The History and Future of APOL1

Nieuwere

M B Rookmaaker

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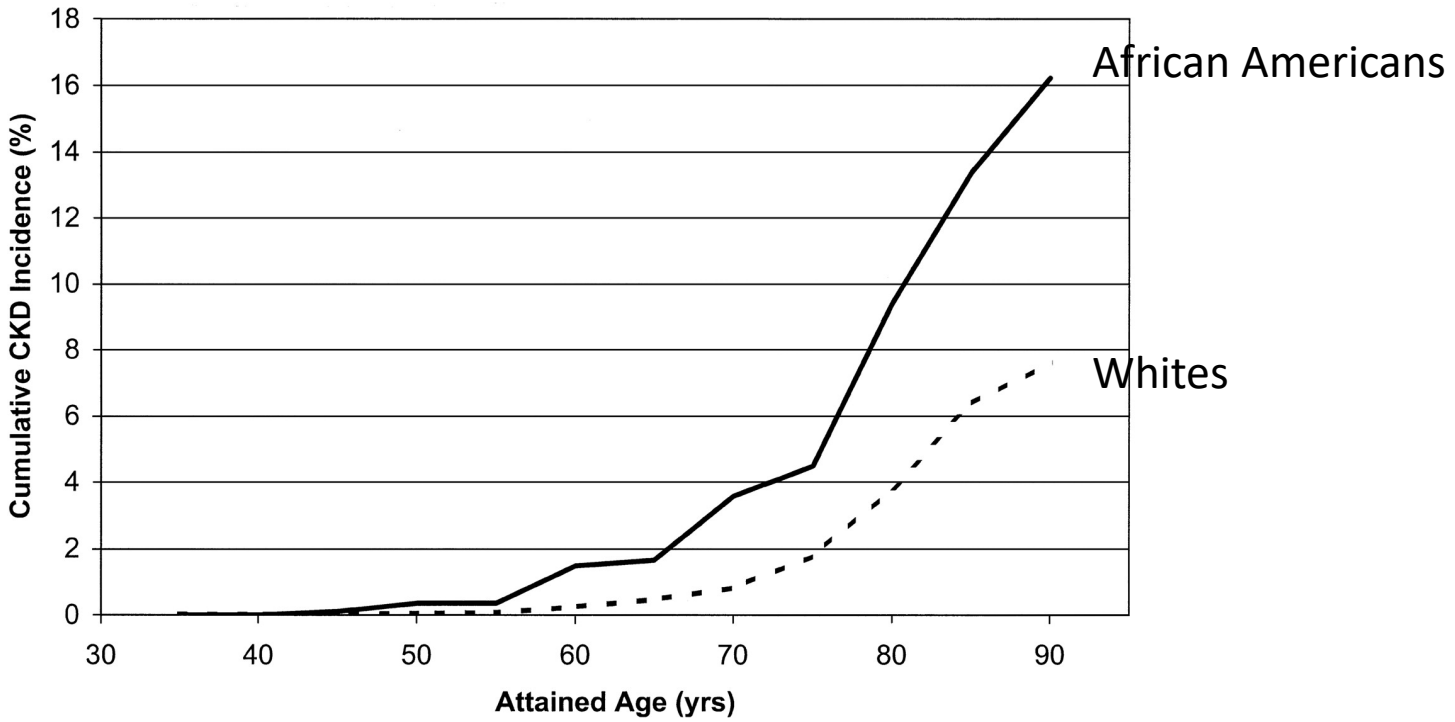
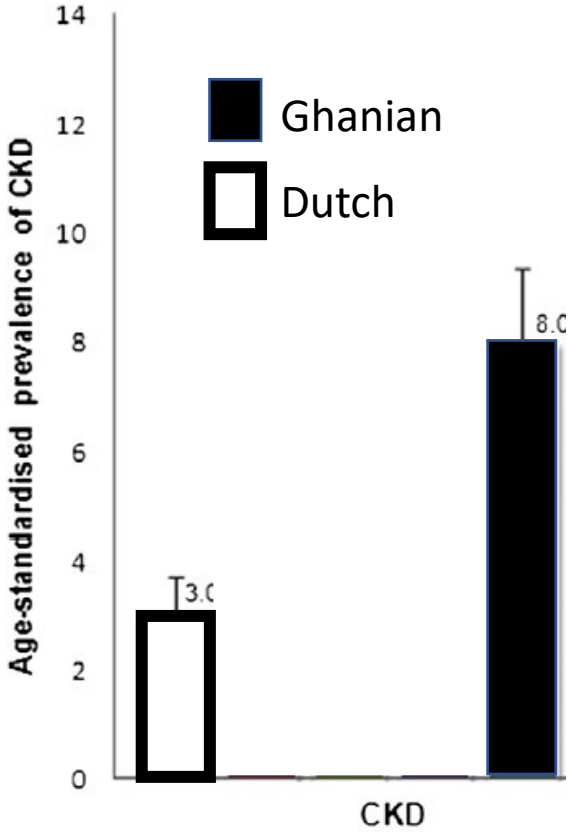
Disclosure belangen spreker

(potentiële) belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	• • • •

Increased CKD risk in people of African descent

Cumulative risk CKD Black vs White in US and NL

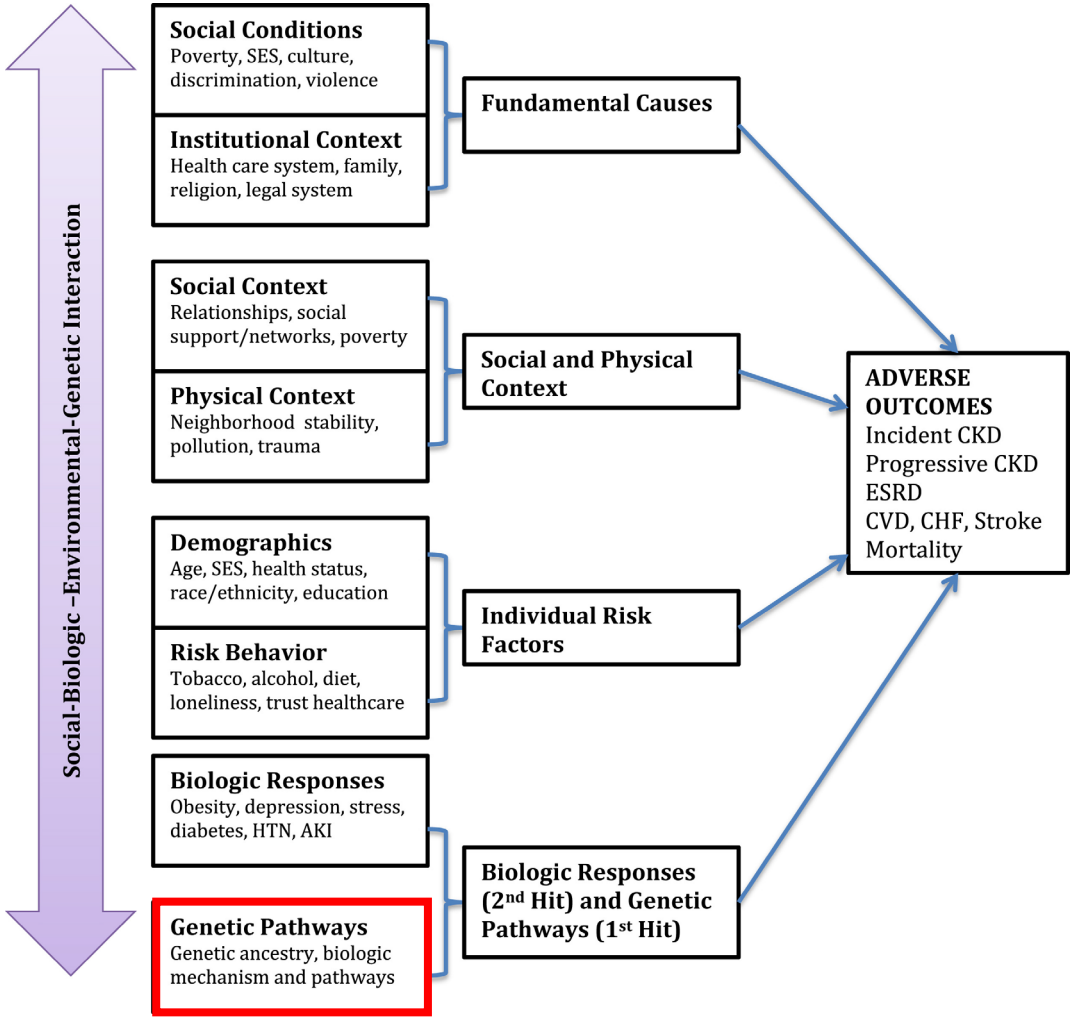


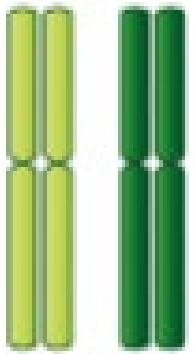


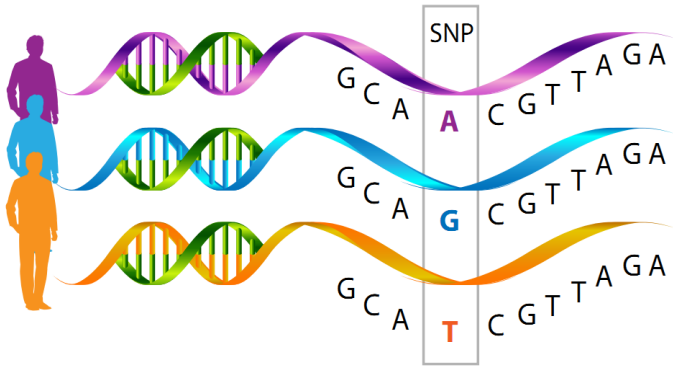
Tarver-Carr JASN 2002
Agyemang AJKD 2016

