al, JASN, 2011

Renal survival and HIVAN



Fine et al, JASN, 2012

Renal function decline

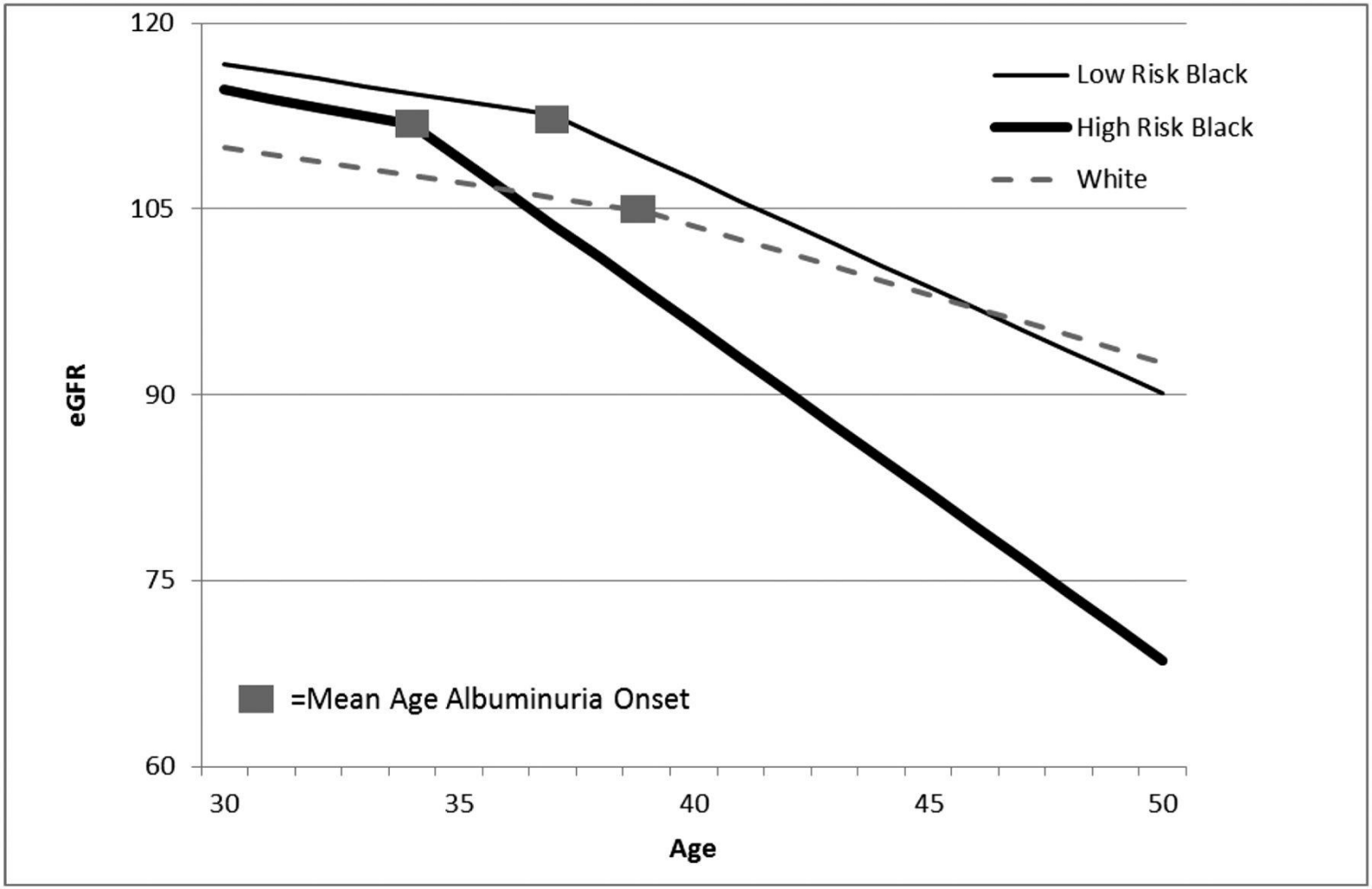


No. at Risk						
0 *APOL1* variants	234	225	208	177	146	80
1 *APOL1* variants	299	283	254	223	179	111
2 *APOL1* variants	160	151	114	85	61	30

