2ND SUMMIT
RARE
DISEASES
COPAC

Differential diagnoses in nephrology of Fabry disease

sanofi

Disclosures

- Consultant: Sanofi Genzyme, Freeline
- Speaker fees: Sanofi Genzyme, Shire, Amicus, Chiesi

FRASE DE SALVAMENTO

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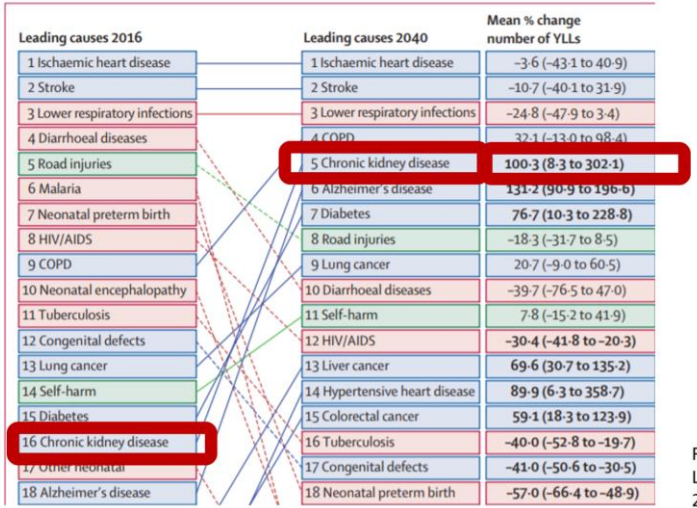
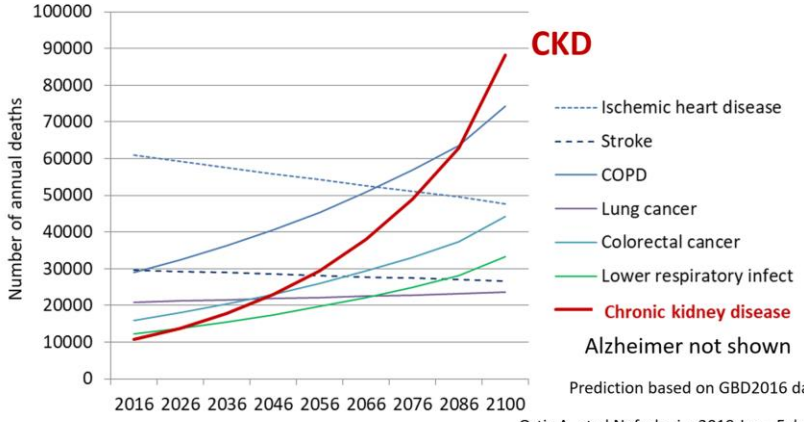
Worldwide top projected causes of death by 2040



YLL: years of life lost

Foreman KJ et al. Lancet 2018; 392: 2052–90

CKD set to become the most frequent cause of death after Alzheimer in Spain within this century



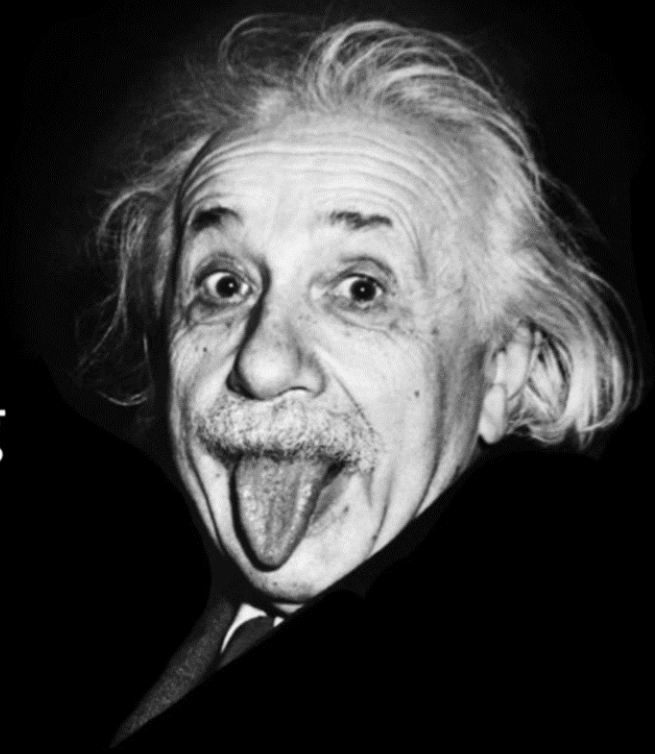
Ortiz A, et al Nefrologia. 2019 Jan - Feb;39(1):29-34

AIRG-E, EKPF, ALCER, FRIAT, REDINREN, RICORS2040, SENEFRO; SET, ONT. CKD: The burden of disease invisible to research funders. Nefrologia. 2022;42(1):65-84.

RICORS2040: the need for collaborative research in chronic kidney disease. Clin Kidney J. 2021;15(3):372-387.

"Insanity is doing the same thing over and over again and expecting different results"

Albert Einstein



Fabry disease is one of the few treatable causes of CKD

Case 1

American Journal of Transplantation 2003; 3: 1030–1032
Blackwell Munksgaard

Case Report

Fabry Disease in a Renal Allograft

Dechu P. Puliyanda*, William R. Wilcox, Suphamai Bunnapradist, Cynthia C. Nast and Stanley C. Jordan

By TUBS - Own workThis vector image includes elements that have been taken or adapted from this: Usa edcp location map.svg (by Uwe Dedering).This vector image includes elements that have been taken or adapted from this: USA Hawaii location map.svg (by NordNordWest).This vector image includes elements that have been taken or adapted from this: Canada location map.svg (by Yug)., CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=15948053

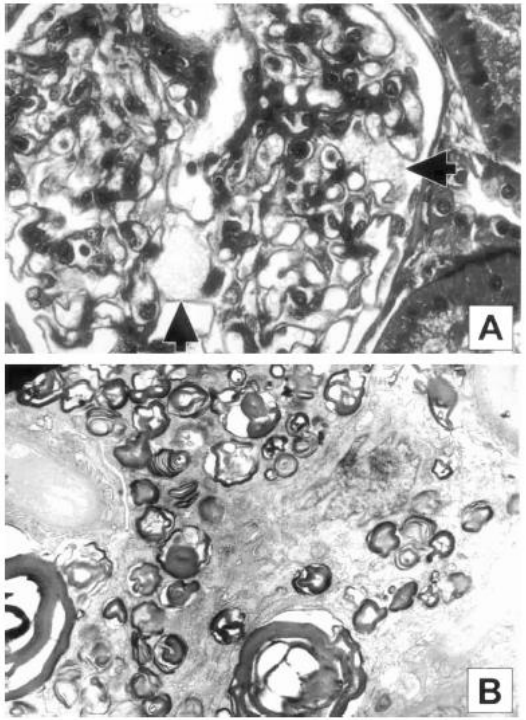
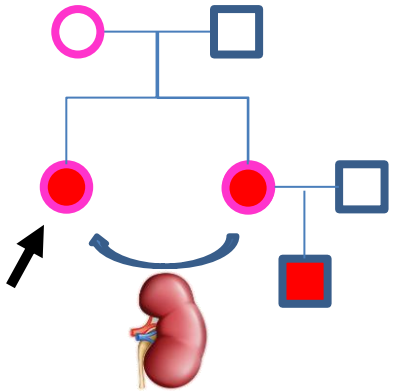


Figure 1: First transplant biopsy.

29-year-old lady

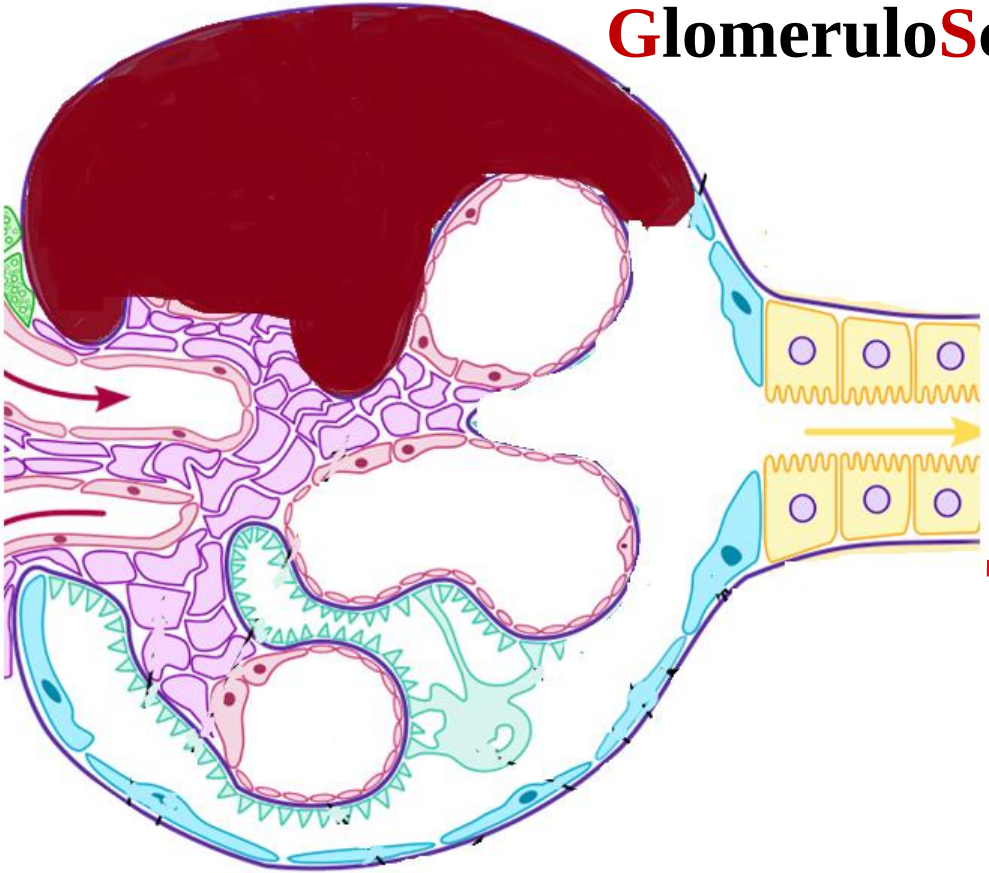
Kidney disease: biopsy
8 of 11 glomeruli completely sclerotic
2 segmental sclerosis.
Electron microscopy: 1 glomerulus, few visceral epithelial cells with scattered myelin bodies
Diagnosis: **FSGS**



- **HLA-identical transplant from sister (pretransplant donor work up normal)**
- **Post-transplant increasing proteinuria**
- **Biopsy extensive myelin figures consistent with Fabry disease**
- **Diagnosis confirmed in recipient, donor and donor's son**

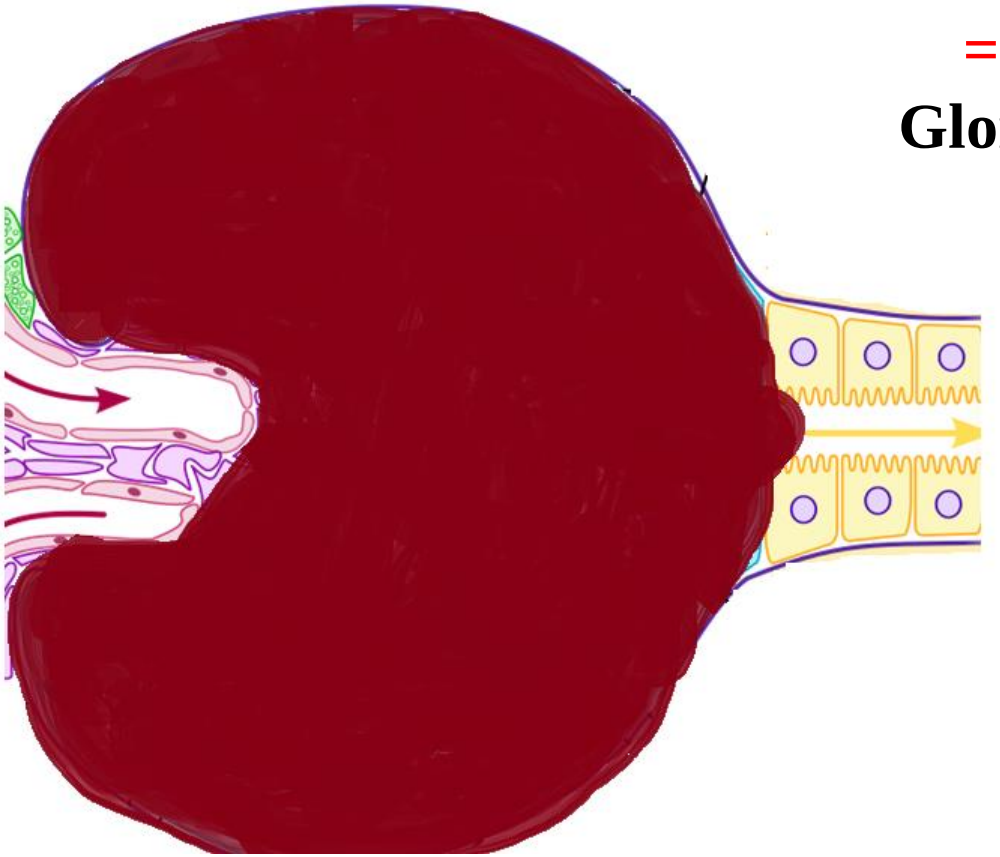
The consequences of knowing the cause of CKD go **beyond** the patient