Increased CKD risk in people of African descent

Complex relation between ethnicity and CKD



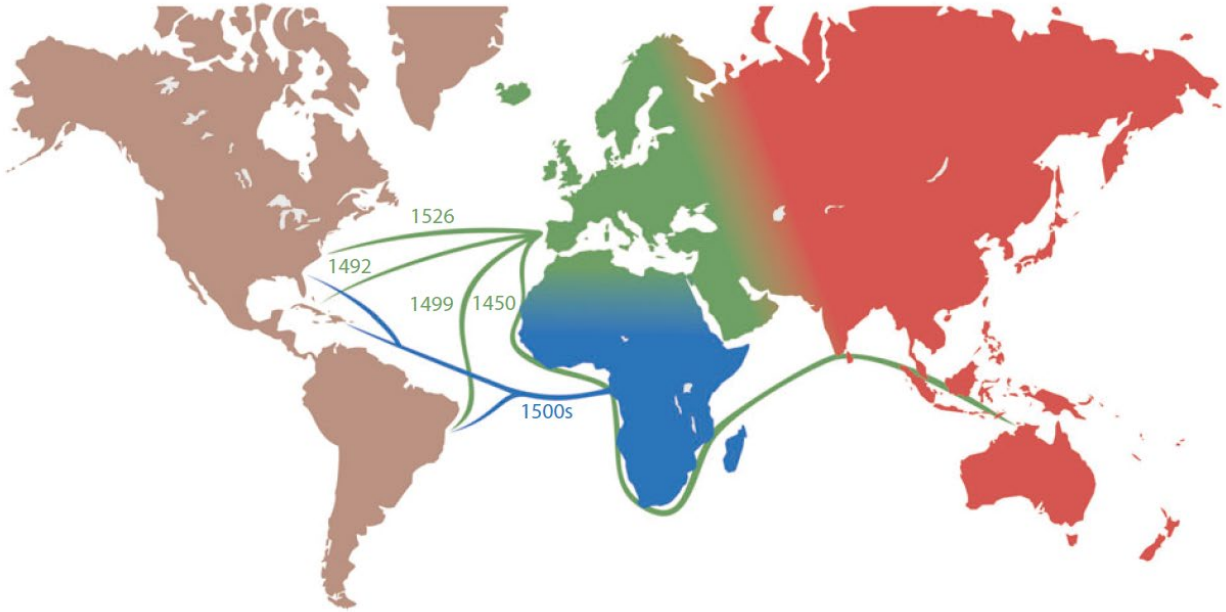




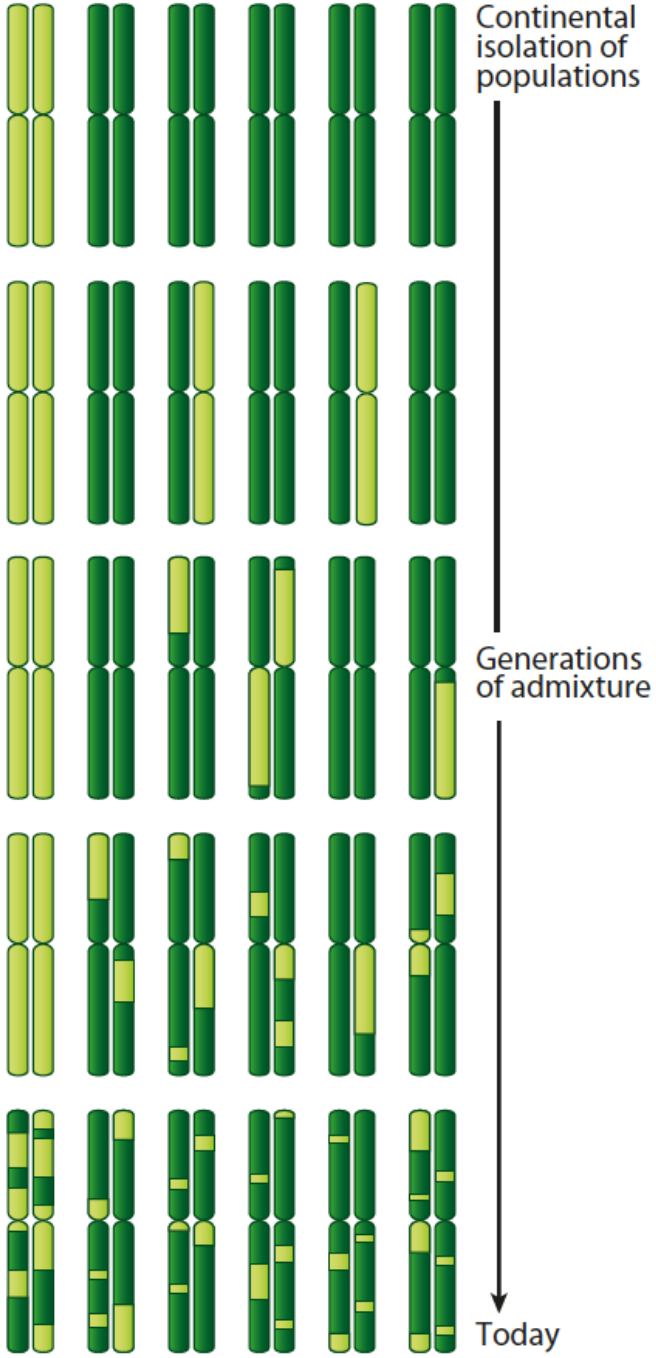
Umeukeje AJKD 2019
Ekulu Ped Neph 2021

Admixture Mapping

migration, recombination and SNPs



- Migration / Ethnic mixing
- Recombination/cross over
- Linkage disequilibrium
- Size of fragments decreases



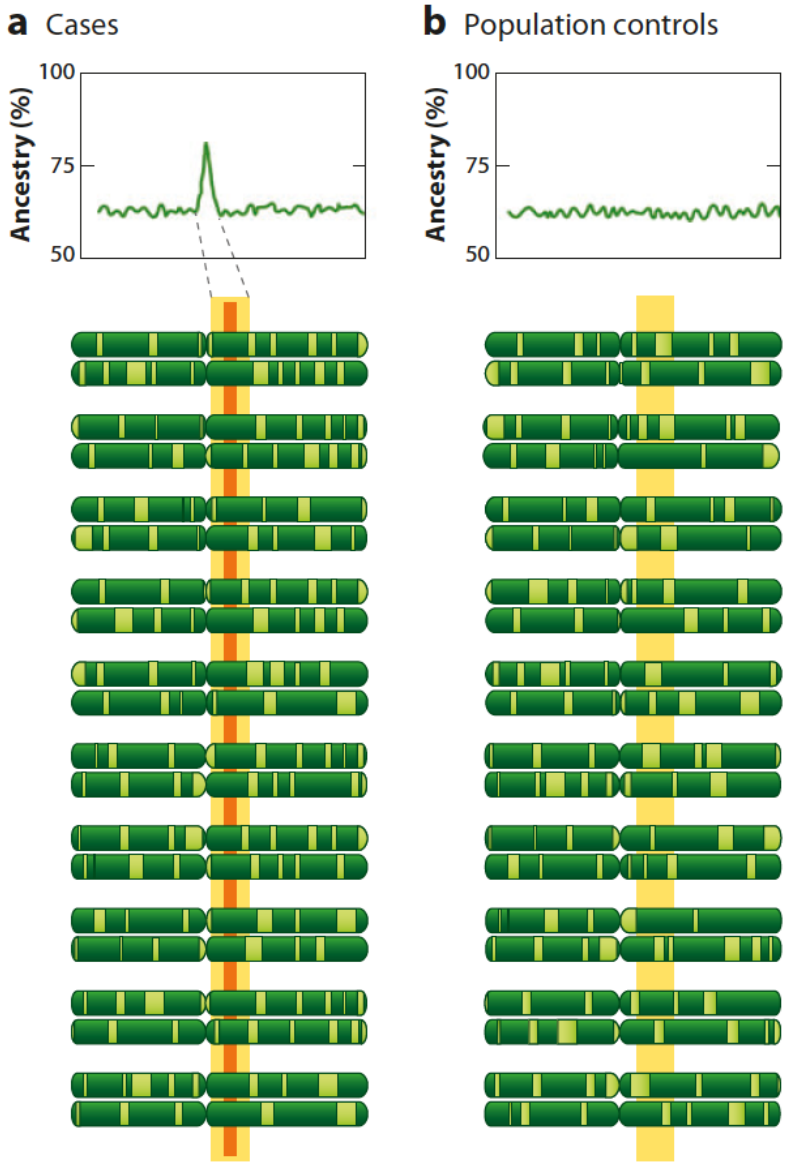
Winkler Ann Rev Gen Hum Gen 2010
Kiberd JASN 2002