693 patients AASK
Doubling of serum creatinine or ESRD

Parsa et al, NEJM, 2013

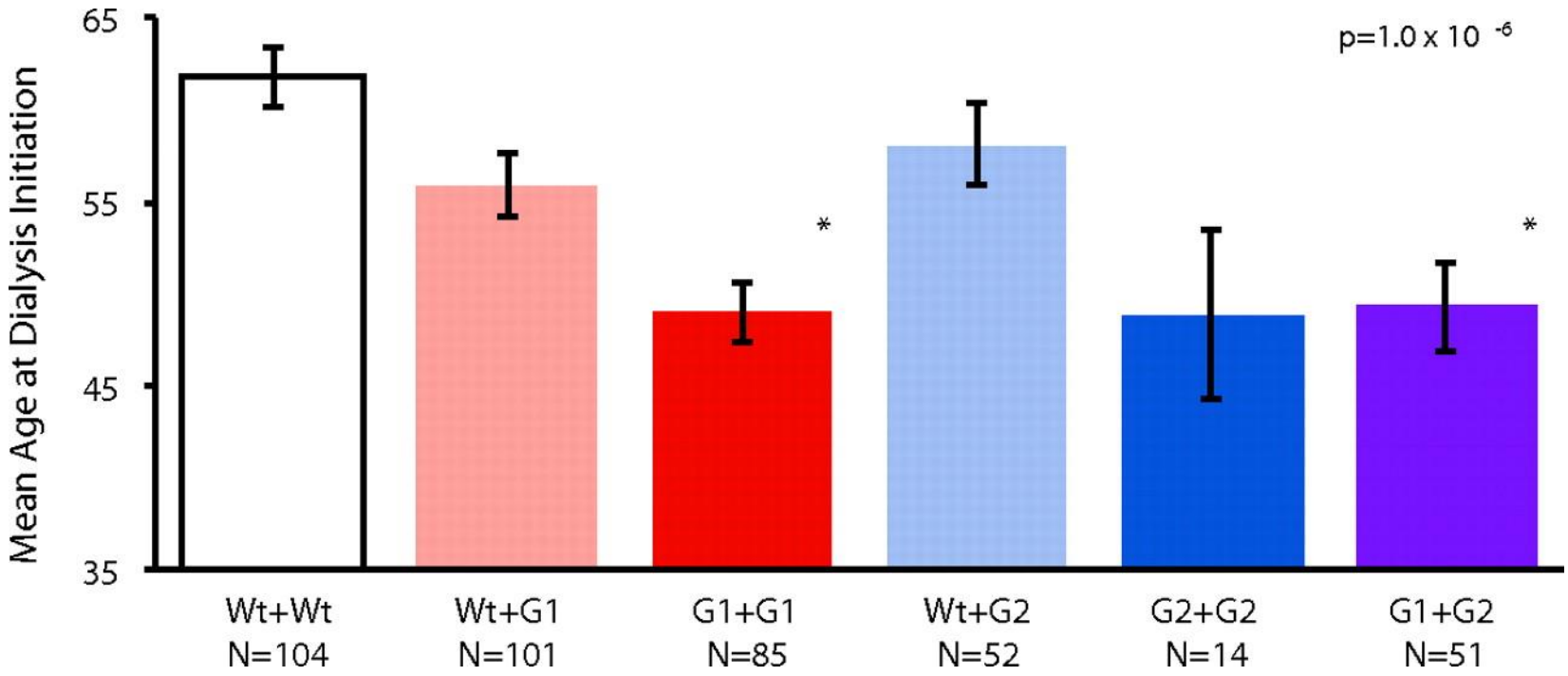
eGFR decline



3030 young adults (CARDIA study)

