Welcome to

ERKNet/ERA Educational Webinars on
Pediatric Nephrology & Rare Kidney Diseases

WEBINAR

05/04/22

Fabry disease

Speakers: Olivier Lidove & Wladimir Mauhin

(Paris, France)

Moderator: Jack Wetzels (Nijmegen, Netherlands)

ERKNet
The European
Rare Kidney Disease
Reference Network

ERA
LEADING EUROPEAN NEPHROLOGY

DISCLOSURE

- Olivier Lidove declares
  - Travel fees, accommodations from Shire-Takeda and Sanofi-Genzyme
  - Honorarium from Shire-Takeda, Sanofi-Genzyme and Amicus Therapeutics

- Wladimir Mauhin declares
  - Travel fees and accommodations from Shire-Takeda, Amicus Therapeutics, Sanofi-Genzyme
  - Honorarium from Shire, Sanofi-Genzyme, Amicus and Chiesi

QUESTION:

- **HOW MANY PATIENTS WITH FABRY DISEASE HAVE YOU SEEN?**

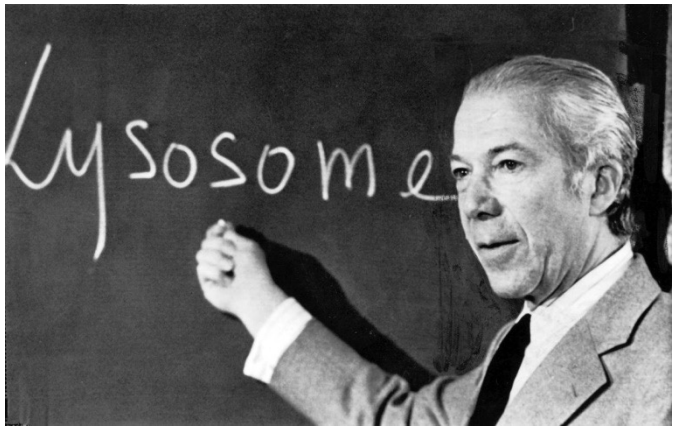
1. ZERO
2. 1 – 5 patients
3. 6 – 10 patients
4. 11 – 20 patients
5. > 20 patients

HISTORY

J. Fabry

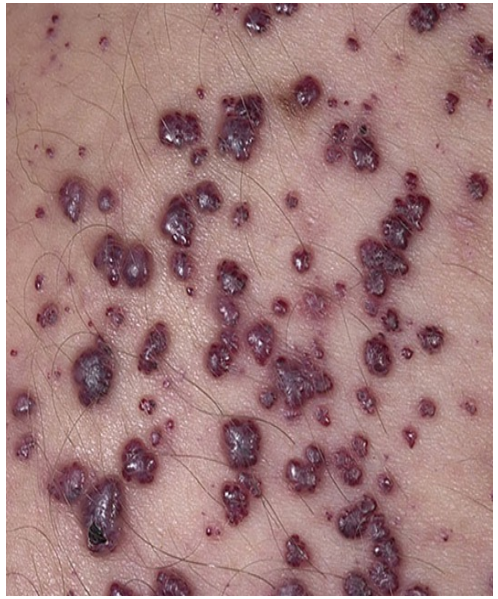
W. Anderson

C. De Duve
1955



1898 — **1950-60**

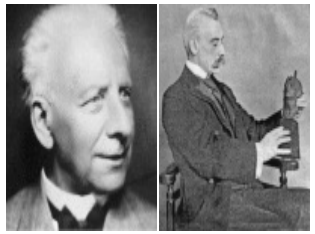
Angiokeratoma corporis diffusum



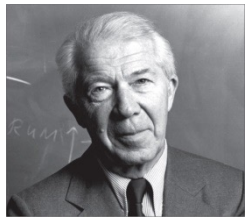
Extensive semiological description of Fabry disease: neurological, renal, cardiac involvement = classic Fabry disease
(Rahman et al. 1961, Burda et al. 1967)

Fabry disease = Lysosomal disease
(K. Hashimoto et al. 1965)