Admixture Mapping

identification of potential disease locus

<u>Admixture mapping:</u>

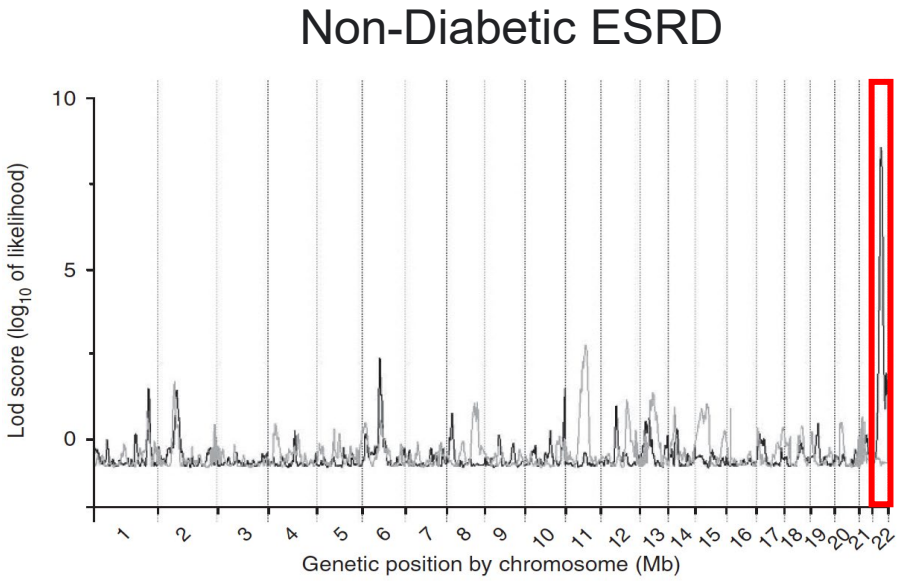
- Gene mapping
- In admixed population
- Find the genetic loci
- Contribute to differences in diseases
- Different ancestral populations

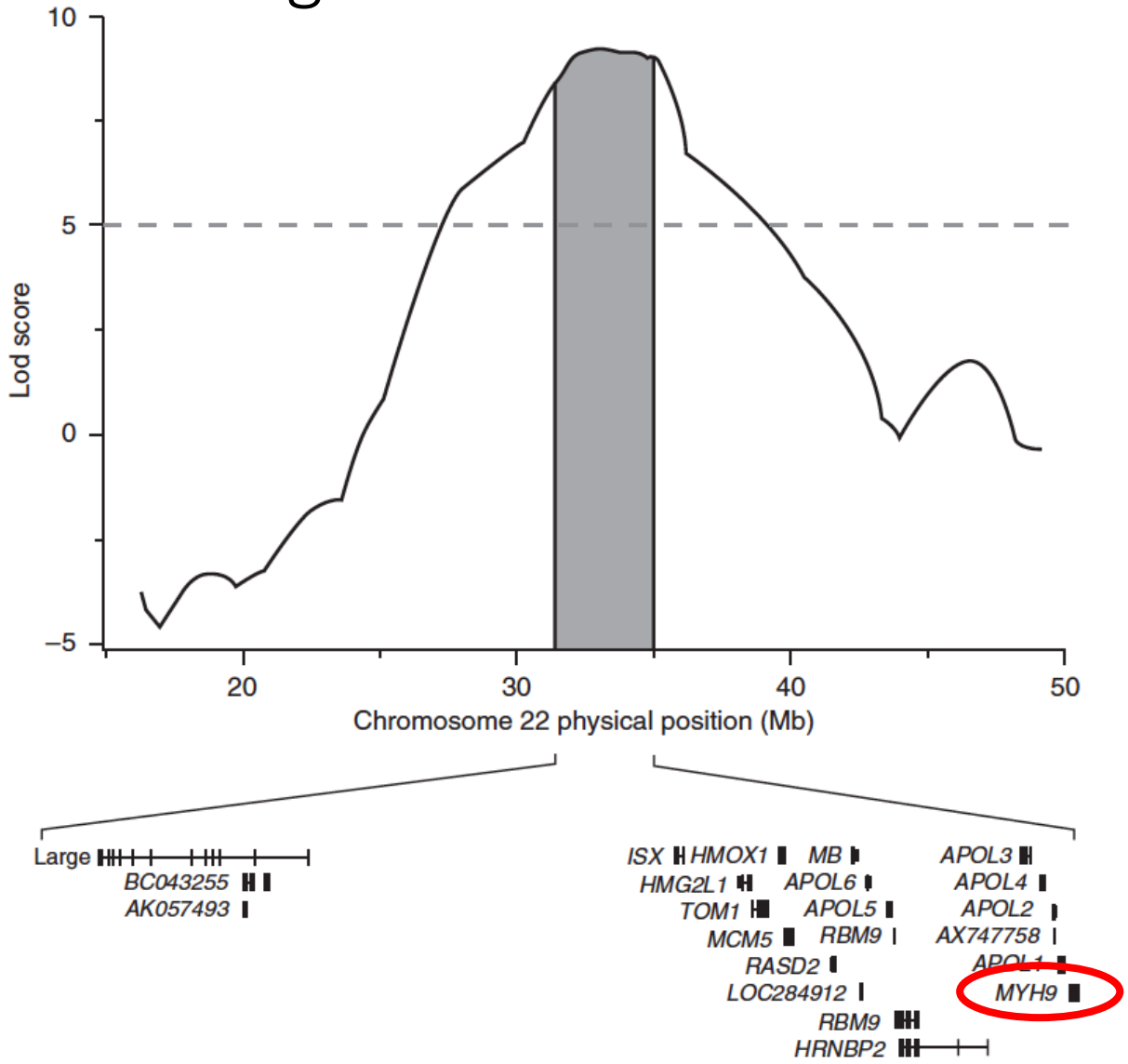


Winkler Ann Rev Gen Hum Gen 2010

Admixture Mapping

From potential disease locus to candidate genes





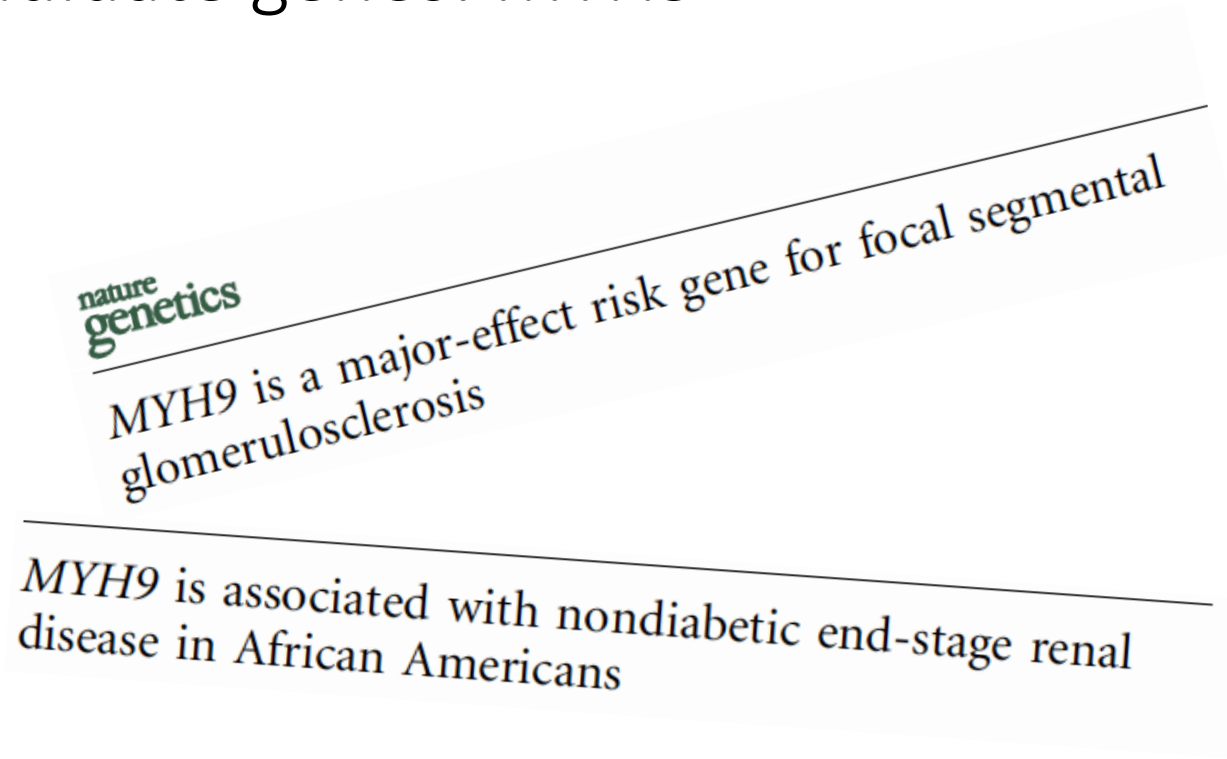
Kao et al Nat Gen 2008

Admixture Mapping

From potential disease locus to candidate genes: MYH9

MYH9

- Non muscle heavy chain myosin IIA
- Epstein Fechtner syndrome
  - Autosomal Dominant
  - Nephritis
  - Macrothrombocytopenia
  - Sensorineural hearing loss