Focal Segmental GlomeruloSclerosis



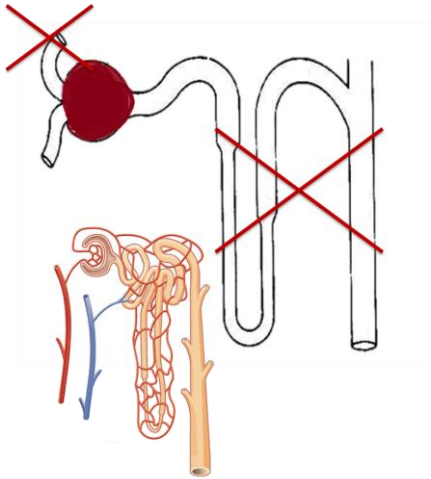
= Dying Glomerulus

Glomerulosclerosis



= Dead Glomerulus

= Dead Nephron

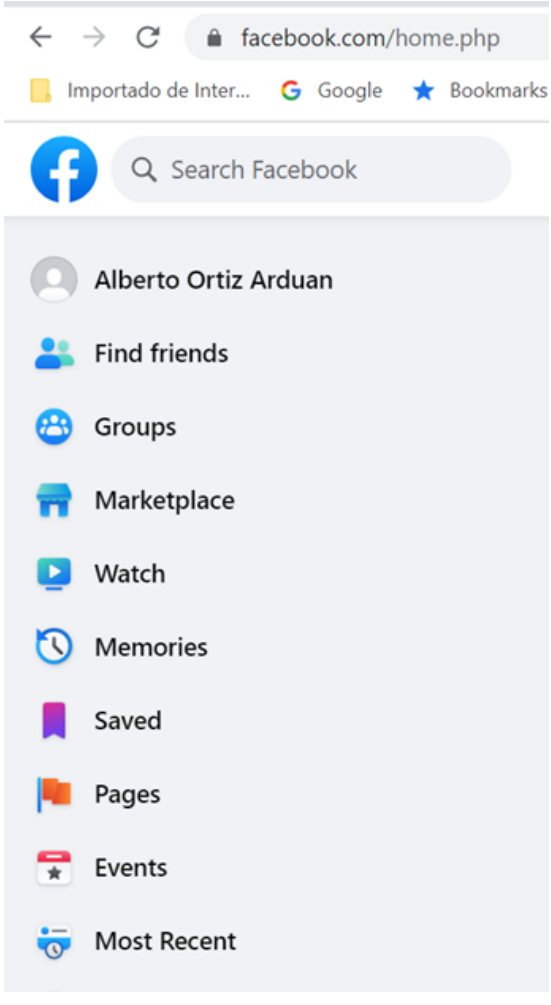


FSGS is a **name**, but a **surname** is needed

Glomeruli are **dying**, but **why**?

Case 2

That was then



This is now

That was then

This is now

Fabry Disease: Renal Involvement Limited to Podocyte Pathology and Proteinuria in a Septuagenarian Cardiac Variant. Pathologic and Therapeutic Implications

Shane M. Meehan, MD, Tipsuda Junsanto, MD, James J. Rydel, MD, and Robert J. Desnick, PhD, MD

Am J Kidney Dis. **2004** Jan;43(1):164-71.

N215S

At age 75 years
he had significant **proteinuria** (1 g/L),
mildly decreased renal function
(serum creatinine, 1.8 mg/dL)
presumably secondary to hypertensive arteriosclerosis.

UACR at least 500 mg/g

eGFR 36 ml/min/1.73 m2

????

Blood pressure 114/72 mmHg

At age 65, **urinary protein** 0.3 g/L

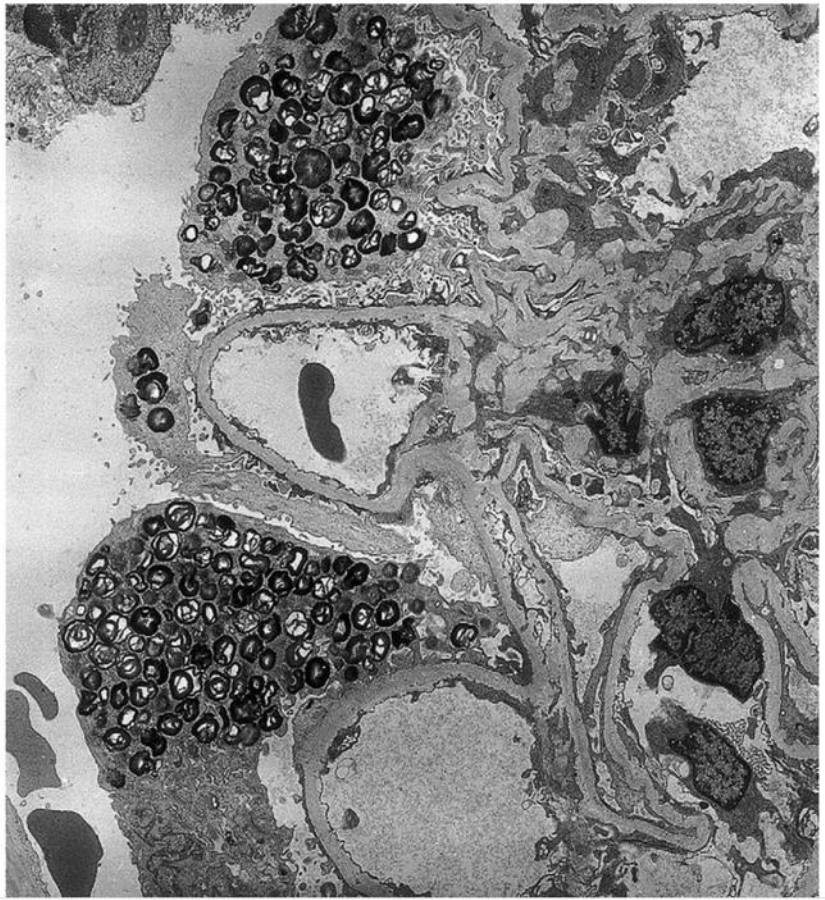


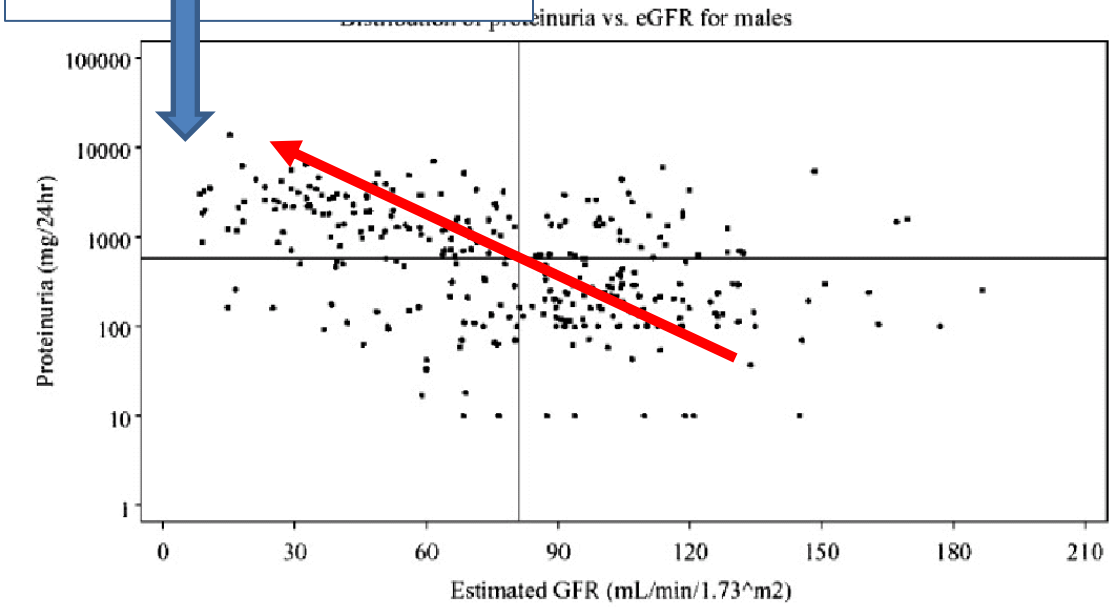
Fig 4. Electron microscopy shows abundant electron-dense myelin figures within the podocyte cytoplasm. The podocyte foot processes are largely effaced. These inclusions were absent from the glomerular and peritubular capillary endothelium, and vascular smooth muscle. (Original magnification ×5,700.)

Meehan et al. Am J Kidney Dis. **2004** Jan;43(1):164-71.

Fabry CKD

Fabry nephropathy is a progressive proteinuric chronic kidney disease of metabolic origin

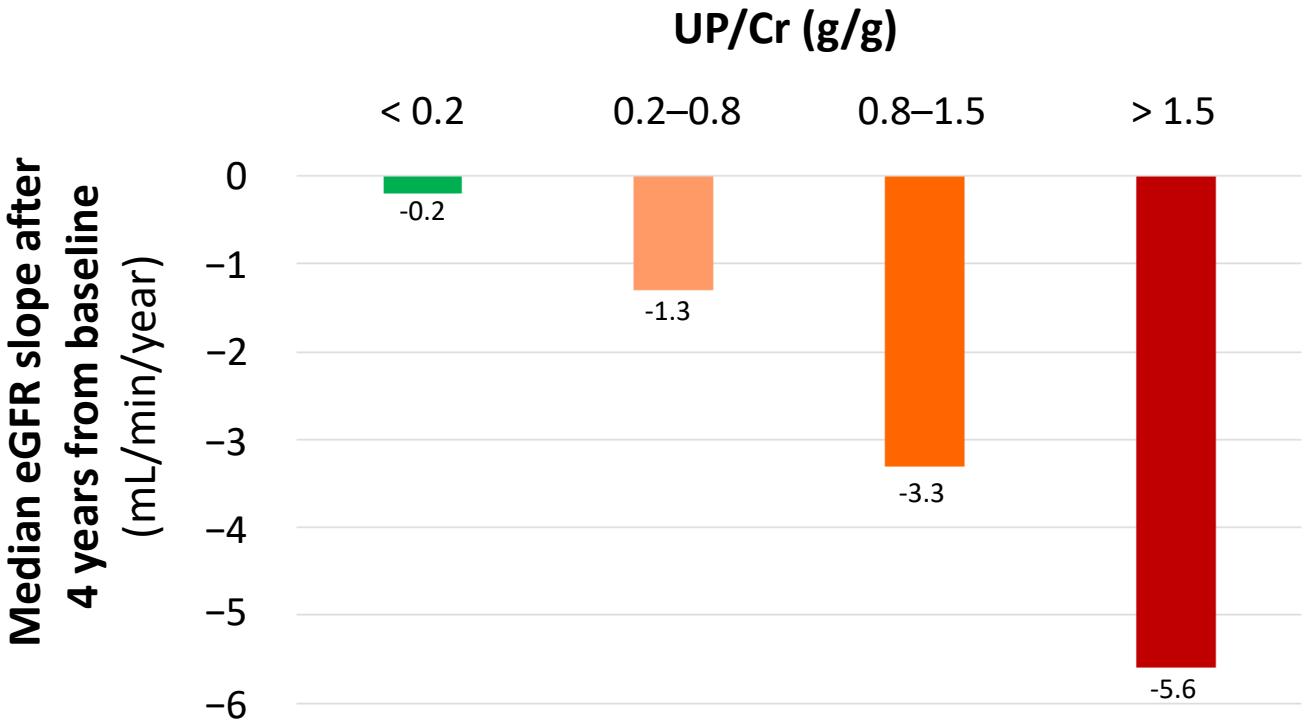
RRT Mean age 40 years



Nephropathy in males and females with Fabry disease: cross-sectional description of patients before treatment with enzyme replacement therapy

Alberto Ortiz[1], João P. Oliveira[2], Steven Waldek[3], David G. Warnock[4], Bruno Cianciaruso[5] and Christoph Wanner[6] on behalf of the Fabry Registry