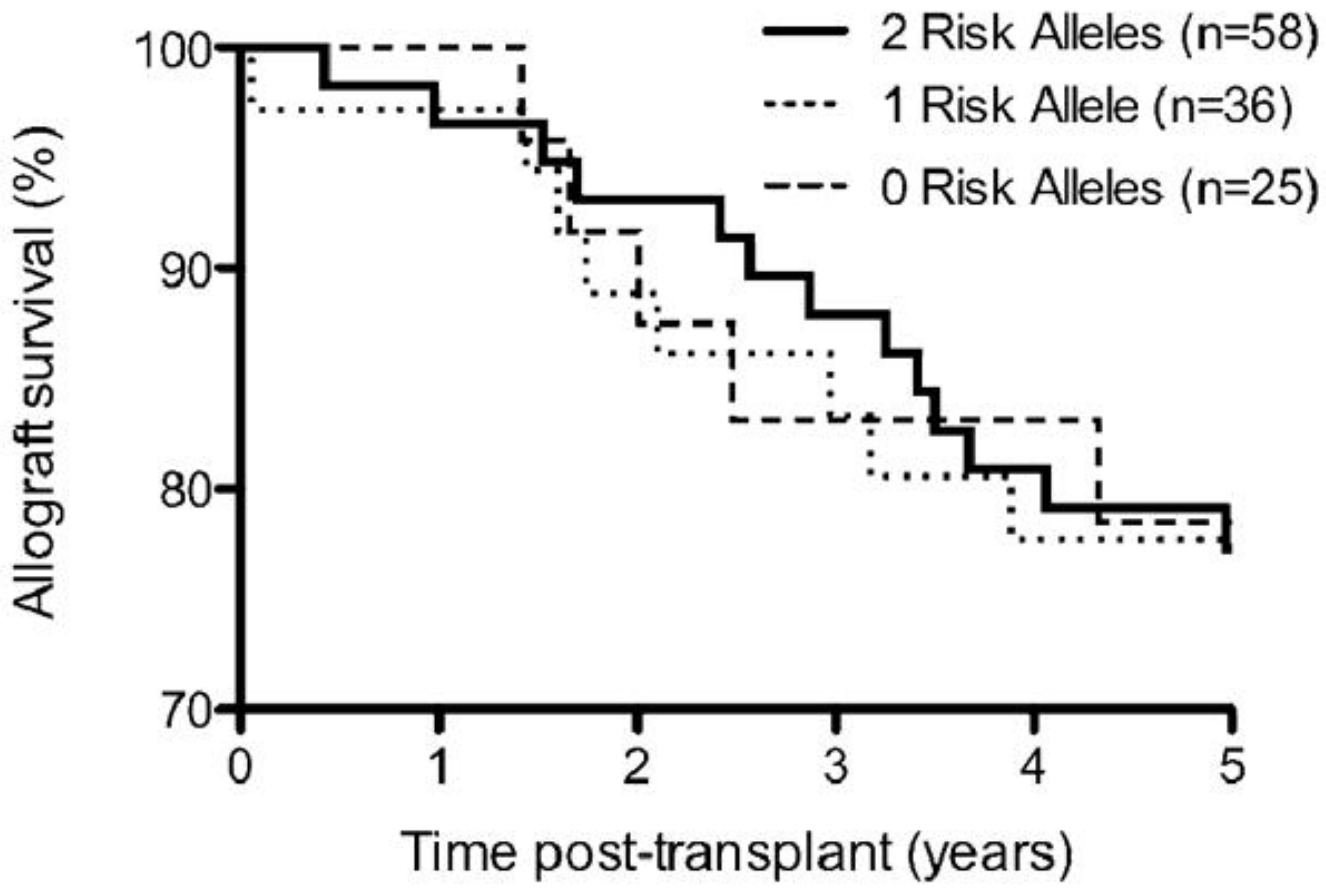
Peralta et al, JASN, 2016

Age at dialysis



Kanji et al, JASN, 2011

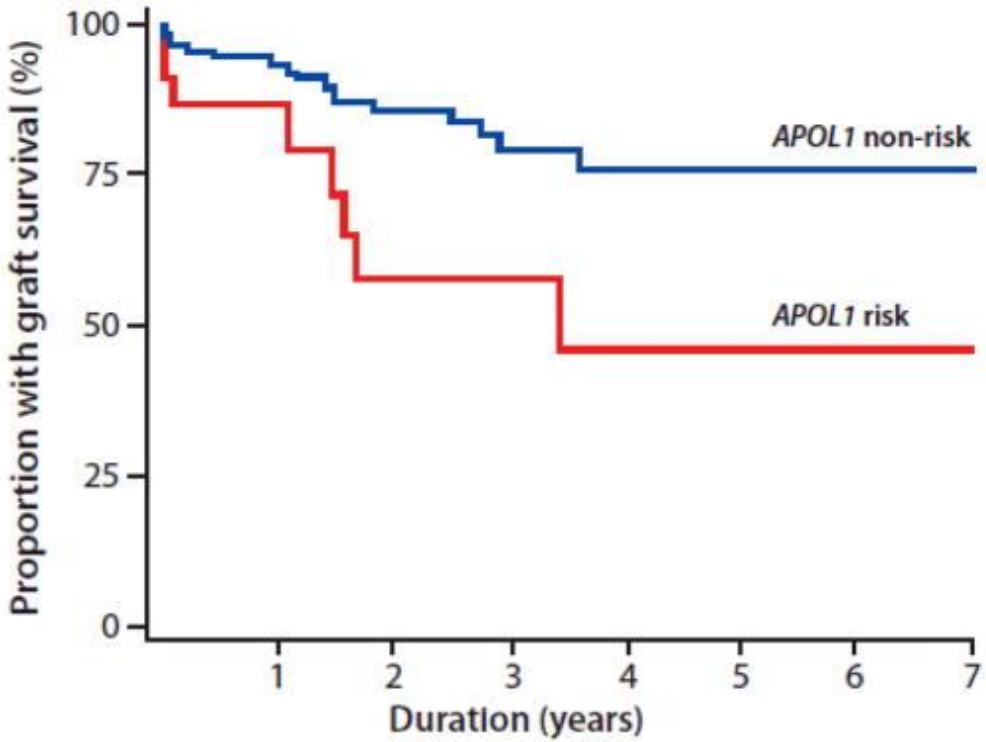
APOL1 and transplantation



Recipient genotype

Lee et al, AJT, 2O12

APOL1 and transplantation

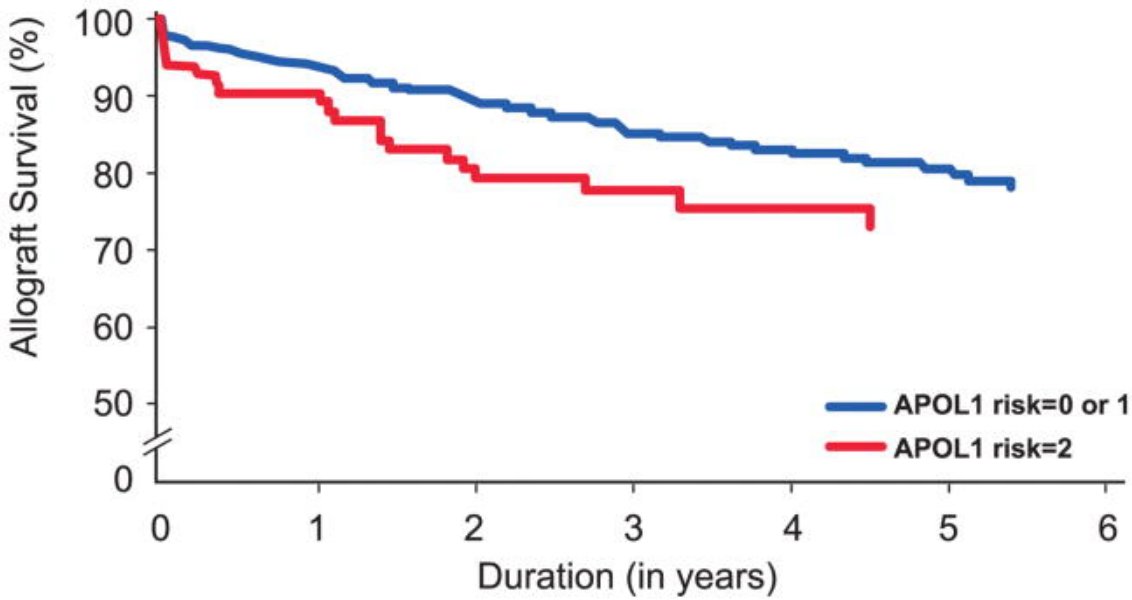


Difference at 20 months
Biopsy: FSGS/ arteriosclerosis

***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

Reeves-Daniel et al, AJT, 2O11

APOL1 and transplantation



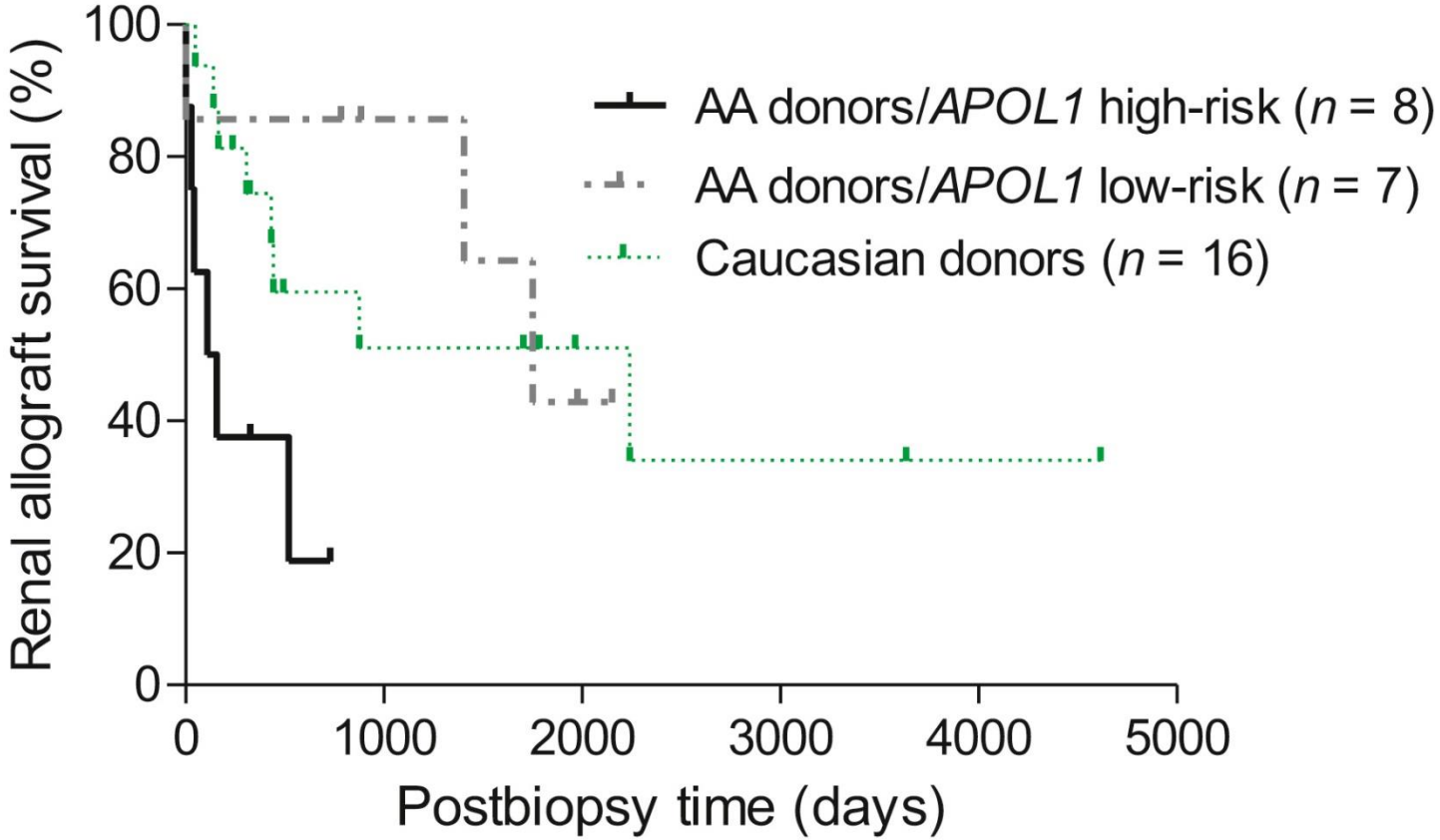
p=0.001

APOL1 risk=0 or 1							
No. at risk	575	486	387	306	213	151	101
No. of graft losses	1	34	53	68	73	78	81
Failure rate	0.2%	6.2%	10.6%	14.8%	16.7%	19.4%	21.7%