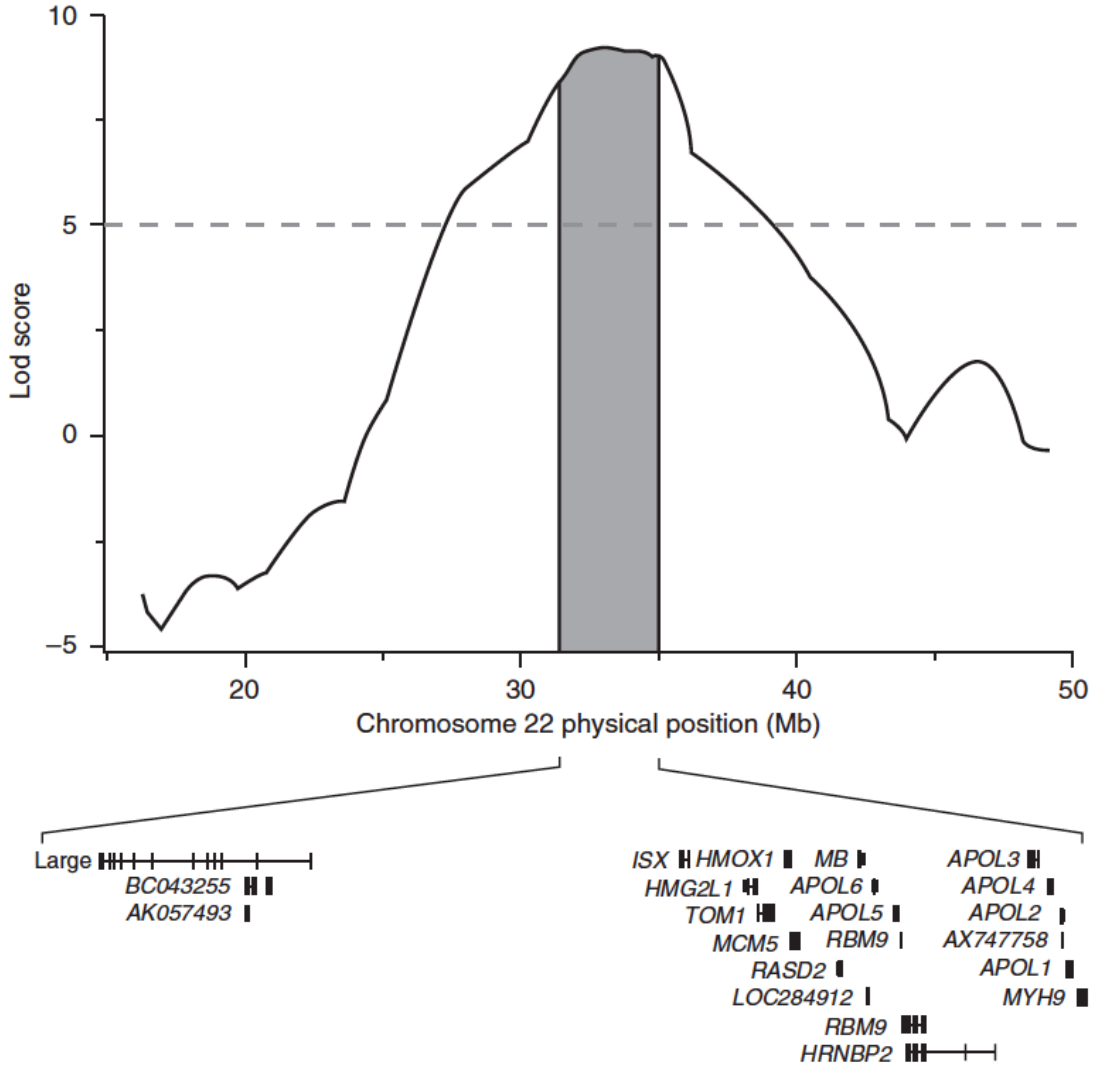


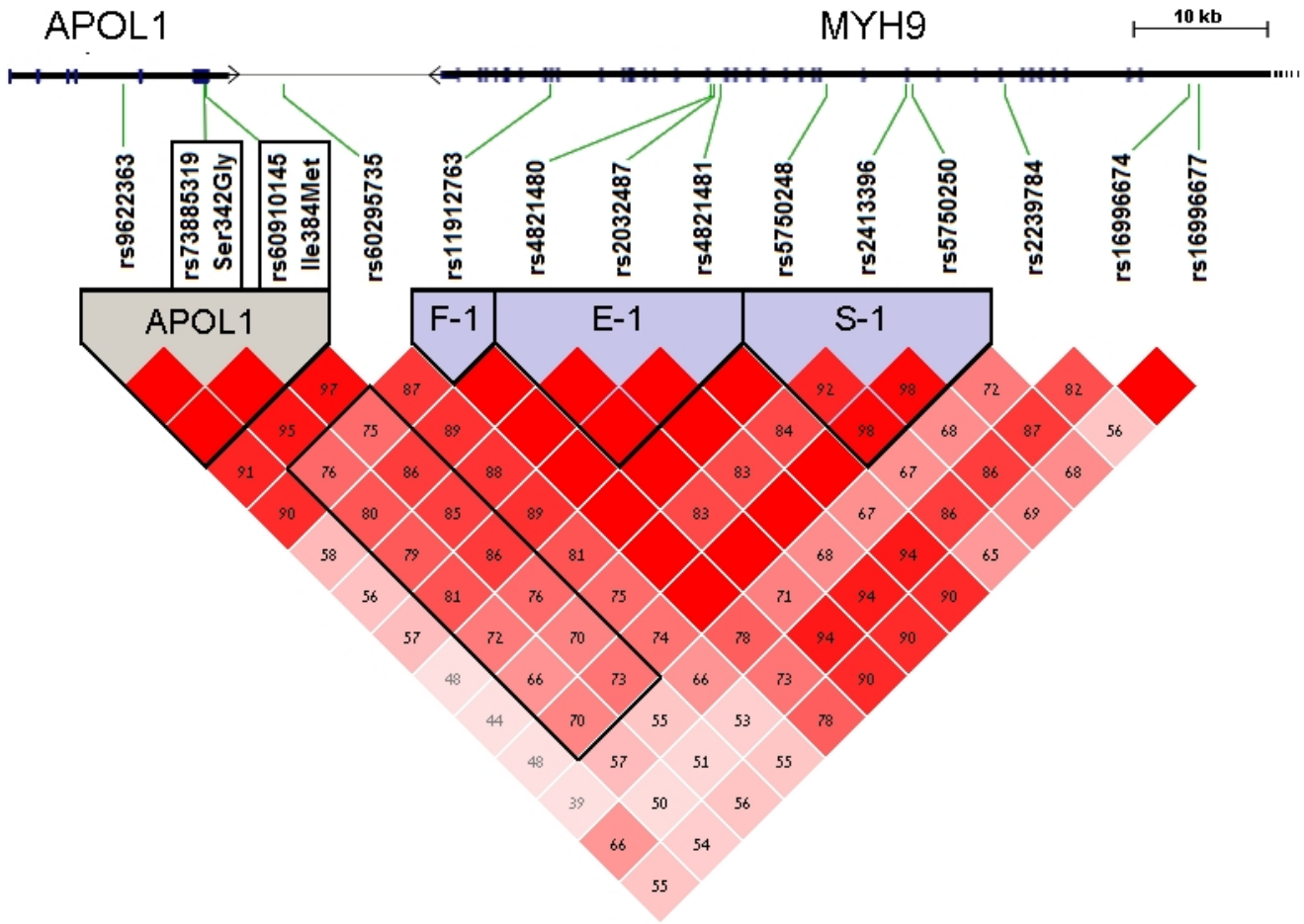
→ no mutations with a clear predicted functional effect