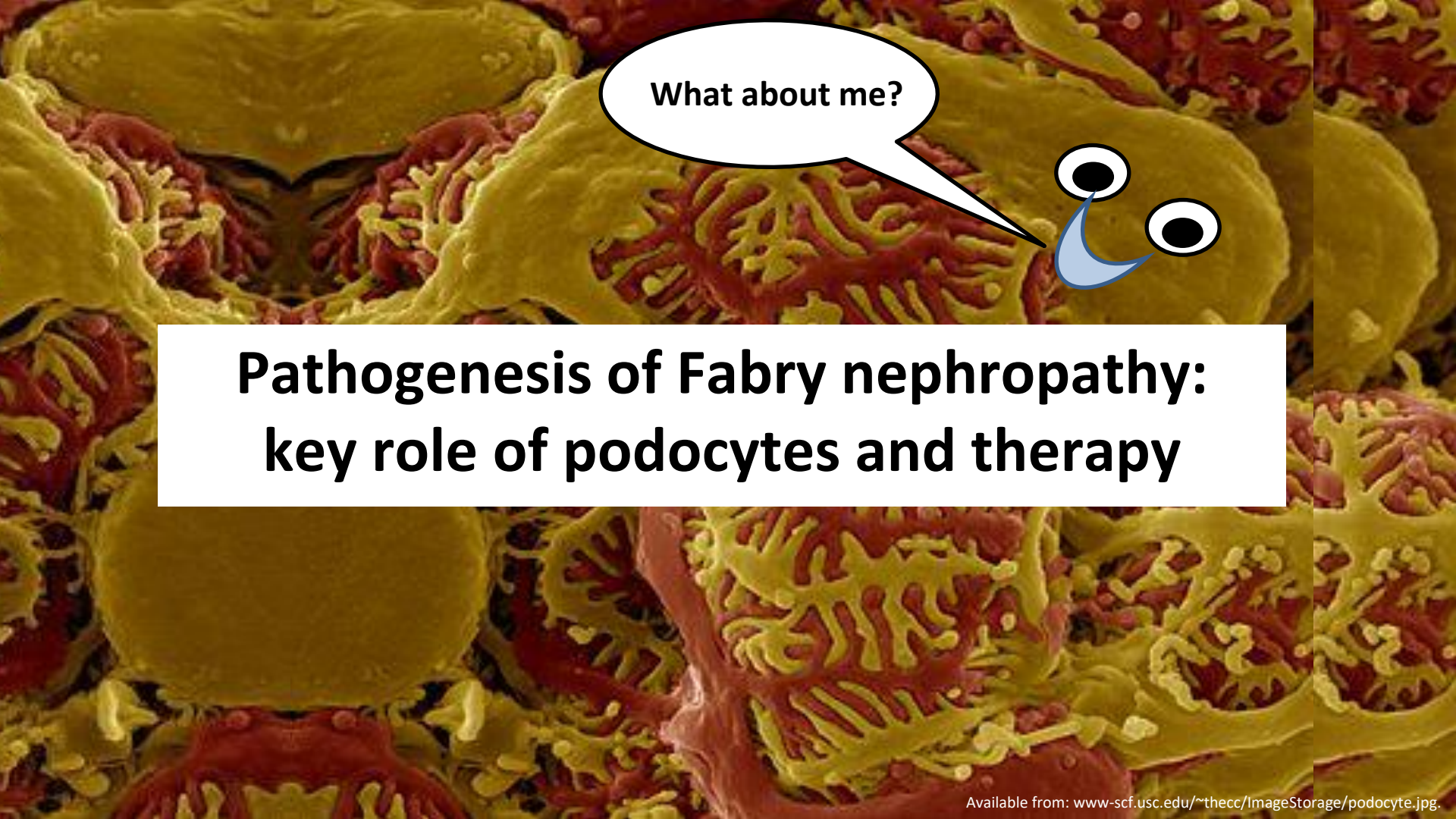
Proteinuria is a major risk factor for CKD progression in Fabry disese



Natural history data from 121 men not on ERT (Fabry Registry)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

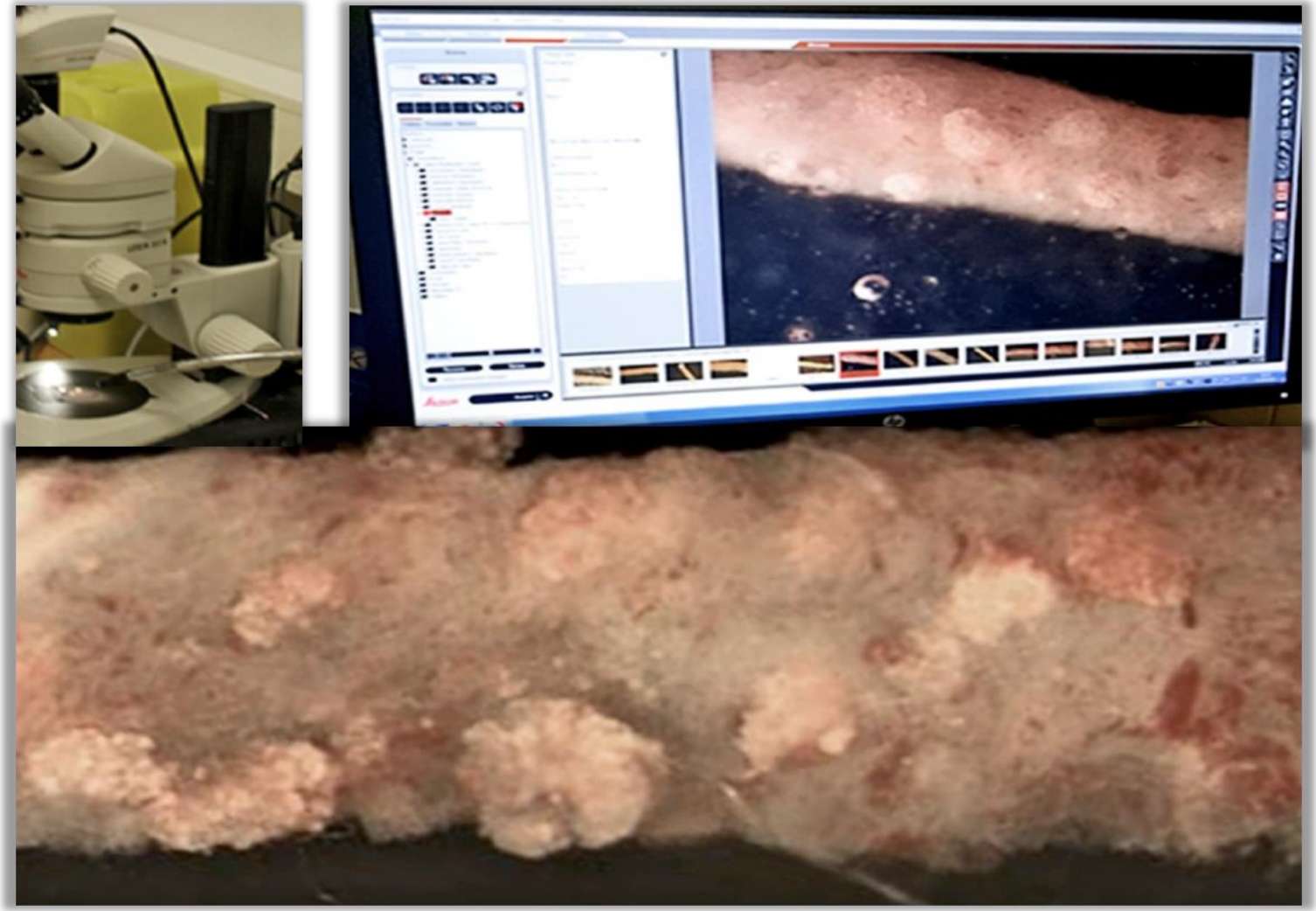
Wanner C, et al. Clin J Am Soc Nephrol. 2010;5:2220-8.



Pathogenesis of Fabry nephropathy: key role of podocytes and therapy

Available from: www-scf.usc.edu/~thecc/ImageStorage/podocyte.jpg.

Fabry podocytes are fuuuuull of glycolipids

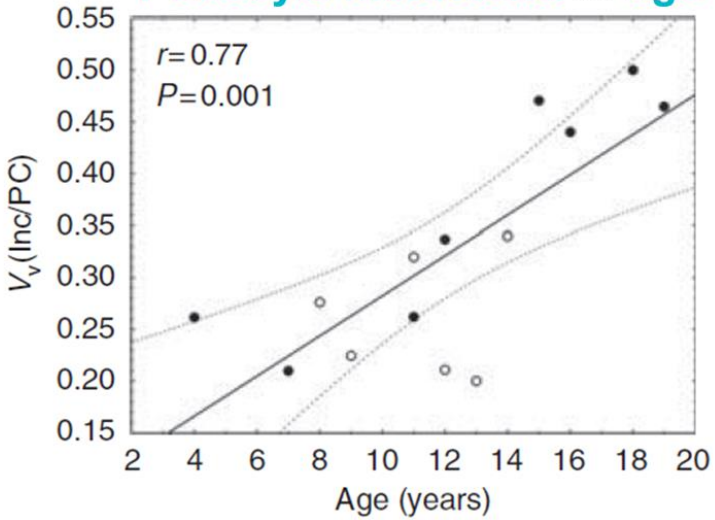


Svarstad E et al. *Nephron*. 2018;138(1):13-21.

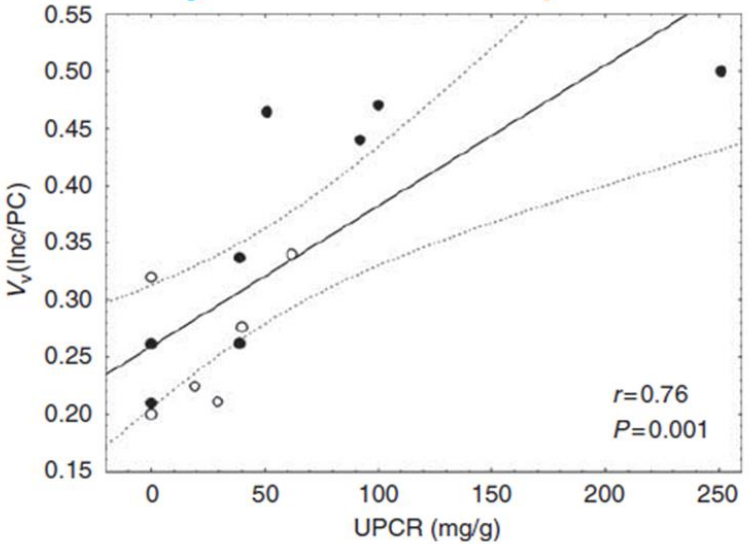
Progressive podocyte injury and globotriaosylceramide (GL-3) accumulation in young patients with Fabry disease

Behzad Najafian [1], Einar Svarstad [2], Leif Bostad [3], Marie-Claire Gubler [4], Camilla Tøndel [5], Chester Whitley [6], Michael Mauer [7]

Podocyte inclusions vs age



Podocyte inclusions vs proteinuria



Relationship between age and podocyte (Vv(Inc/PC)), and endotheli cell (Vv(Inc/Endo)) GL-3 fractional volume of inclusions per cytoplasi

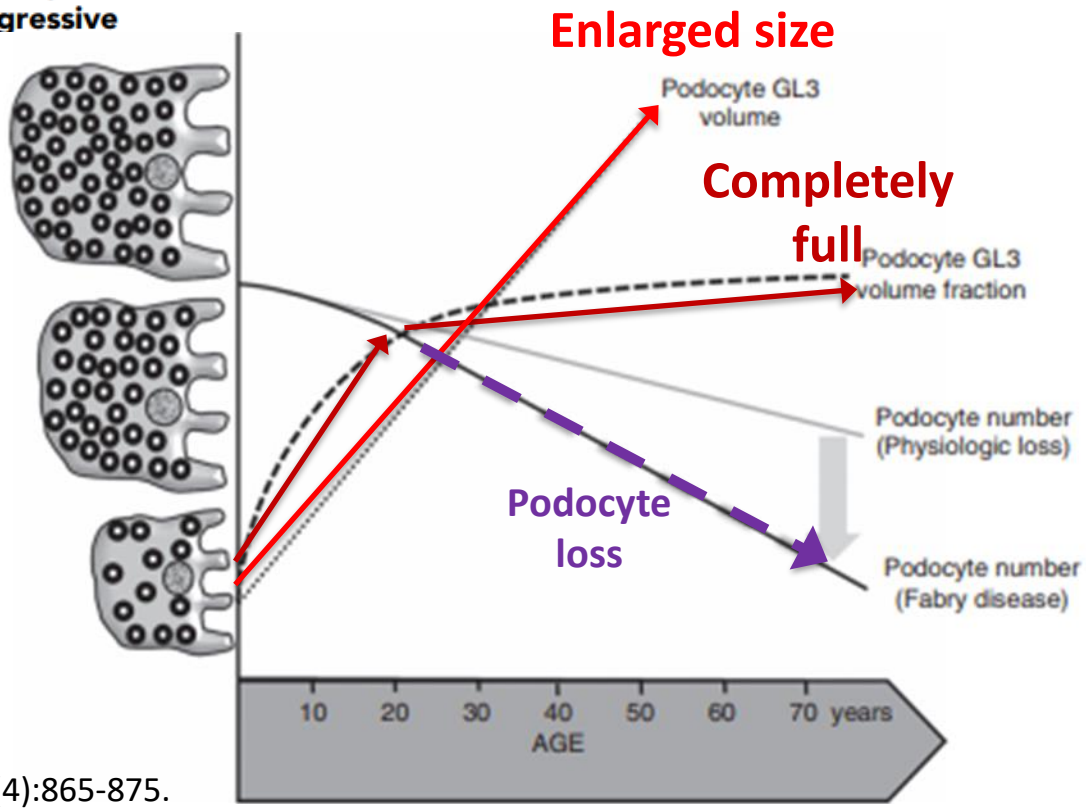
Segmental foot process effacement
was present in **all glomeruli**

Gb3 accumulation and podocyte loss

CLINICAL RESEARCH www.jasn.org

Accumulation of Globotriaosylceramide in Podocytes in Fabry Nephropathy Is Associated with Progressive Podocyte Loss

Behzad Najafian,[1] Camilla Tøndel,[2,3] Einar Svarstad,[3] Marie-Claire Gubler,[4] João-Paulo Oliveira,[5,6] and Michael Mauer[7,8]



Najafian B et al. J Am Soc Nephrol. **2020** Apr;31(4):865-875.