J. Fabry W. Anderson



C. De Duve



K. Hashimoto

R. Brady

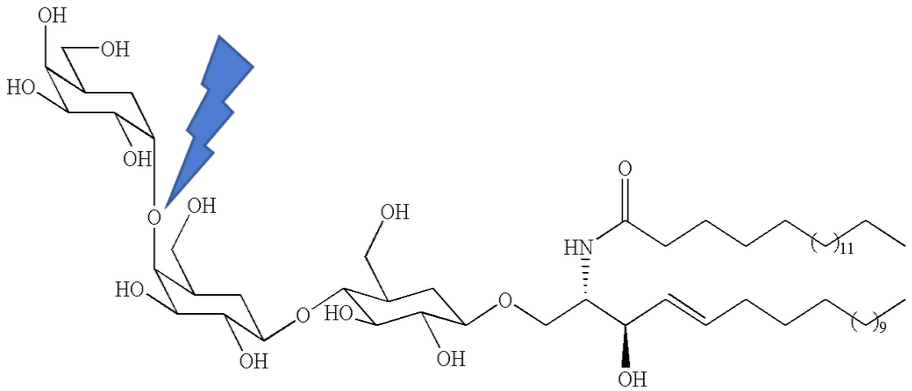
1898 — **1950'** — **1965** — **1960-70**

Angiokeratoma corporis diffusum

Lysosome

Fabry = lysosomal

Fabry disease = **Enzymatic defect in α- Galactosidase A** (R. Brady, 1967)

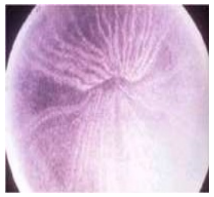


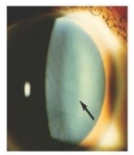
Globotriaosylceramide = Gb3 = GL3 = CD77

GLA gene on the X **chromosome** (MN. Hamers et al. 1977)

> 1000 mutations en 2022

Classic Fabry Disease





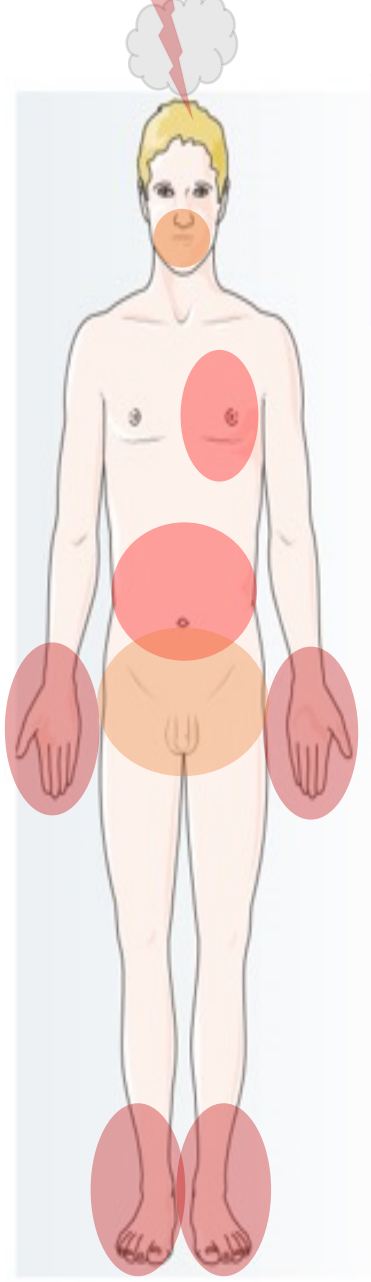
Cornea verticillata
Cataract

Deafness
Vertigo

Proteinuria
Kidney failure

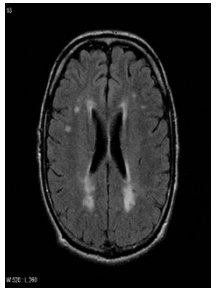
GI disorders: pain, bloating, diarrhea..

Hypo/anhidrosis
Sport or heat intolerance

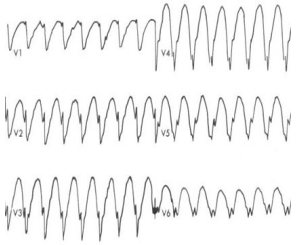


Symptoms XY > XX

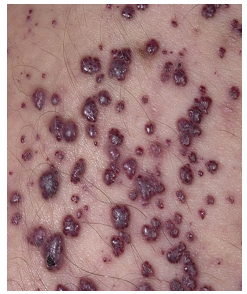
Early strokes
Cognitive disorders
Anxiety/ depression