Seri Human Gen 2002
Kopp Nat Gen 2008
Kao Nat Gen 2008

Admixture Mapping

Linkage disequilibrium: MYH linked to APOL1



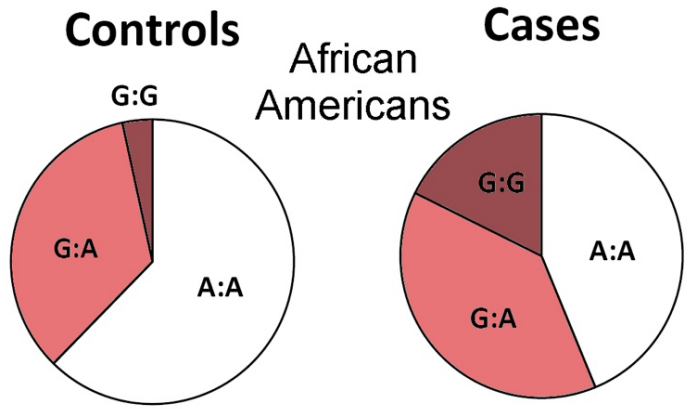


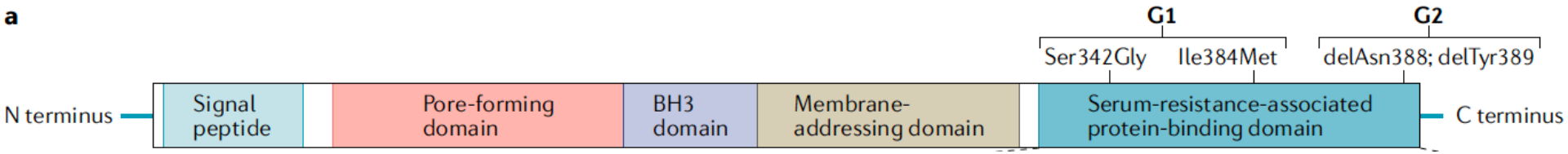
Tzur Human Gen 2010

Admixture Mapping

From potential disease locus to candidate genes: APOL1

rs number	Gene	Type	Mode[d]	OR	*p* value
			non-diab ERSD		
rs73885319[e]	*APOL1*	exon 5	Recessive	6.7	2.71E−06
rs60910145	*APOL1*	exon 5	Recessive	6.74	9.89E−06
rs11912763	*MYH9*	intron 33	Recessive	2.38	2.86E−02
rs5750250	*MYH9*	intron13	Recessive	2.48	4.29E−05

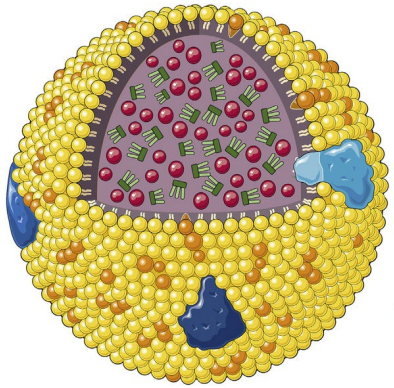


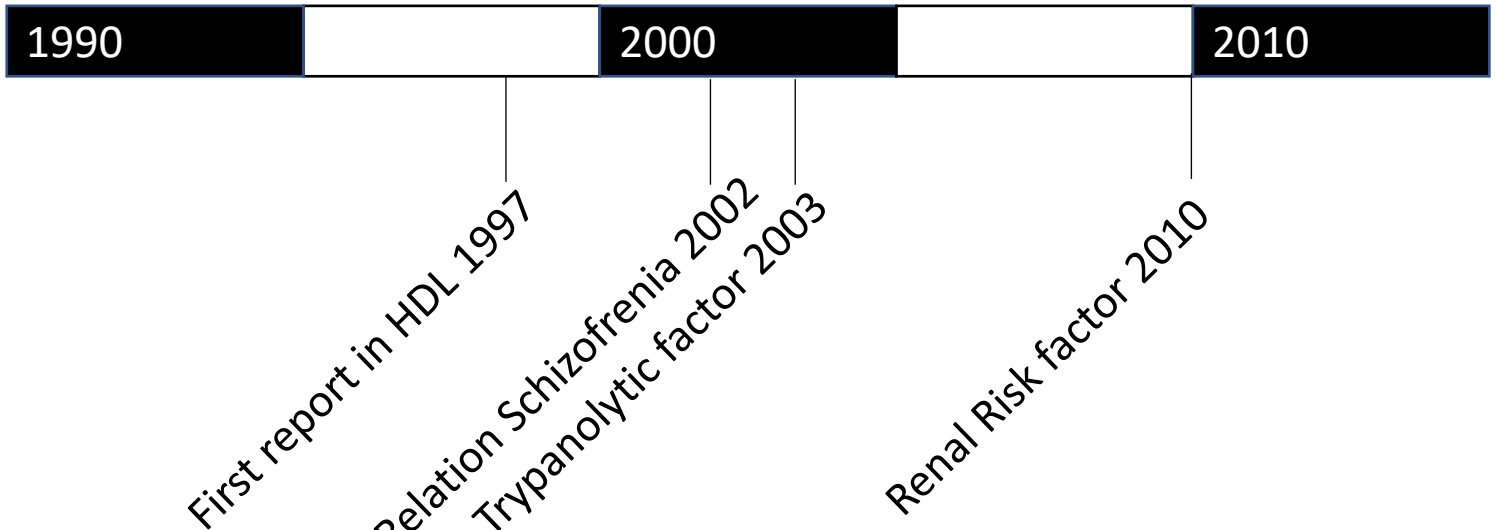


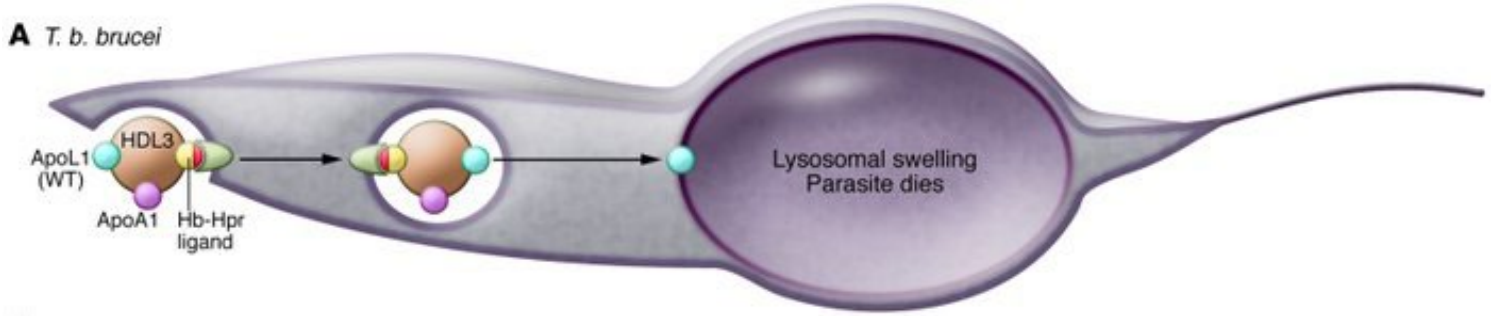
Tzur Human Gen 2010

Apolipoprotein L1

History of Apolipoprotein L1





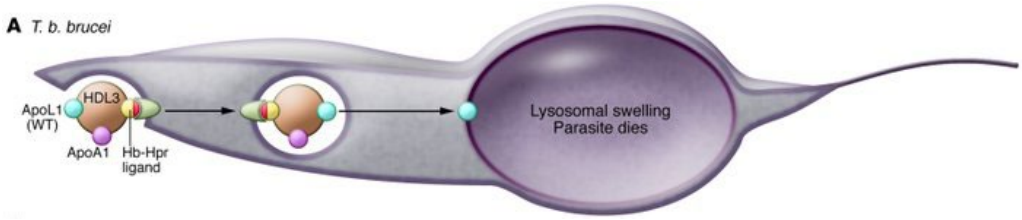


Duchateay J Biol Chem 1997
Mimmack PNAS 2002
Genovese Science 2010
Friedman JCI 2011