This is not what it seems!!!!

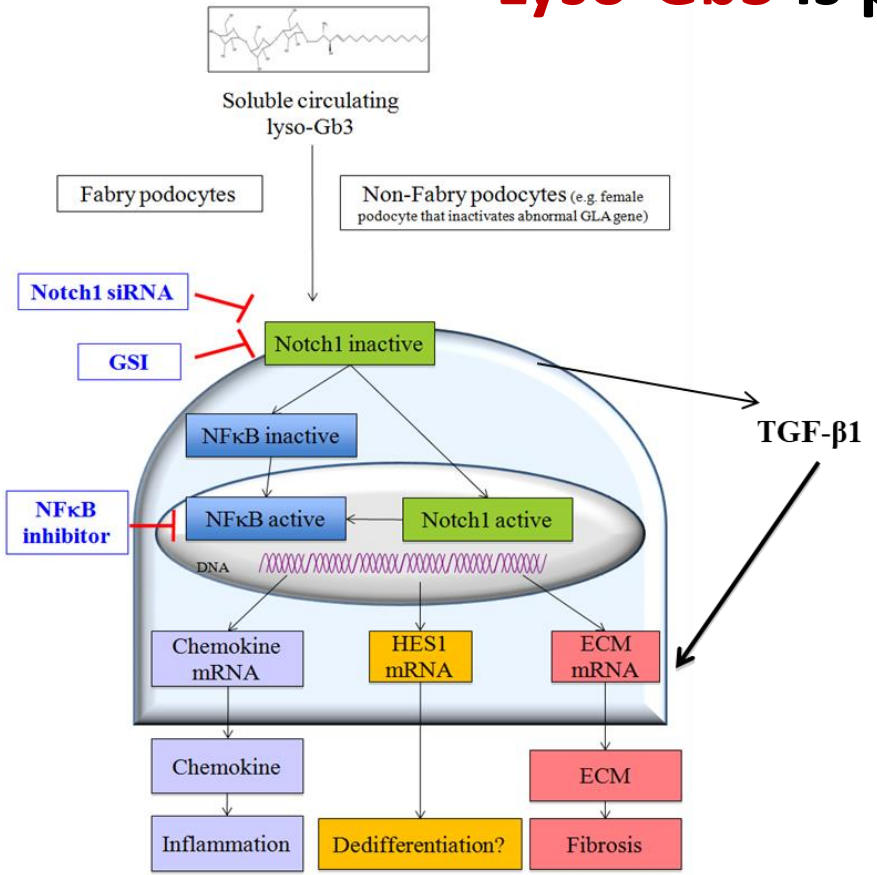
But they are **not** always immortal

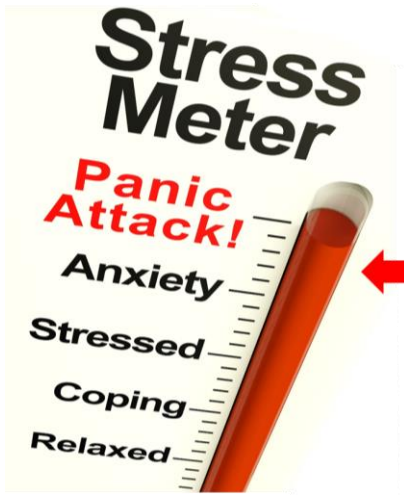
Shplotch!

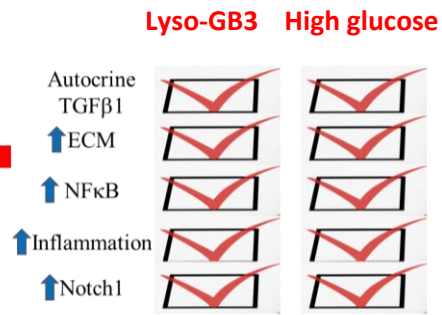
(podocyte crashing against toilet)

Podocyte farewell ceremony by cell biology scientist

Lyso-Gb3 is pathogenic







ECM, extracellular matrix; GSI, gamma secretase inhibitors; Hi, high; lyso-Gb3, globotriaosylsphingosine; NFκB, nuclear factor kappa B; siRNA, small interfering RNA; TGFβ1, transforming growth factor beta 1.

Ortiz A, Sanchez-Niño MD. Port J Nephrol Hypert. 2017;31:200-6.
Sanchez-Niño MD, et al. Nephrol Dial Transplant. 2011;26:1797-802.
Sanchez-Niño MD, et al. Hum Mol Genet. 2015;24:5720-32.

Key concepts – diagnosis

- Suspect Fabry disease in any **CKD** with pathological **albuminuria**

- **Specially** if
  - Male < 55 years
  - No obvious cause for CKD (although Fabry does not protect from other causes of kidney injury)
  - No hypertension or milder hypertension than expected
  - Family or personal history compatible with Fabry

- **Who** should be tested?
  - Eventually… every CKD.. as part of etiologic evaluation

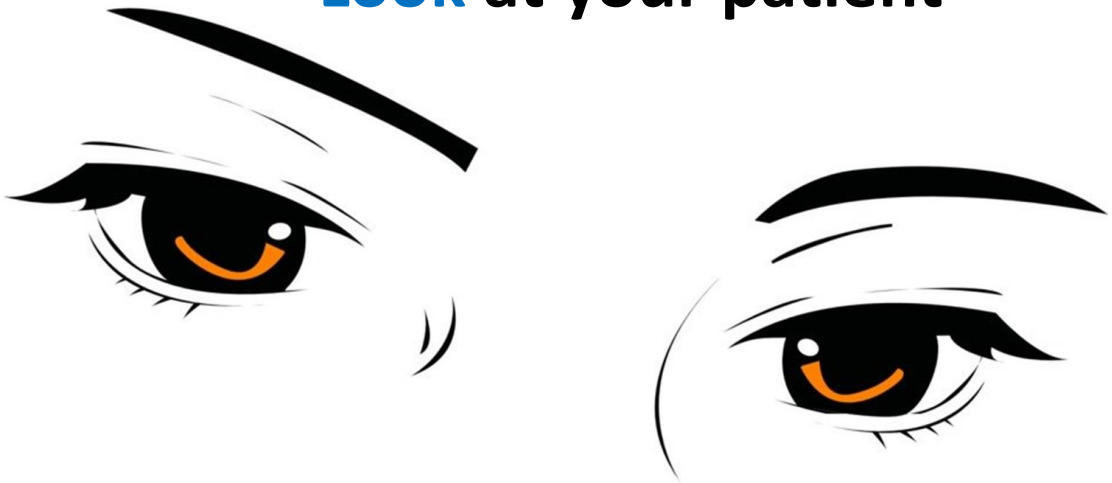
Fabry disease diagnosis step 1

Talk to your patient

Diagnostic work up

- Is my patient a male?
- How old is he?
- Did I ask about childhood?
- Did I ask about family?
- Is albuminuria pathological?
- Is there an obvious reason for that albuminuria?
- Is there a biopsy available?
- Was EM performed?

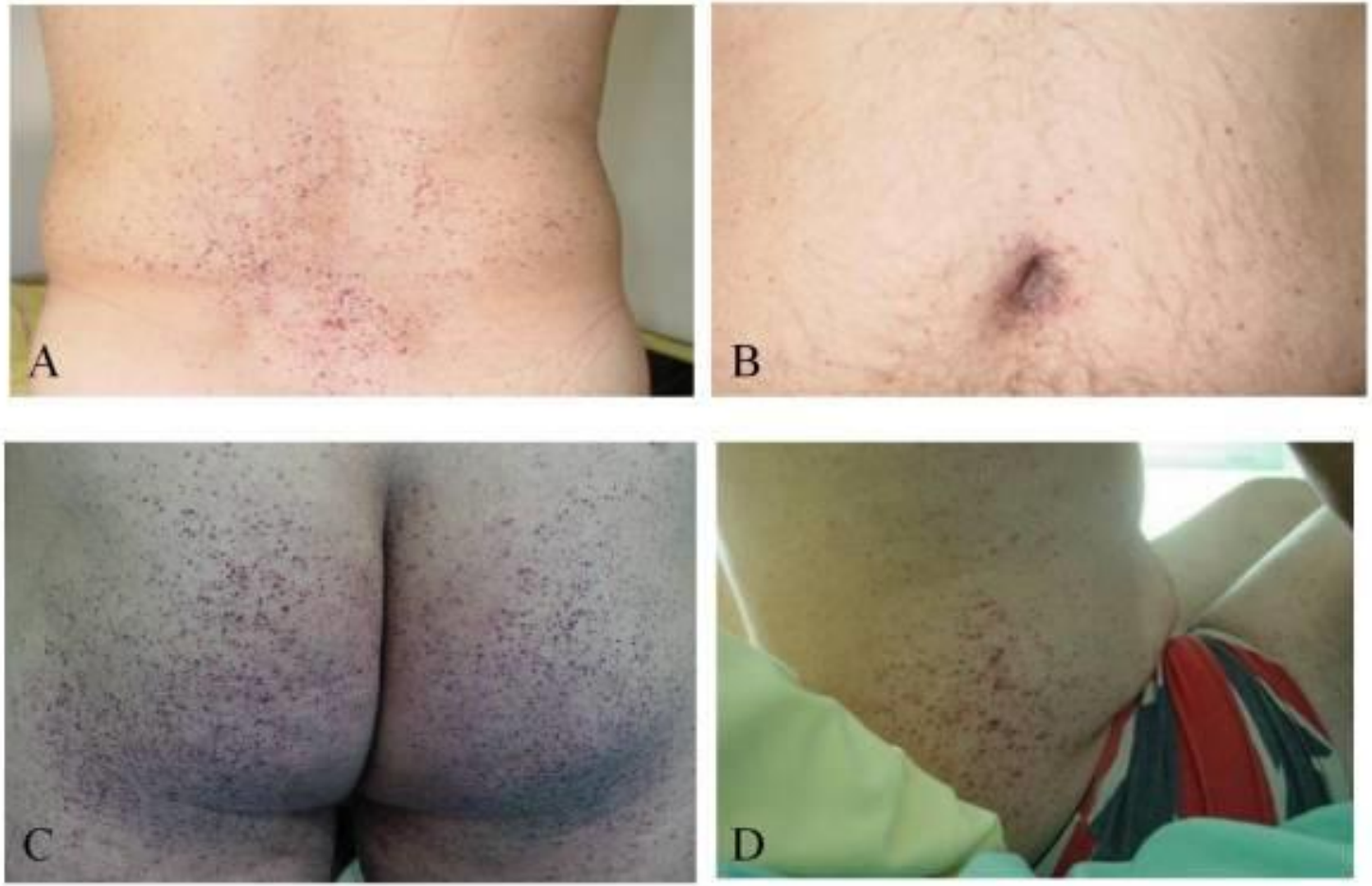
Look at your patient

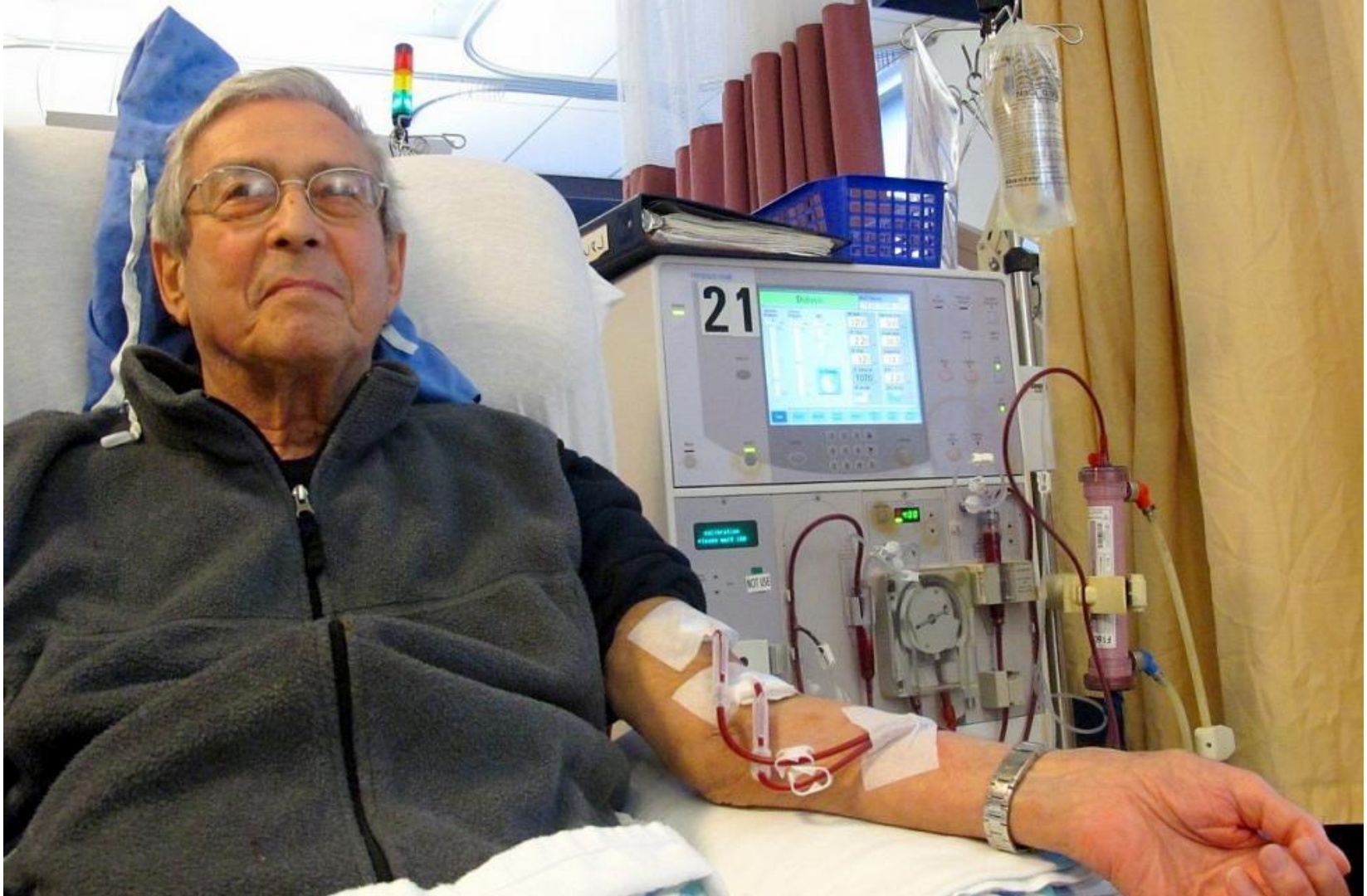


How to identify **your** Fabry hemodialysis patient while doing **rounds**?