No. censored	0	56	136	202	290	347	394
APOL1 risk=2							
No. at risk	99	86	63	45	35	29	29
No. of graft losses	2	9	18	19	20	21	21
Failure rate	2.0%	9.4%	20.6%	22.3%	24.5%	27.0%	27.0%
No. censored	0	4	18	35	44	49	49

Freedman et al, AJT, 2O15

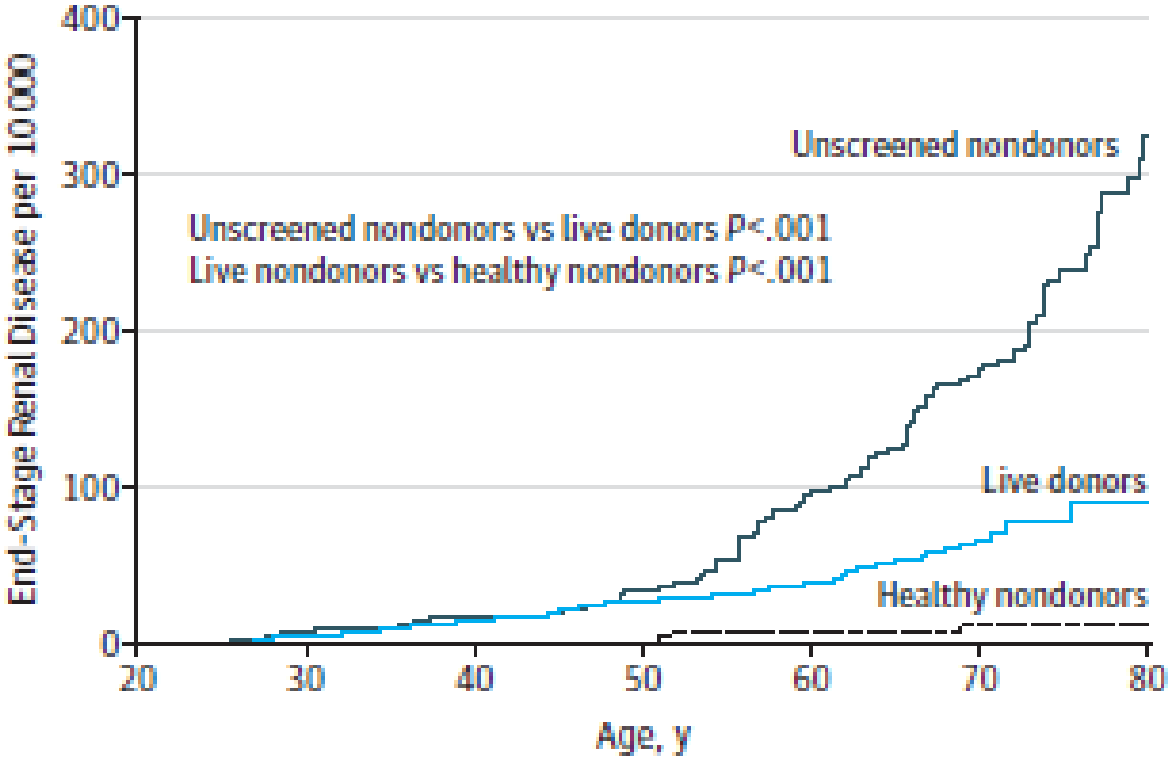
De novo collapsing FSGS after transplantation

47% African American donors, including 53% *APOL1 HR*



Santoriello et al, KI, 2018

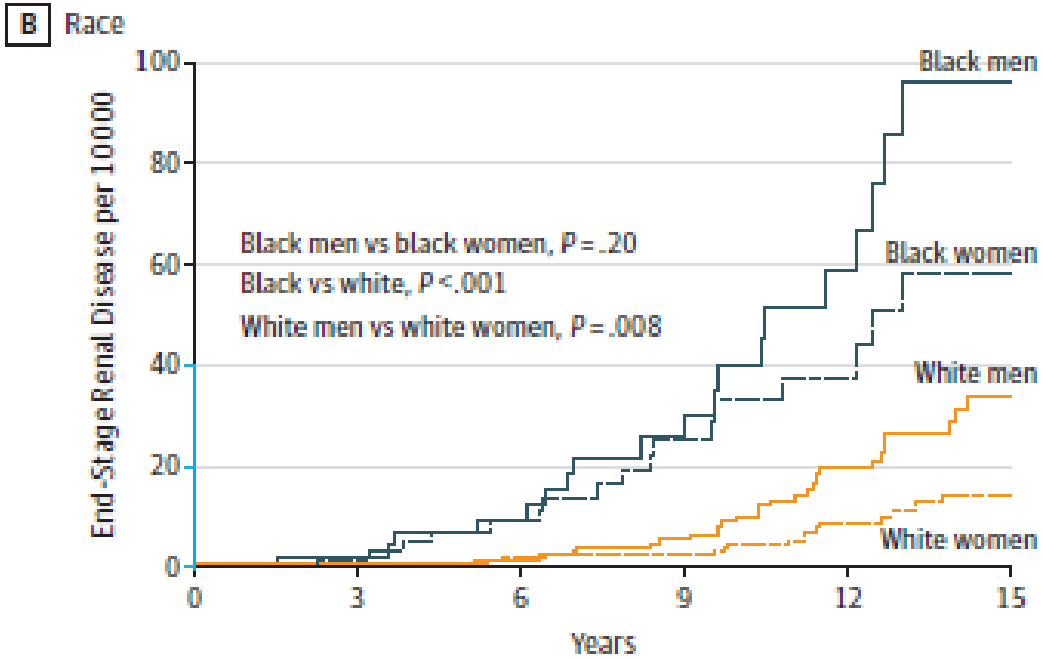
Living donors



No. at risk							
Unscreened nondonor	1296	18 436	36 272	40 863	26 982	7990	647
Live donor	1143	13 144	22 647	22 944	12 151	2575	218
Healthy nondonor	1306	18 487	36 397	40 961	28 358	9011	870