Apolipoprotein L1

APOL1 protects against Trypanosomiasis

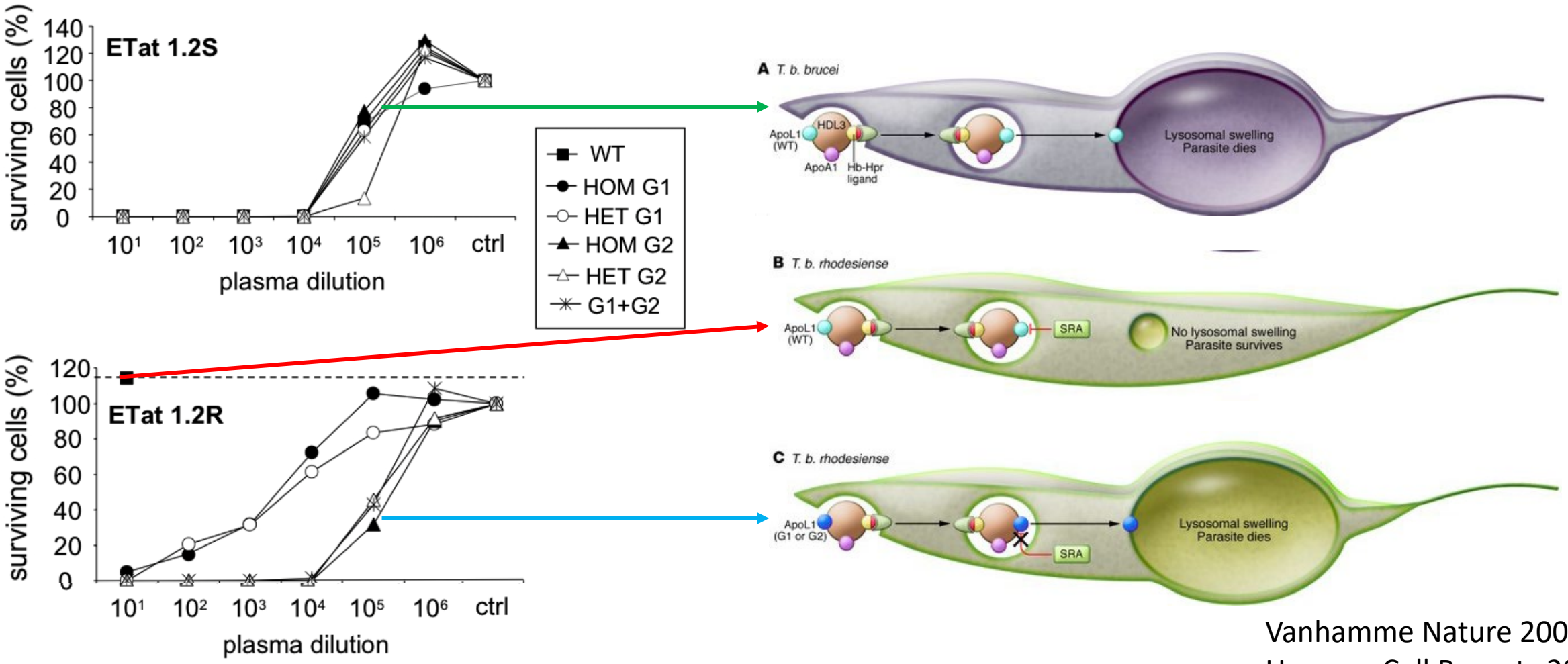
- Innate immunity gene
- APOL1 limited to few primates (relevance animal experiments)
- Expressed in many organs
- No known role in renal development
- Part of circulating HDL
- Creates holes in trypanosomal organelles



Friedman CJASN 2021
Ekulu Ped Neph 2021
Friedman JCI 2011

Apolipoprotein L1

High risk APOL1 variants protect against Resistant Trypanosomiasis



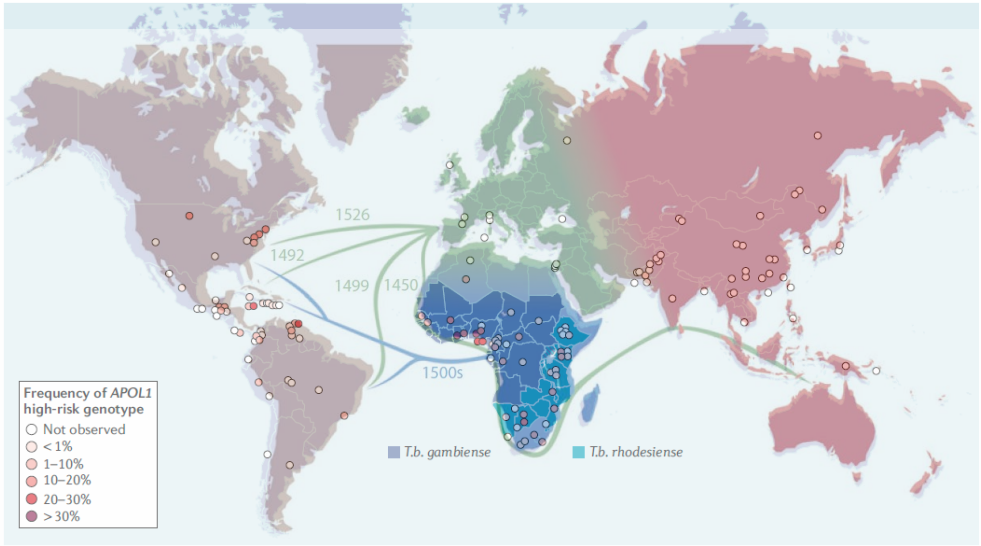
Vanhamme Nature 2003

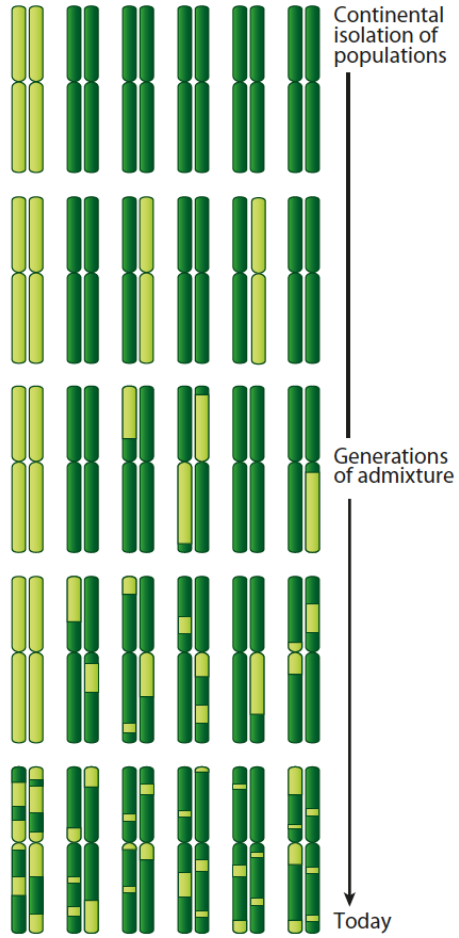
Uzureau Cell Reports 2020

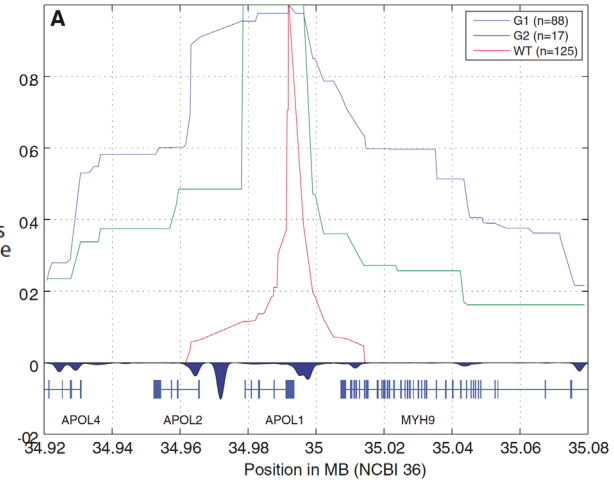
Apolipoprotein L1

High risk APOL1 variants protect against Resistant Trypanosomiasis

c	*T.b. rhodesiense*	*T.b. gambiense*	CKD
G0/G0	Susceptible to acute HAT	Susceptible to chronic HAT	Not at greater risk of CKD
G0/G1	Susceptible to acute HAT	Latent asymptomatic infection	Not at greater risk of CKD
G1/G1	Susceptible to acute HAT	Latent asymptomatic infection	Increased risk of CKD
G0/G2	Protected against acute HAT	Susceptible to chronic HAT	Not at greater risk of CKD
G2/G2	Protected against acute HAT	Susceptible to chronic HAT	Increased risk of CKD
G1/G2	Protected against acute HAT	Latent asymptomatic infection	Increased risk of CKD







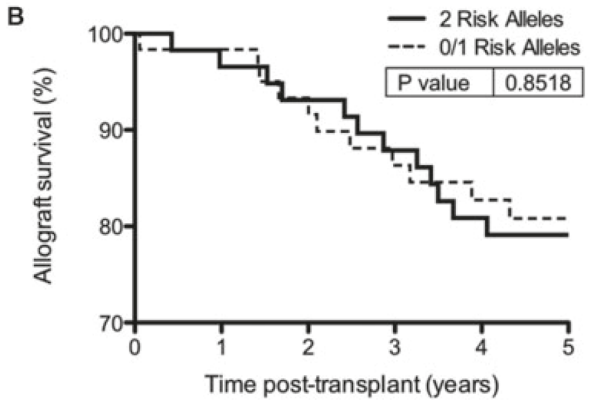
Daneshpajouhnejad Nat Rev Neph 2022
Cuadros-Espinoza Am J Hum Gen 2022