It should be very easy:

angiokeratoma


A
B
C
D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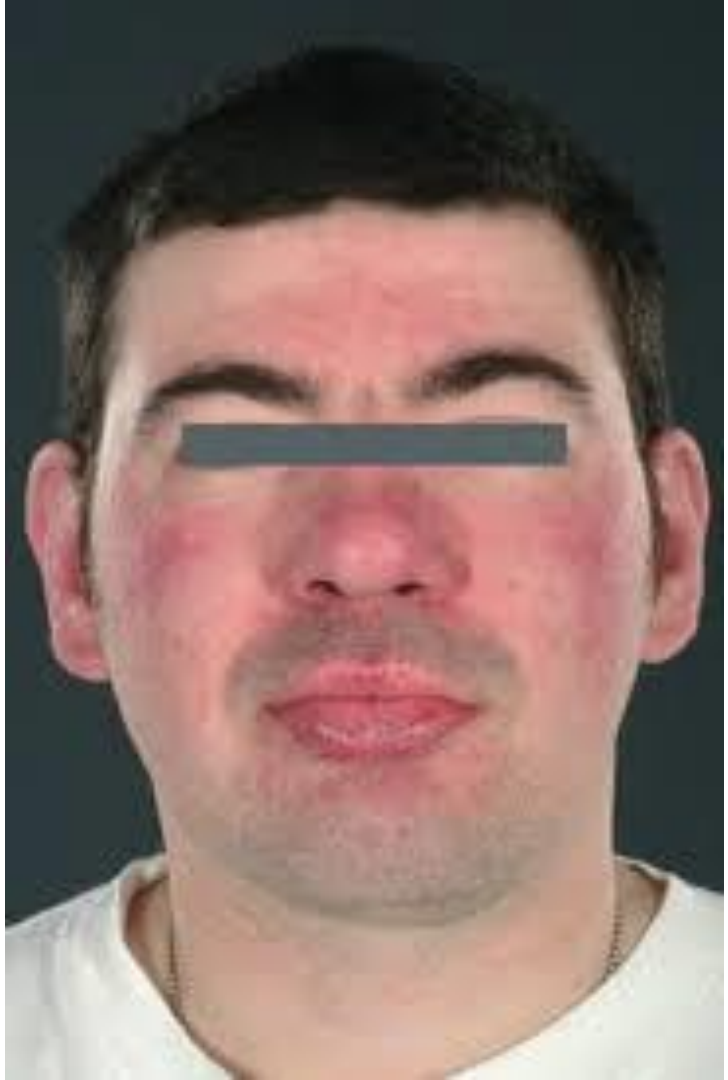
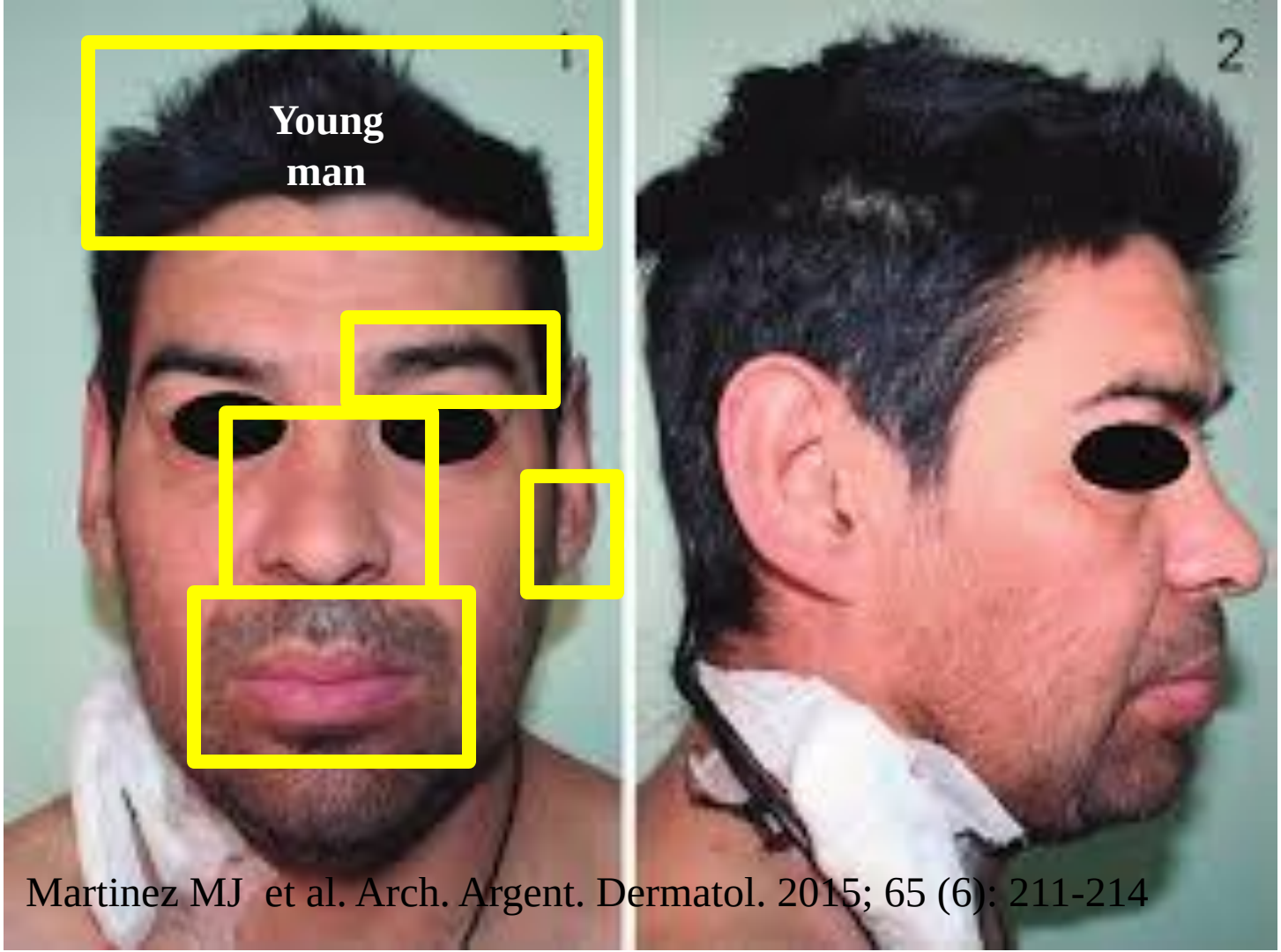
Diagnosing Fabry disease doing the dialysis rounds

- Males
- <**55**-year-old
- With a face that you have **seen before**

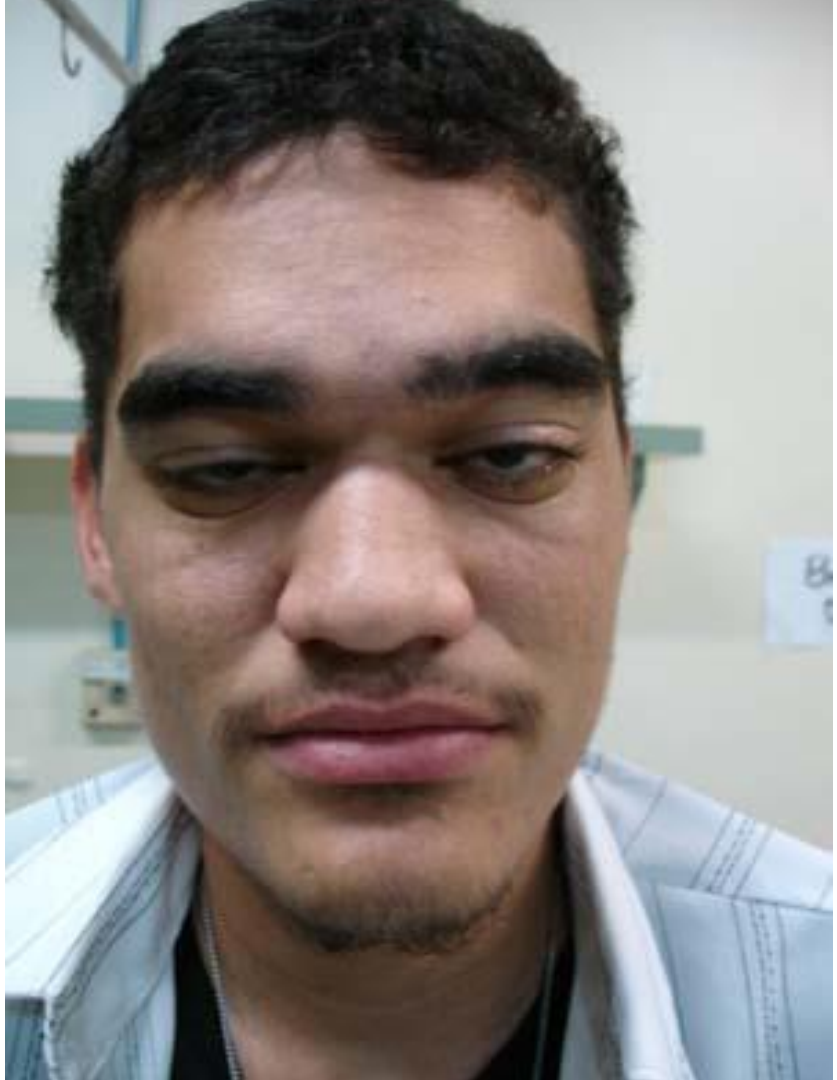
The déjà vu diagnosis



V. Hogarth D. Hughes C. H. Orteu. Clinical dermatology 2012 https://doi.org/10.1111/j.1365-2230.2012.04420.x



Martinez MJ et al. Arch. Argent. Dermatol. 2015; 65 (6): 211-214

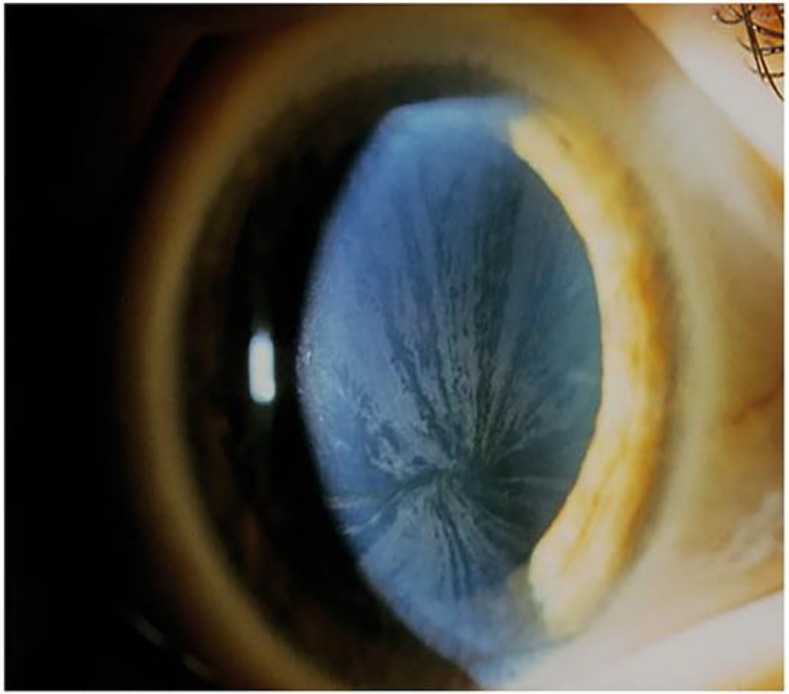


https://www.researchgate.net/publication/282837469_Manifestaciones_musculoesqueleticas_de_la_Enfermedad_de_Fabry/figures?lo=1

Fabry disease diagnosis step 3

Read the clinical records

Cornea verticillata
(slit lamp, Fabry)



https://plos.figshare.com/articles/figure/Cornea_verticillata_grade_3_in_patient_suffering_from_Morbus_Fabry_/4548745/1

When should Fabry be suspected in kidney patients in kidney patients ?