Muzale et al, JAMA, 2014

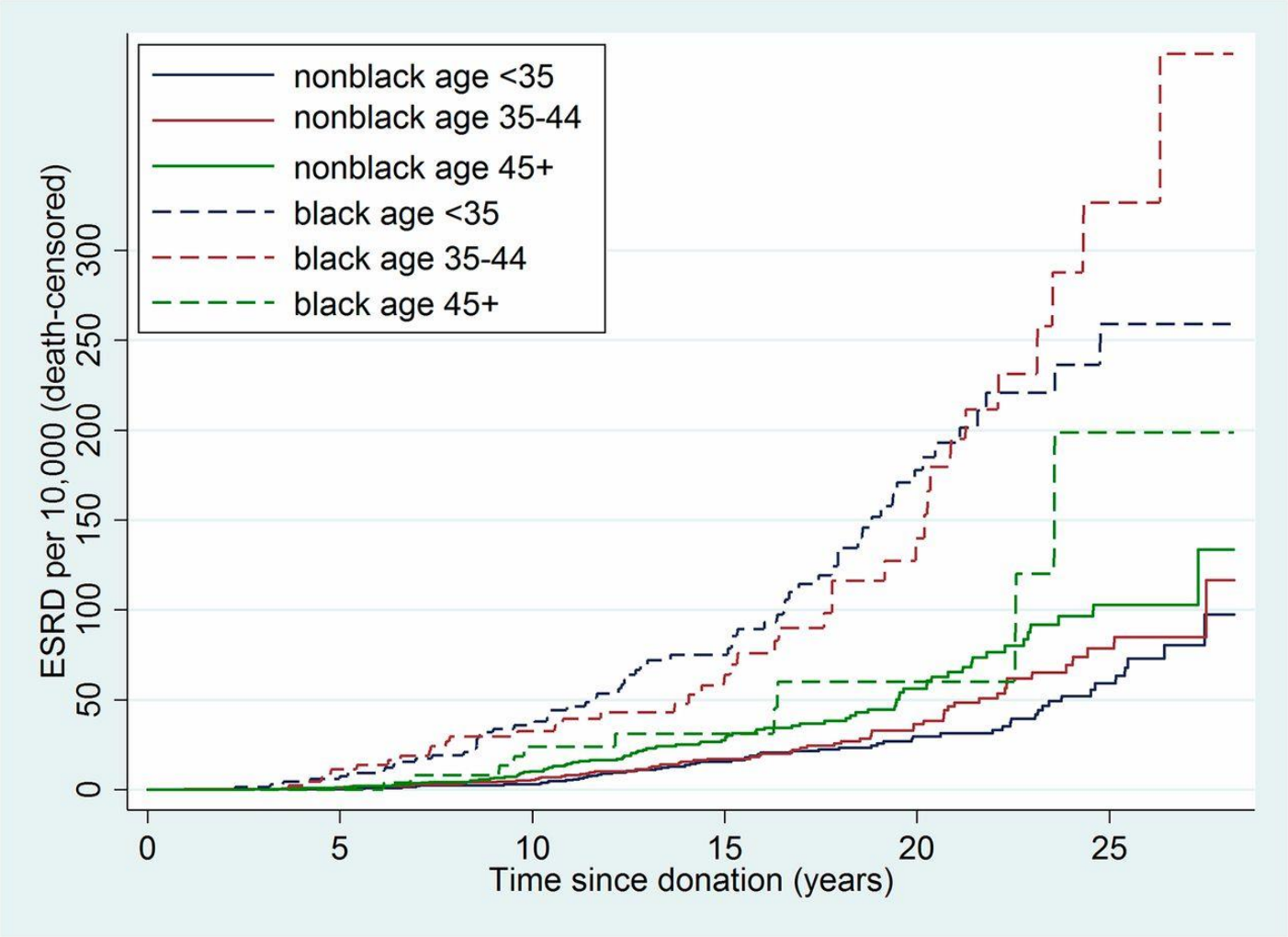
Cumulative incidence of ESRD



No. at risk						
Black						
Men	5330	4409	3449	2247	1238	470
Women	7057	5773	4461	2968	1649	680
White						
Men	28941	23689	18120	12206	6744	2784
Women	42828	34266	25960	17278	9490	3886