Pathophysiology

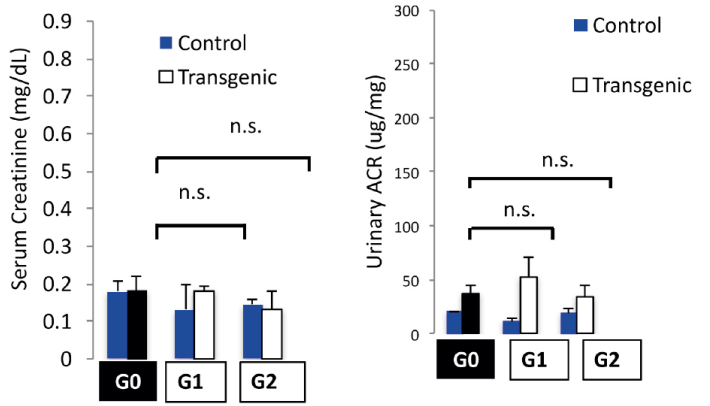
Podocyte probably culprit of disease

Freedman Transplantation 2016
Lee Am J Transpl 2012
Beckerman Nat Med 2017
Reeves-Daniel Am J Transpl 2011
Zhang JCI 2021

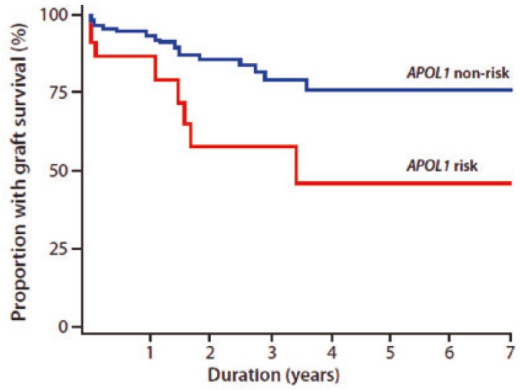
High Risk **Recipient**: = survival



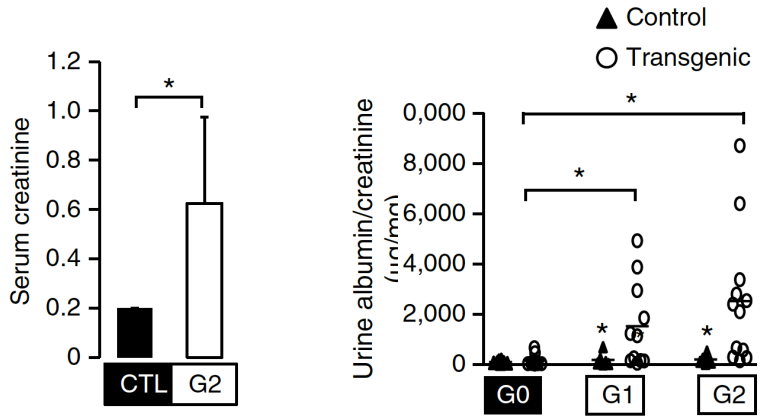
Tubular expression: Creat= / Proteinuria =



High Risk **Kidney**: ↓ survival

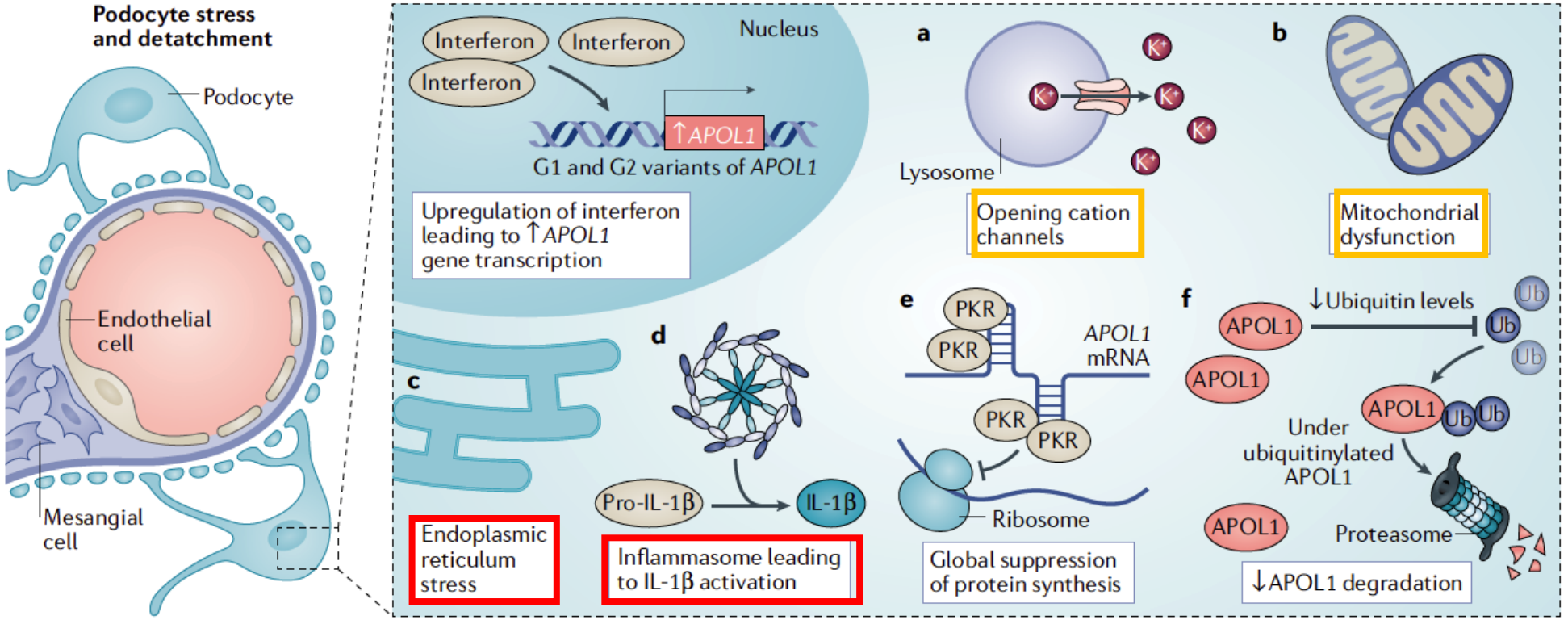


Podocyte expression: Creat ↑/ Proteinuria ↑



Pathophysiology

Proposed mechanisms, no consensus



Pore formation

Inflammation ⟳

Daneshpajouhnejad Nat Rev Neph 2022

Epidemiology

United States

- One high risk mutation (no increased risk of ESRD)
  → 39% of Black individuals
- Two high risk mutations (increased risk of ESRD)
  - 13% of Black individuals
  - 30% Clinically significant kidney disease

  →50% ESKD
- APOL1 high risk genotype explains 70% of increase ESRD in blacks

Friedman CJASN 2021
Reidy Curr On Ped 2018
Freedman AJKD 2022

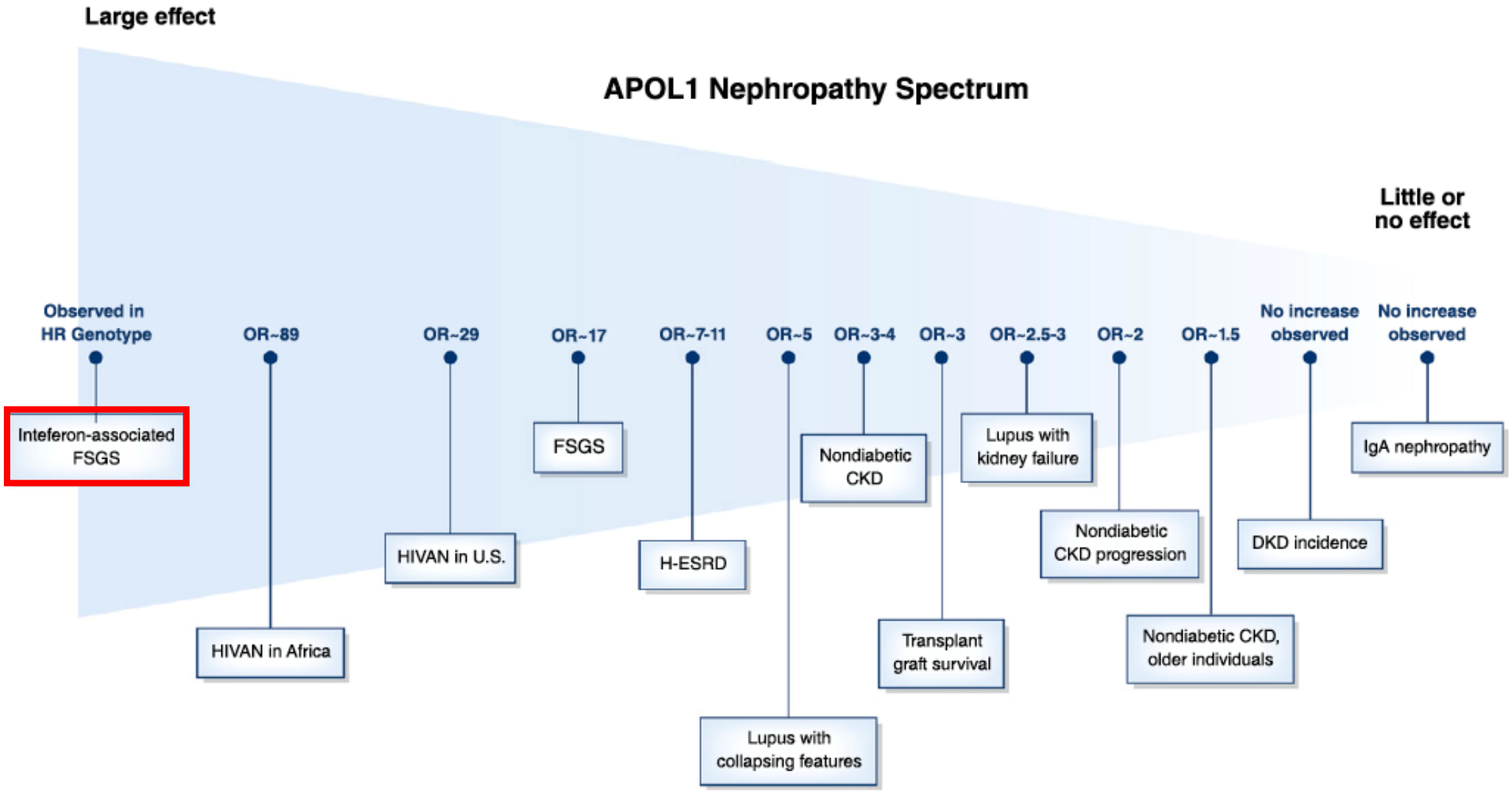
Epidemiology
IFN second hit for APOL1 mediated disease