- **Family** history of n… …athy or other manifestation of Fabry

or

- **Classical** symptom… …plications

or

- **Unexplained CKD**, especially if
  - **Proteinuric, Lack of hypertension** or mild hypertension
  - **< 55**-year-old (male)

May be absent!!!

May be absent!!!

Terryn W, et al. Nephrol Dial Transplant. 2013;28:505-17

When should Fabry be suspected?

- **Family** history of n… athy or other manifestation of Fabry

or

- **Classical** symptom… plications

or

- **Unexplained CKD**, especially if
  - **Proteinuric, Lack of hypertension** or mild hypertension
  - **< 50** year-old (male)

or

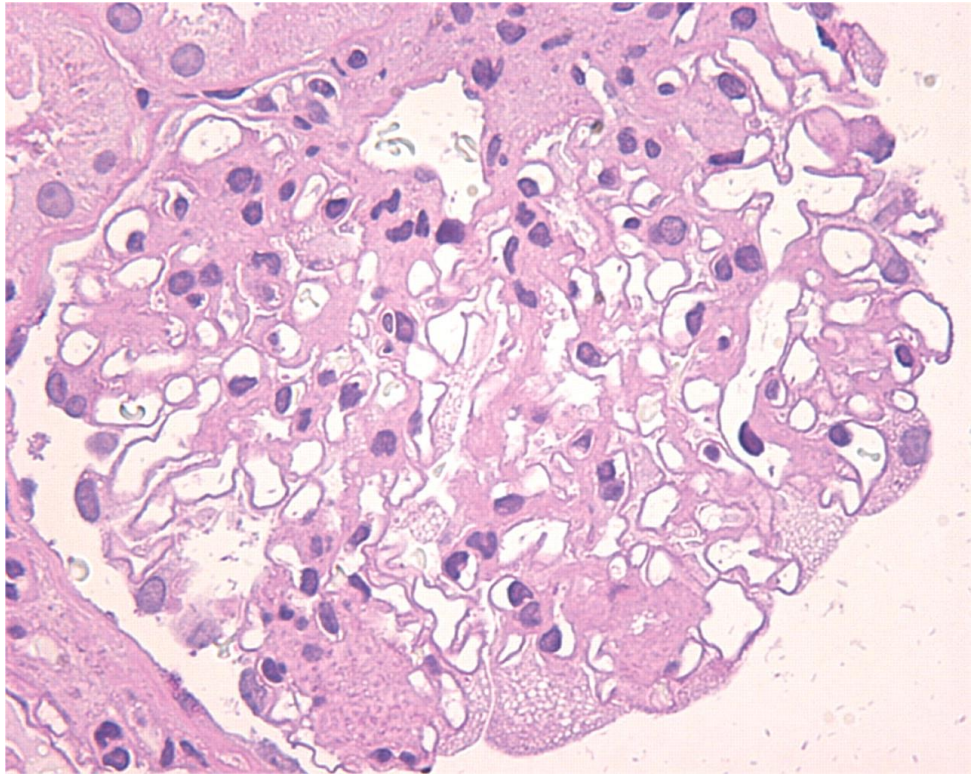
- **renal biopsy** findings: **white** glomeruli in biopsy cylinder, **foamy** cells in histology, or typical **EM** inclusions

May be absent!!!

May be absent!!!

Or… **screen all** CKD patients

Fabry nephropathy may be missed by an unexperienced pathologist



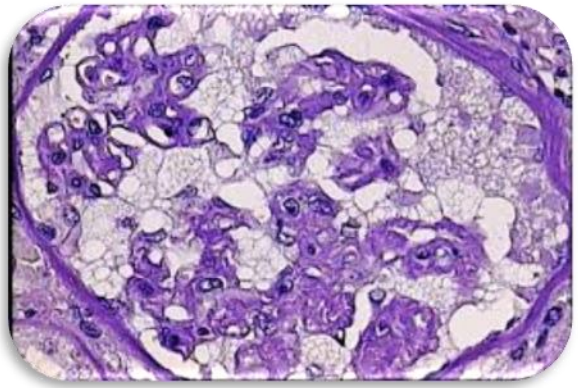
Foamy inclusions within podocytes and tubular epithelial cells (renal biopsy, haematoxylin/eosin stain, 400x magnification)

Woywodt, A. et al. Nephrol. Dial. Transplant. 2007 22:3074-3077;

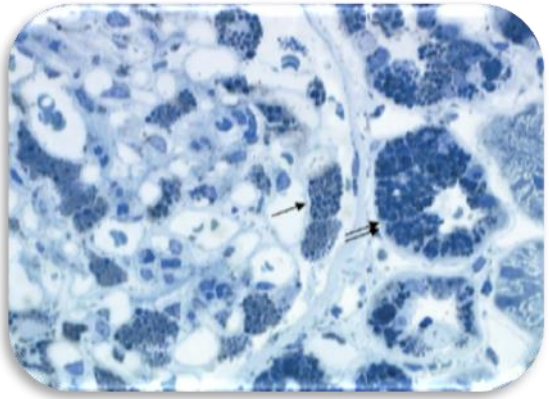
NDT
Nephrology Dialysis Transplantation

Fabry podocytes are fuuuuull of glycolipids

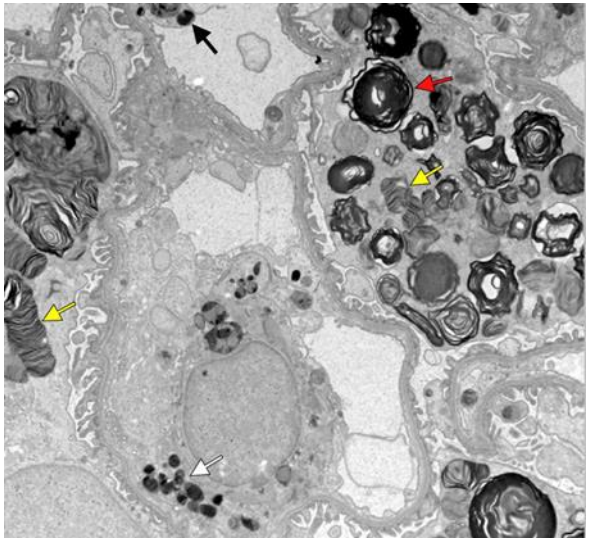
Fabry nephropathy may be missed by an unexperienced pathologist



PAS



Toluidine blue



Basic-Jukic et al Current Pharmaceutical Design 2013

Najafian et al. American Journal of Kidney Diseases 2015 66, e35-e36DOI: (10.1053/j.ajkd.2015.08.006)

Najafian et al. American Journal of Kidney Diseases 2015 66, e35-e36DOI: (10.1053/j.ajkd.2015.08.006
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Undiagnosed Fabry CKD as part of a **wider pattern** of **misdiagnosis** in CKD


YOU'LL NEVER WALK ALONE
LIVERPOOL
FOOTBALL CLUB
EST·1892

UEFA Champions League · May 28

Full-time

Liverpool	0	-	1	Real Madrid

Final

⚽ Vini Jr. 59'

TIMELINE | LINEUPS | STATS | NEWS

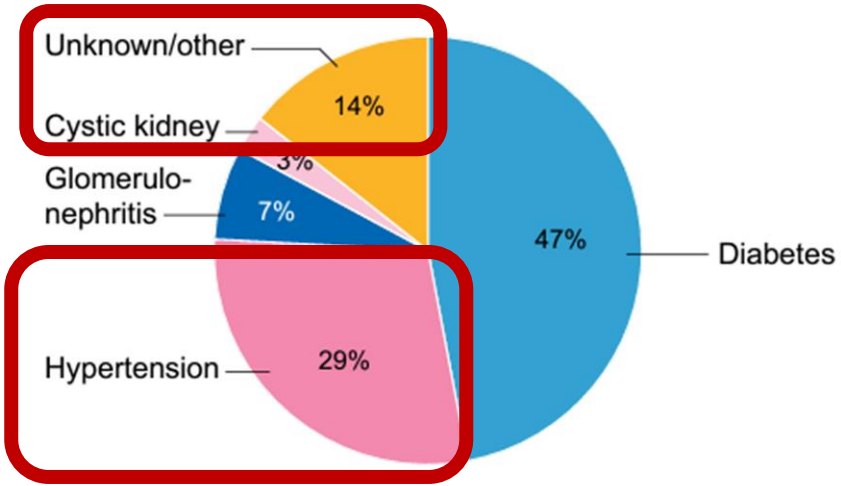
	TEAM STATS	
24	Shots	4
9	Shots on target	2

Problema 3: el dilema Rumsfeld

"There are **known knowns** — there are things we know we know,"
"There are **known unknowns** — that is to say, we know there are some things we do not know.
"But there are also **unknown unknowns**, the ones we don't know we don't know."

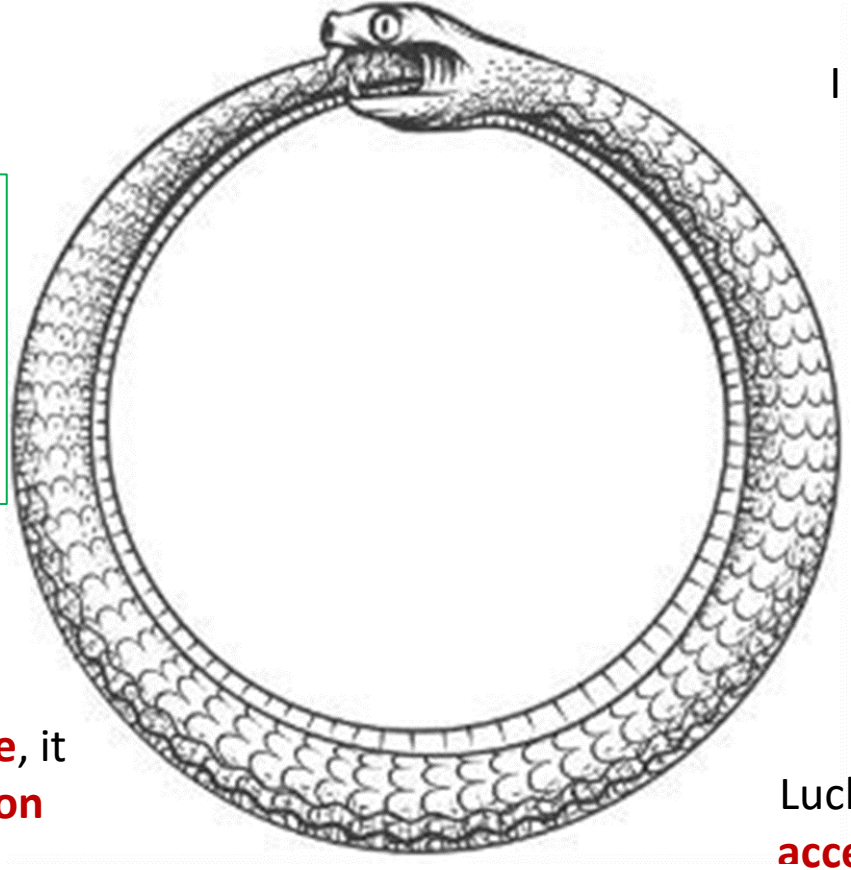
known knowns: this is not true

known unknown: the contribution of genetics



Torra R et al. Clin Kidney J. 2021 Mar 12;14(8):1879-1885.

It is the **most common** cause of CKD in non-diabetics



I diagnose **hypertensive nephropathy**

80% of CKD patients have hypertension

I just need **hypertension**

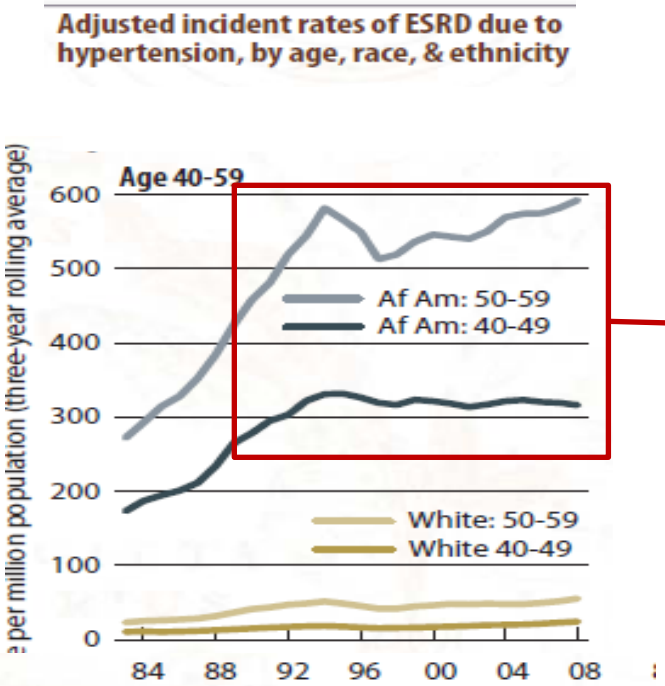
If I **do not know the cause**, it is **likely** the **most common** cause

Luckily, there are **no widely accepted diagnostic** criteria

Uma cobra comendo sua cauda

Genetic kidney disease: the **elephant** in the room

ESRD due to hypertensive nephropathy: African Americans



New concept:
genetic nephropathy:
APOL1-associated glomerulosclerosis

USRDS 2010

http://www.usrds.org/2010/pdf/V2_02.pdf

What is the mean age at KRT initiation in ADPKD?