Muzale et al, JAMA, 2014

Living donors: risk factors of ESRD



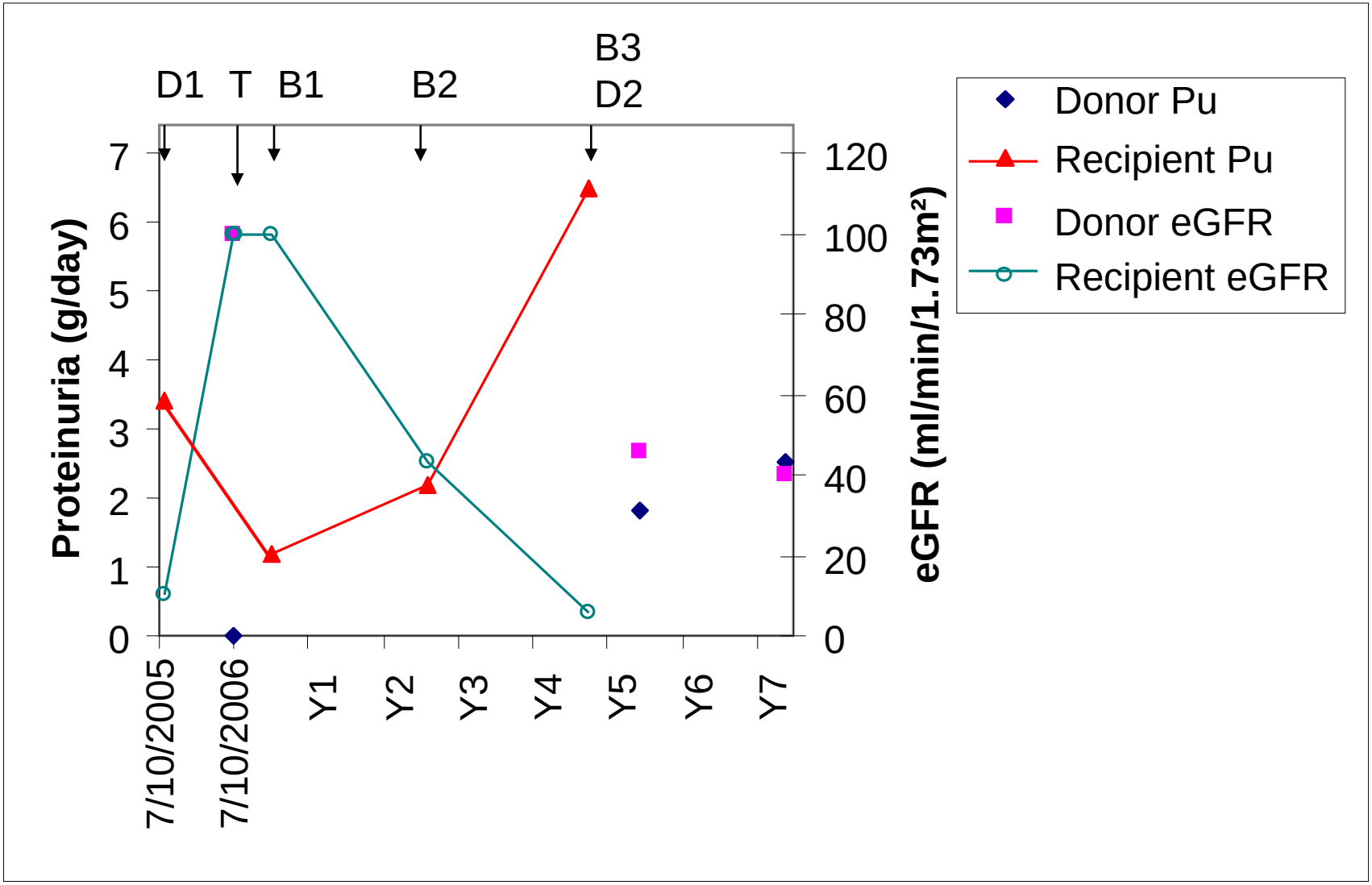
Among nonblack donors, older age groups had higher cumulative incidence of ESRD, whereas among black donors, older age groups had lower risk of ESRD.

Massie et al, JASN, 2017

Living donors and FSGS

- 2 cases of living donors *APOL1* HR who developped FSGS and renal failure after donation

Zwang et al, AJT, 2016
Kofman et al, AJKD, 2014



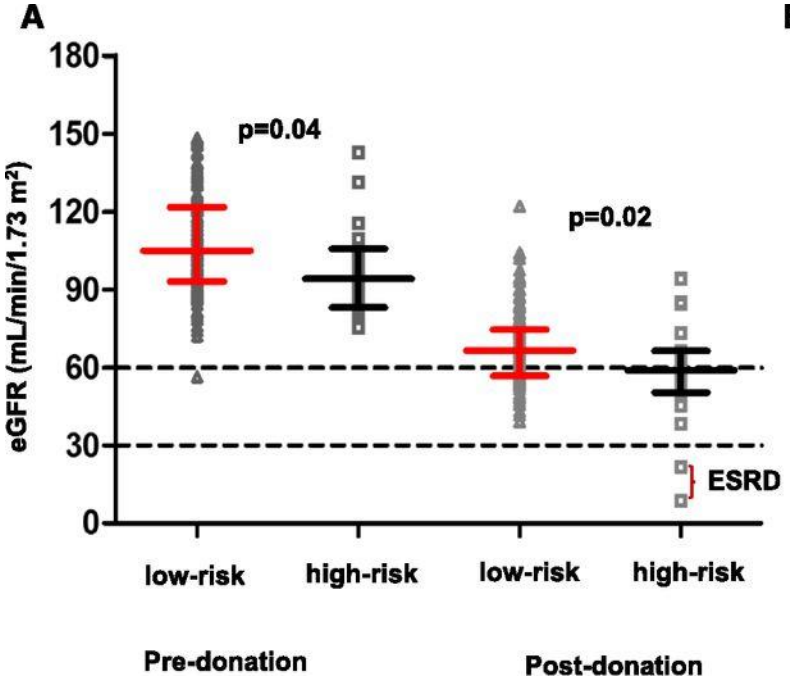
Donor: renal failure and PU 7 yrs after donation

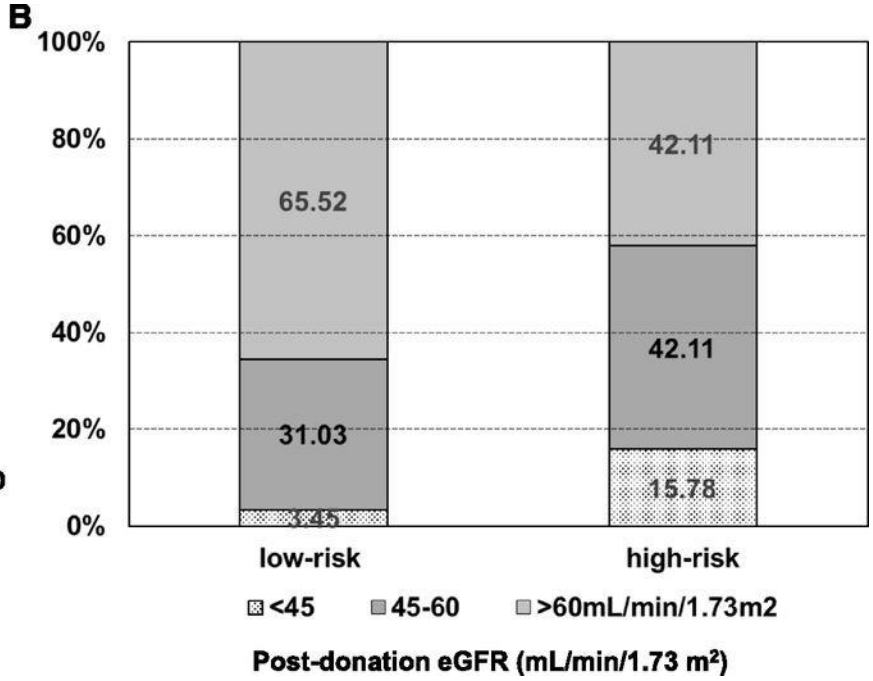
Donation to his twin brother: graft lost due to FSGS after 5 yrs