- Conditions of high IFN state
  - IFN therapy
  - Viral infections
    - HIVAN
    - Parvo B19
    - CMV
    - BK
    - JC
    - SARS-COV-2
  - Hemophagocytic LymphoHistiocytosis (HLH)

Friedman CJASN 2021
Nichols KI 2014

Epidemiology

Many Diseases across the APOL1 Spectrum



Friedman CJASN 2021

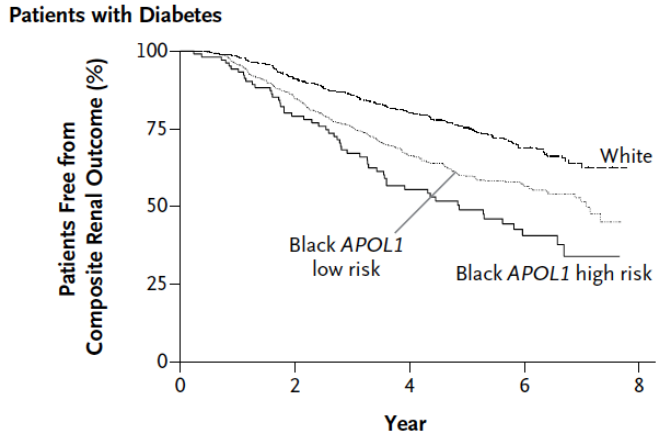
Clinical implications

Genetic testing

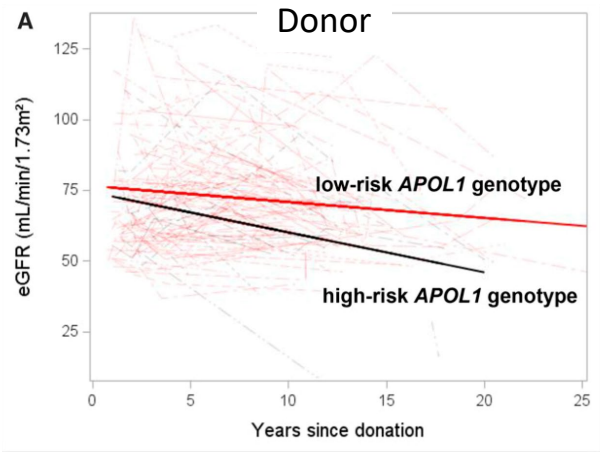
Indications

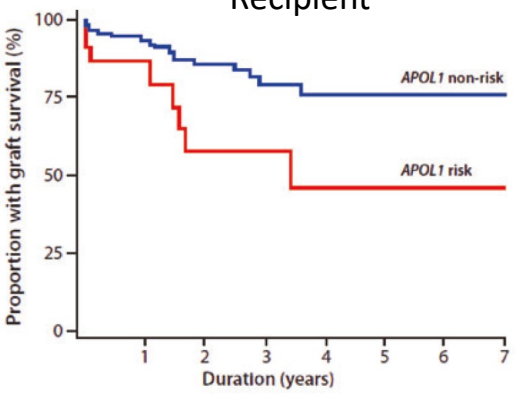
- Provide explanation for disease
  - Proteinuria after IFN event in Blacks
- Prognostic consequences
- Family planning
- Prior to kidney donation
- Therapeutic consequences

Accelerated DKD



Accelerated Renal Function Decline after KTX



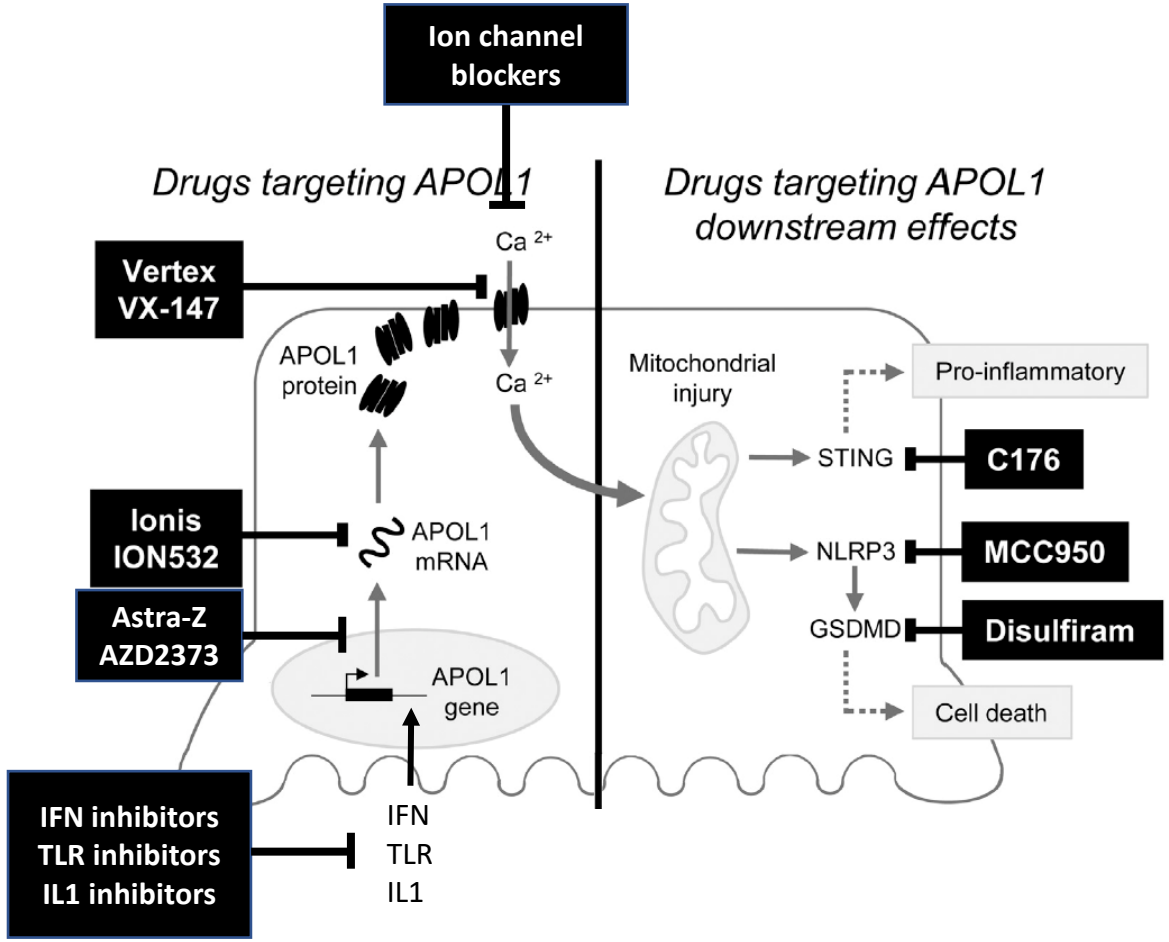


Parsa NEJM 2013
Doshi JASN 2018
Friedman Transplantation 2016
Reeves-Daniel Am J Transpl 2011

Clinical implications

Prevention and treatment

- Annual check up of
  - GFR
  - Albuminuria
  - Blood pressure
- Lifestyle
  - Avoid smoking
  - Regular exercise
  - Healthy body weight
- Avoid IFN invoking events



Bruggeman AJKD 2022
Friedman Curr O Neph Hyp 2022

Conclusion

- APOL1
  - Innate immune system (HDL - Parasytes)
- Resistant Trypanosomes and APOL1 variants (G1, G2)
- APOL1 recessive risk factor for CKD
- IFN second hit
- African Americans
  - 13% high risk genotype
  - 30% CKD
  - 50% ESRD
- Clinical presentation
- Indications for genetic testing