Approx **60** years

Then, **other** genetic kidney diseases can also result in KRT at around the same age

Does **diabetes protect** from having a genetic kidney disease?

Clinical Practice: Case Report

Family History is Important to Identify Patients with Monogenic Causes of Adult-Onset Chronic Kidney Disease

Granhøj J.[a] · Tougaard B.[b] · Lildballe D.L.[a] · Rasmussen M.[a,c]
Author affiliations

Keywords: Monogenic kidney disease · Family history · Autosomal dominant tubulointerstitial kidney disease-*MUC1* · Idiopathic infantile hypercalcemia · X-linked Alport syndrome

Nephron 2022;146:49–57
https://doi.org/10.1159/000518175

Case 1 is a 60-year-old male with slowly progressive CKD **initially ascribed to hypertension and diabetes** despite a family history with several affected first-degree relatives.
A **pathogenic *MUC1* variant**: *MUC1*-associated autosomal dominant tubulointerstitial kidney disease.

Etiology diagnostic tools

	Safety	Cost	Availability
Past history	✓	✓	✓
Serology	✓	✓	✓
Imaging	✓	✓	✓
Biopsy	✓	✓	✓
Genetics	✓	✓	✓

The NEW ENGLAND JOURNAL of MEDICINE

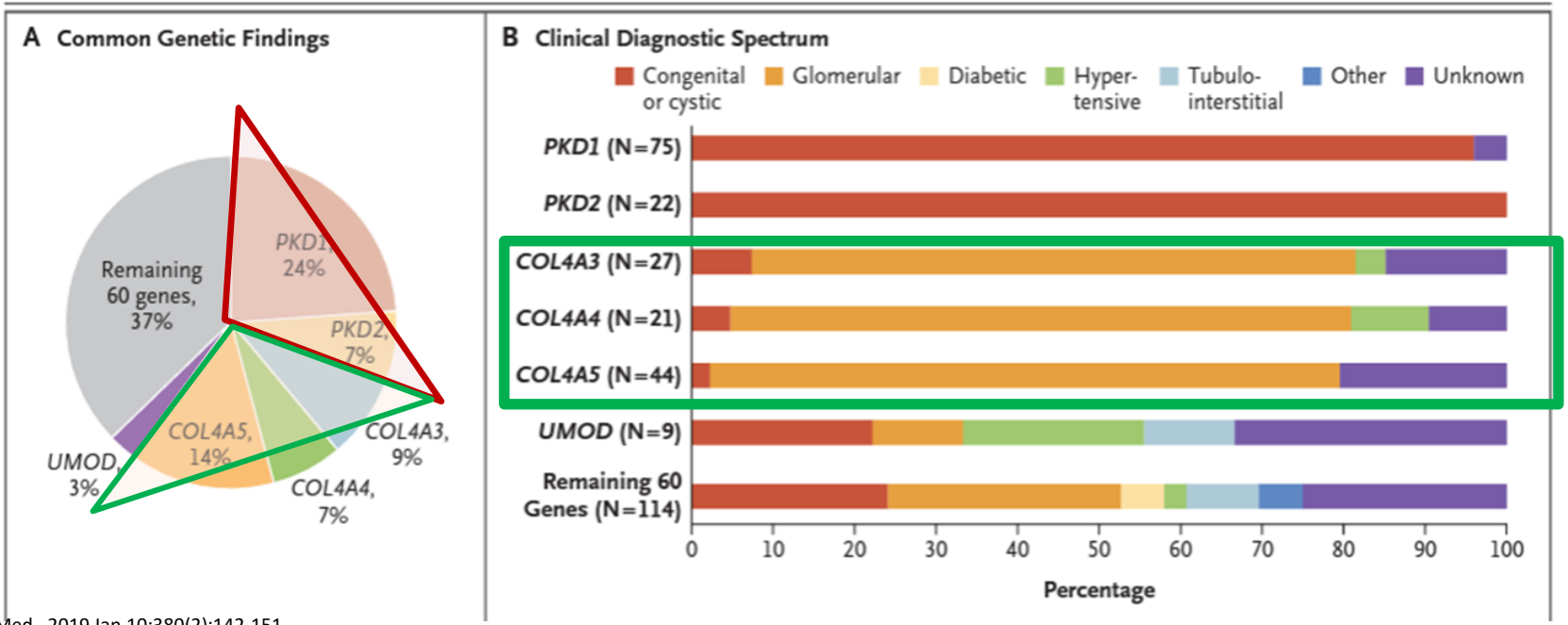
ORIGINAL ARTICLE

Diagnostic Utility of Exome Sequencing for Kidney Disease

E.E. Groopman, M. Marasa, S. Cameron-Christie, S. Petrovski, V.S. Aggarwal,

If you care for **less Alport** patients than ADPKD patients…
you are **misdiagnosing** Alport patients as….

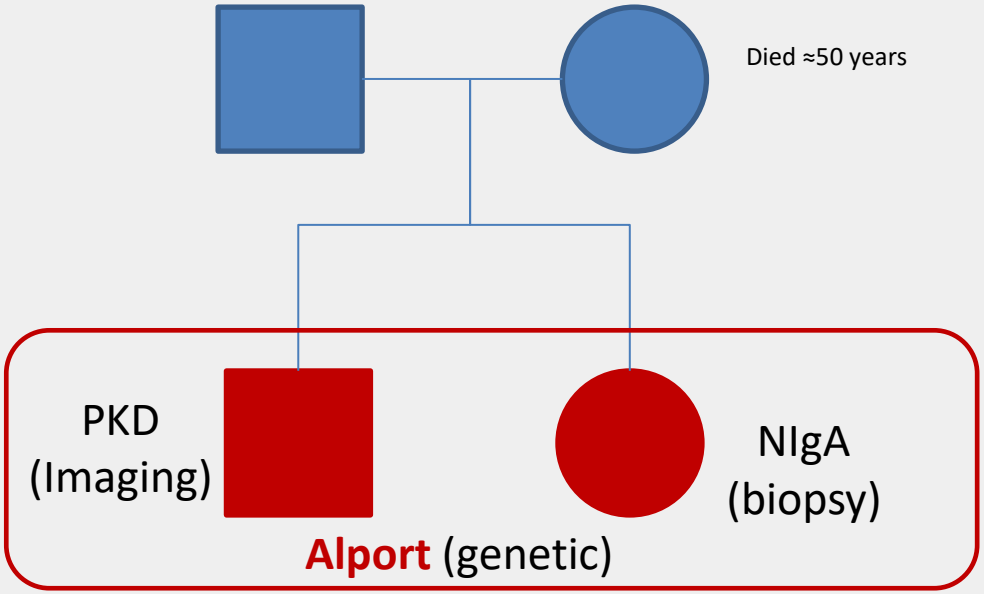
The urine sediment in DKD is usually bland, but patients with severely increased albuminuria commonly have microscopic hematuria (Uptodate 2022)



N Engl J Med . 2019 Jan 10;380(2):142-151.

Hemizygous loss of function mutations in *CLCN5* causing end-stage kidney disease without Dent disease phenotype

Gary Leggatt et al. Clin Kidney J (accepted, May **2022**)



Genetic testing based on phenotype

21

21 century genetics: **genome**

PLOS Genetics 2019

Check for updates

news & views

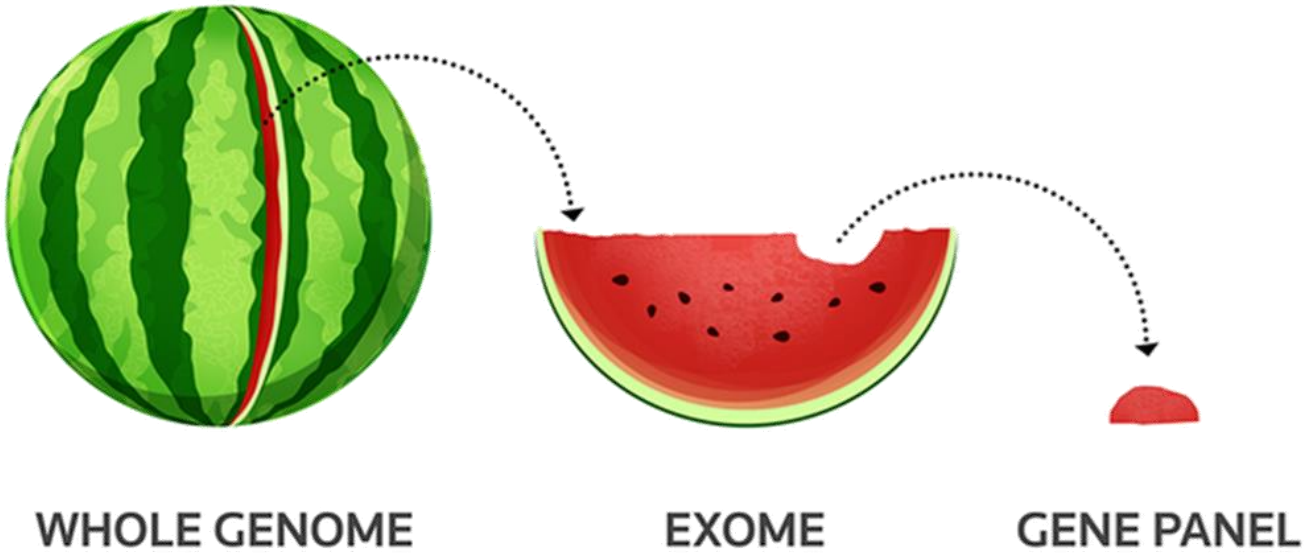
Discovering missing heritability in whole-genome sequencing data

The gap between heritability estimates from twin studies and those from genotyping array data has puzzled researchers for over a decade. New research suggests that much of the 'missing' heritability is due to rare variants that can only be captured by whole-genome sequencing (WGS) data.

Alexander I. Young

gap between heritability estimates

'**missing**' heritability: **whole-genome** sequencing (WGS).



https://www.garvan.org.au/research/kinghorn-centre-for-clinical-genomics/learn-about-genomics/dna-base/collection1/types-of-genomic-test

21 century genetics: response **speed**

Feb 2022

N Engl J Med. 2022 Feb 17;386(7):700-702. doi: 10.1056/NEJMc2112090. Epub 2022 Jan 12.

Ultrarapid Nanopore Genome Sequencing in a Critical Care Setting

John E Gorzynski [1], Sneha D Goenka [1], Kishwar Shafin [2], Tanner D Jensen [1], Dianna G Fisk [3], Megan E Grove [3], Elizabeth Spiteri [1], Trevor Pesout [2], Jean Monlong [2], Gunjan Baid [4], Jonathan A Bernstein [1], Scott Ceresnak [1], Pi-Chuan Chang [4], Jeffrey W Christle [1], Henry Chubb [1], Karen P Dalton [1], Kyla Dunn [5], Daniel R Garalde [6], Joseph Guillory [6], Joshua W Knowles [1], Alexey Kolesnikov [4], Michael Ma [1], Tia Moscarello [3], Maria Nattestad [4], Marco Perez [1], Maura R Z Ruzhnikov [1], Mehrzad Samadi [7], Ankit Setia [7], Chris Wright [6], Courtney J Wusthoff [1], Katherine Xiong [1], Tong Zhu [7], Miten Jain [2], Fritz J Sedlazeck [8], Andrew Carroll [4], Benedict Paten [2], Euan A Ashley [9]