Kofman et al, AJKD, 2014

APOL1 and kidney donation

136 donors, median follow up 12 yrs
78% 1st degree relatives
2 risk alleles 14%

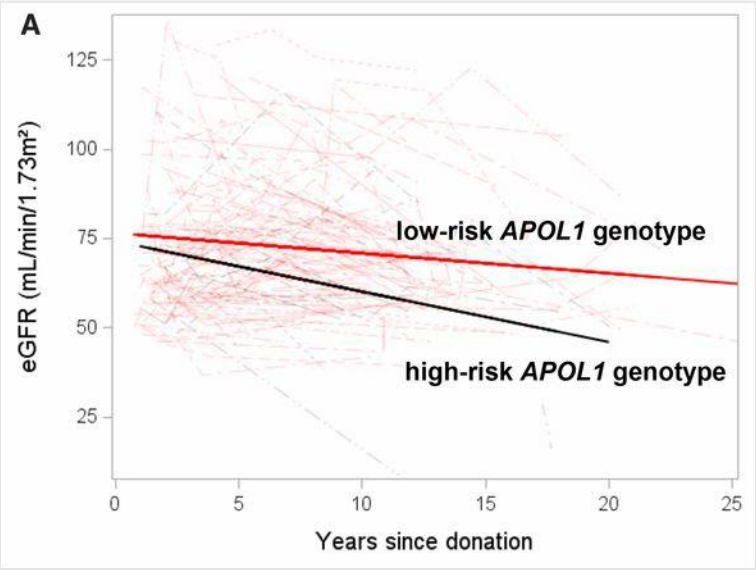


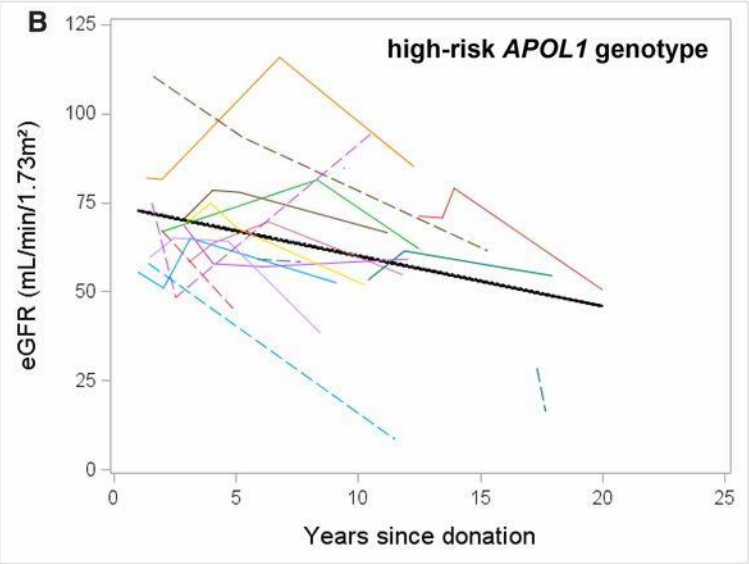


10 ml/min lower pre- and post-donation eGFR in donors with HR *APOL1* genotype
2 ESRD (10, 18 yrs) among 19 patients HR *APOL1*

Doshi et al, JASN, 2017

APOL1 and kidney donation

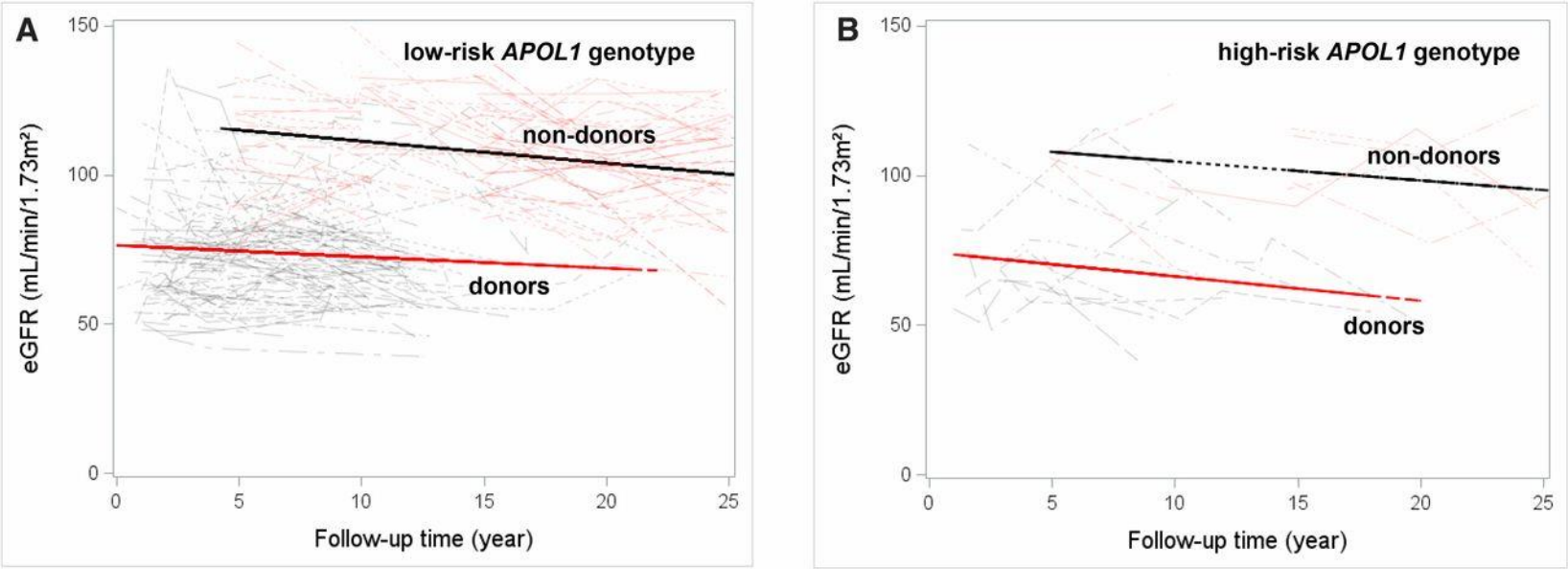




Rate of decline in postdonation eGFR is greater among donors with high-risk versus low-risk *APOL1* genotype

Doshi et al, JASN, 2017

APOL1 and kidney donation



Similar rate of decline in eGFR between donors and matched nondonors grouped by *APOL1* genotype

Doshi et al, JASN, 2017

APOL1 low risk donors

	Caucasian donors	*APOL1* LR African origin donors	P value
1 year eGFR (mL/min/1.73m^2)	66.1 (14.1)	62.4 (12.9)	0.22
Relative eGFR loss (%)	31.5 (9.6)	35.9 (10.2)	0.04
Relative FG (%)	39 (23)	29 (24)	0.05
Absolute FG (mL/min/1.73m^2)	18.1 (11.2)	13.2 (10.9)	0.03

31 donors of African descent with low-risk *APOL1* genotype matched with 62 caucasian living kidney donors
Fonctionnal gain (FG): eGFR 1 yr post donation – eGFR pre donation of remaining kidney

Gaillard et al, Transplantation, 2018

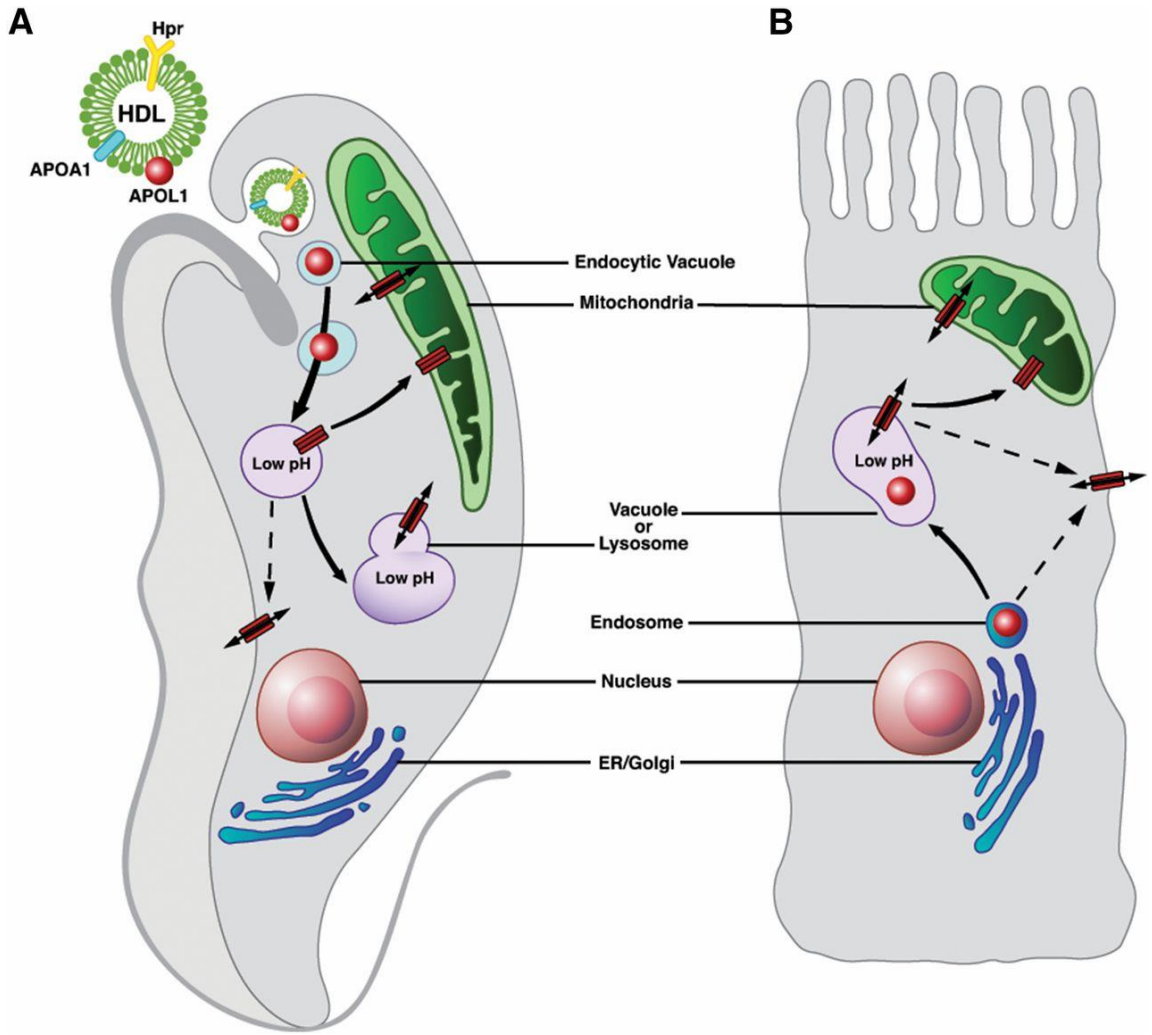
Renal volume

	Caucasian donors	*APOL1* LR African origin donors	P value
Total renal volume (mL/1.73m^2)	264.2 (38.8)	245.3 (37.0)	0.02
Remaining kidney volume (mL/1.73m^2)	130.3 (18.8)	122.4 (20.1)	0.04

Even low-risk *APOL1* donors have lower compensatory response of the remaining kidney, compared to Caucasian donors

Gaillard et al, Transplantation, 2018

Mecanisms of toxicity of *APOL1*



- Increase of endocytic activity
- Reduced acidification of endosomes
- Alteration of endosomal trafficking
- Accumulation of autophagosomes
- Mitochondrial defect

  - Cell death

Bruggeman et al, JASN, 2017; Fu et al, JASN, 2017; Kruzel-Davila et al, JASN, 2017; Granado et al, JASN, 2016; Beckerman et al, Nat Med, 2017; Winkler et al, Nat Med, 2017

Conclusion

- The two risk allele *APOL1* genotype is frequent in FSGS patients with African ancestry
- Young adult disease, but also found in children
- Associated with poor renal survival
- Familial disease, but not associated with other mutations in known monogenic SRNS genes
- Risk of renal failure after kidney donation in *APOL1* HR living donors has to be investigated

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Next webinar

Dr. Jan Becker (Cologne, Germany)

“Histopathology of antibody-mediated rejection”

09 April 2019, 4 pm CET