Affiliations + expand

PMID: 35020984 DOI: 10.1056/NEJMc2112090

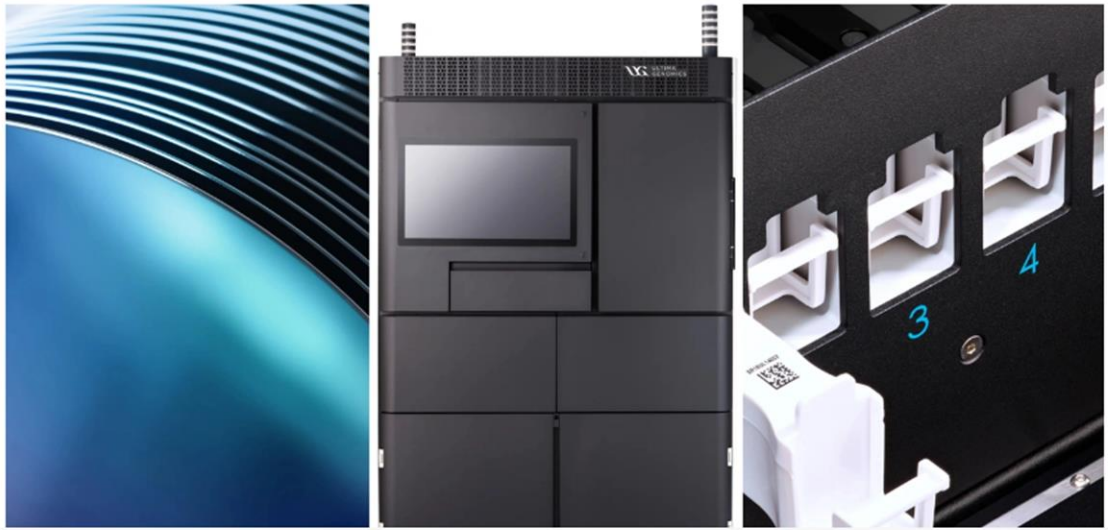
21 century genetics: **cost**

Ultima Genomics claims $100 full genome sequencing after stealth $600M raise

May 31 2022

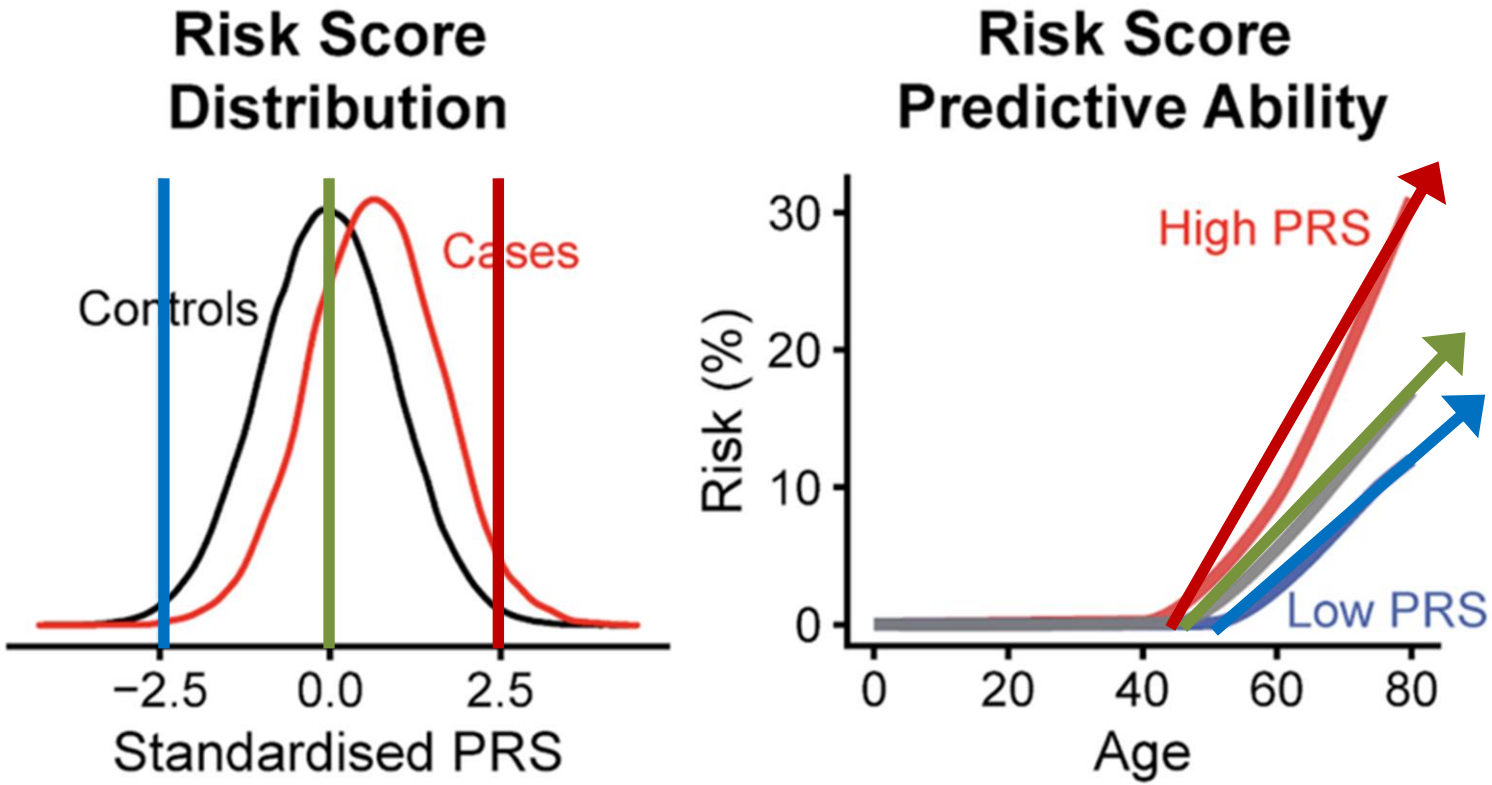
Devin Coldewey @techcrunch / 11:25 PM GMT+2 • May 31, 2022

Comment

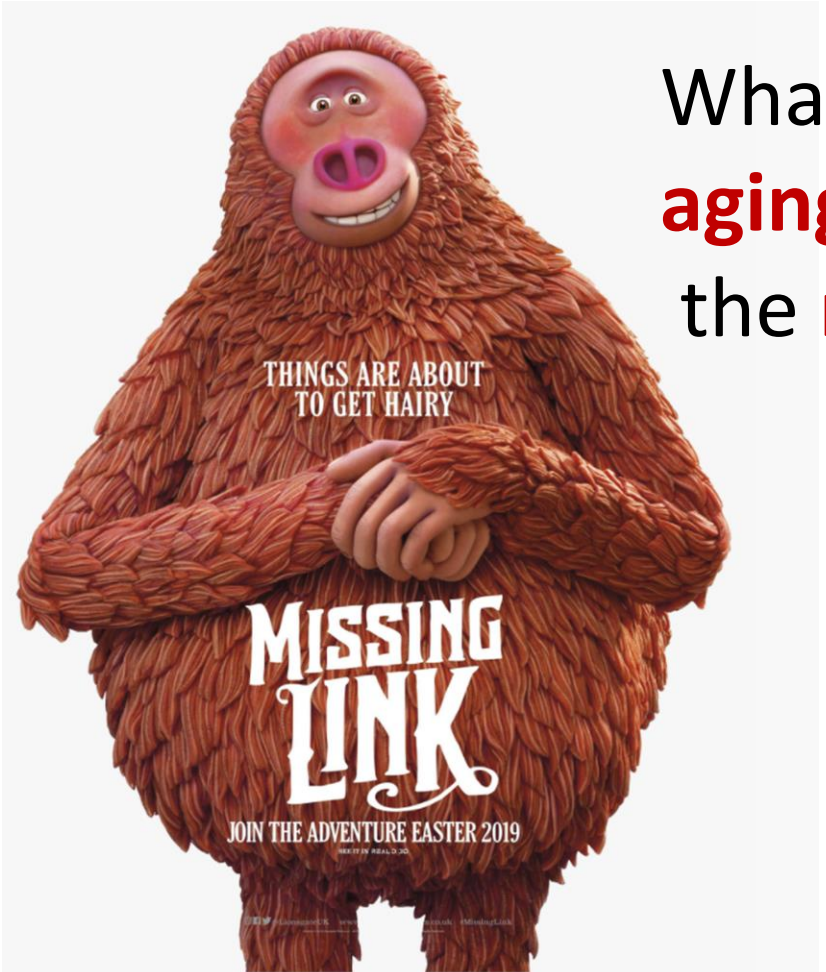


21 century genetics: **risk prediction**

Polygenic risk scores



https://commons.wikimedia.org/wiki/File:PRS_Illustration.png

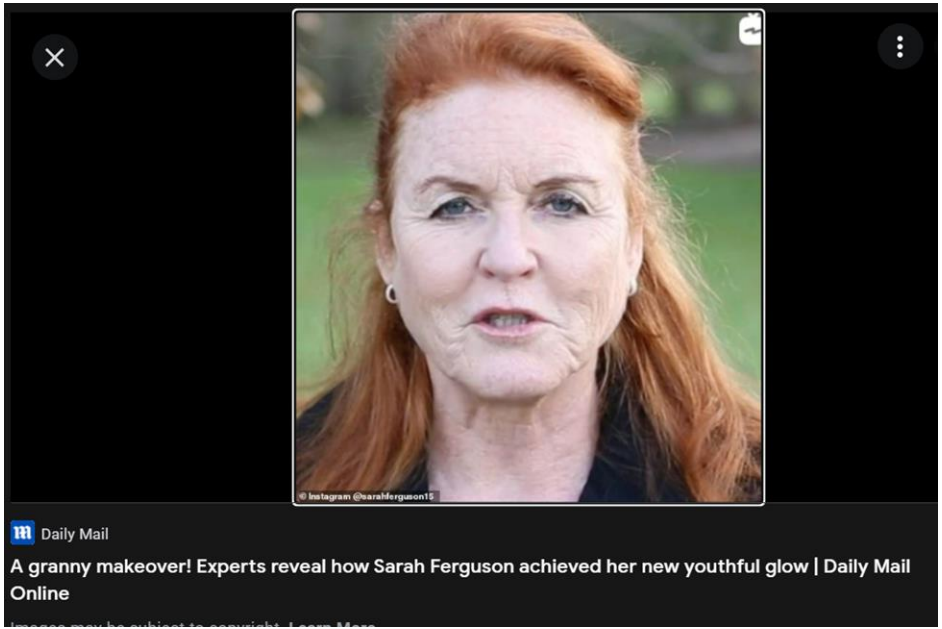


What if **accelerated kidney aging** was the missing link, the **missing cause** of CKD?

Not all of us **age biologically** at the same rate

Not **all organs within the same person** age at the same rate

Aging rate may result from the interaction of **genetic** background and the **environment**, e.g. redheads and the sun



Can we identify the “**redhead kidneys**” and prevent their premature aging?

When should we start preventing kidney aging?

A blast from the past

Decreased Glomerulosclerosis in Aging by Angiotensin-Converting Enzyme Inhibitors[1]

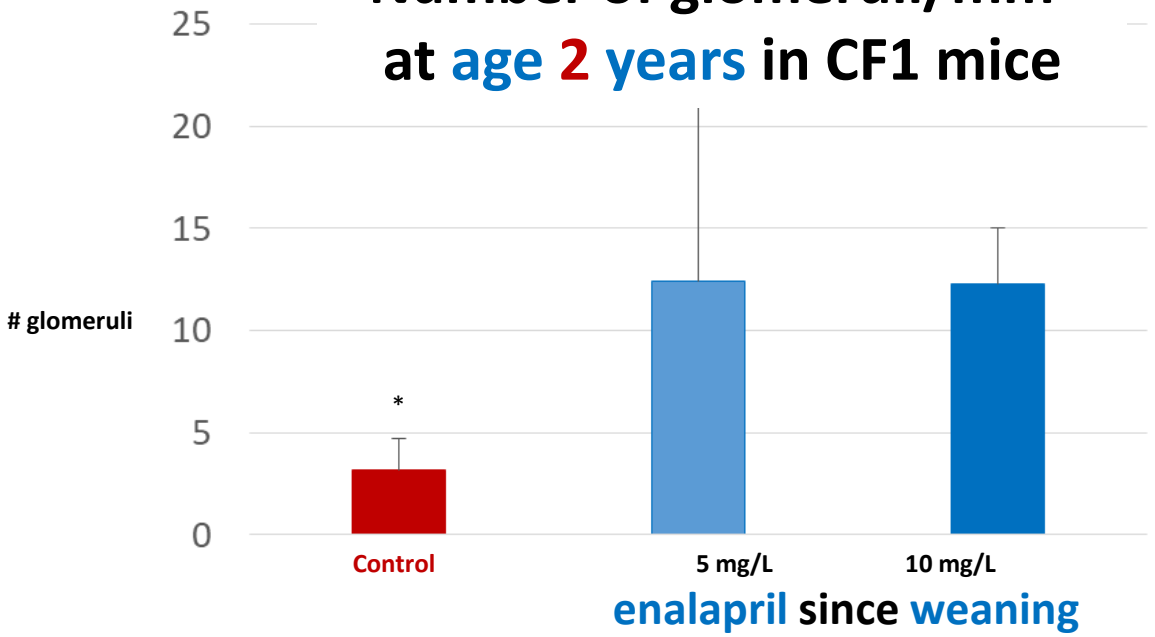
Leon Ferder,[2] Felipe Inserra, Luis Romano, Liliana Ercole, and Viviana Pszenny

L. Ferder, F. Inserra, L. Romano, L. Ercole, V. Pszenny, Institute of Nephrology, Jewish Hospital of Buenos Aires, University of Buenos Aires, Buenos Aires, Argentina

(J. Am. Soc. Nephrol. 1994; 5:1147–1152)

Renin
Angiotensin
System
Blockade

Number of glomeruli/mm^2 at age 2 years in CF1 mice



Take home message

- CKD progressing to **ESRD** is frequent in **classic Fabry males**, but not so much in other Fabry subpopulations
- **Talk** to, **look** at your patient and **read** clinical records for evidence of Fabry
- In any case, test for Fabry disease if cause of CKD unclear, especially in **males** under the age of **55** with **proteinuric** CKD
- **DBS**: alfa-galactosidase activity **+** lyso-Gb3
  - **Lyso-Gb3** should be **high**
  - When in doubt about pathogenicity: **biopsy**

In the future, genomic **sequencing** will be the **starting** point of the evaluation of the CKD patient