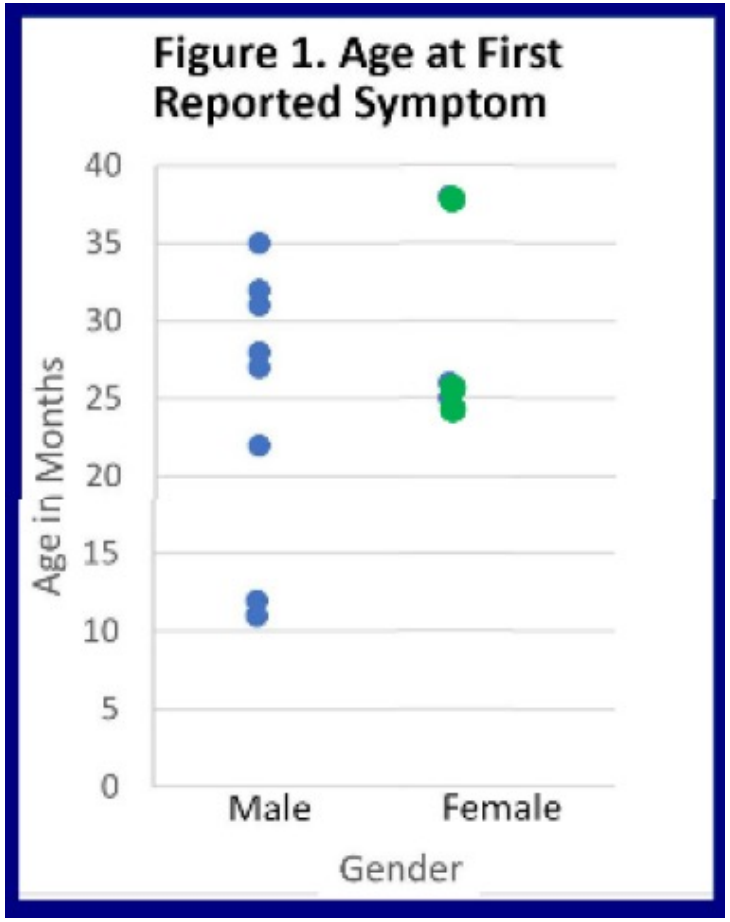
Hypertrophic cardiomyopathy, arrhythmia



Angiokeratoma



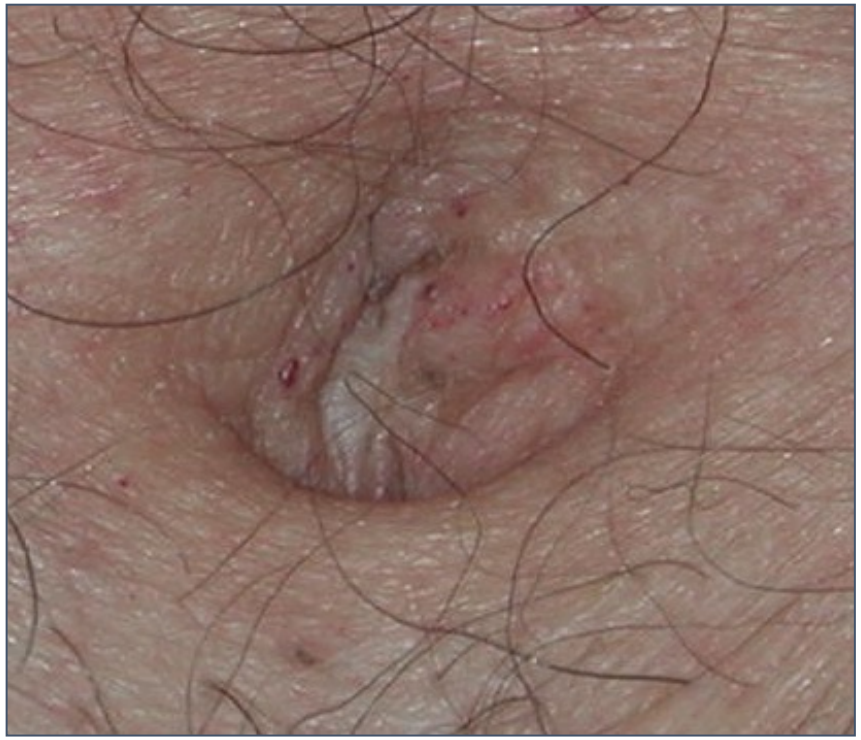
Acroparesthesia

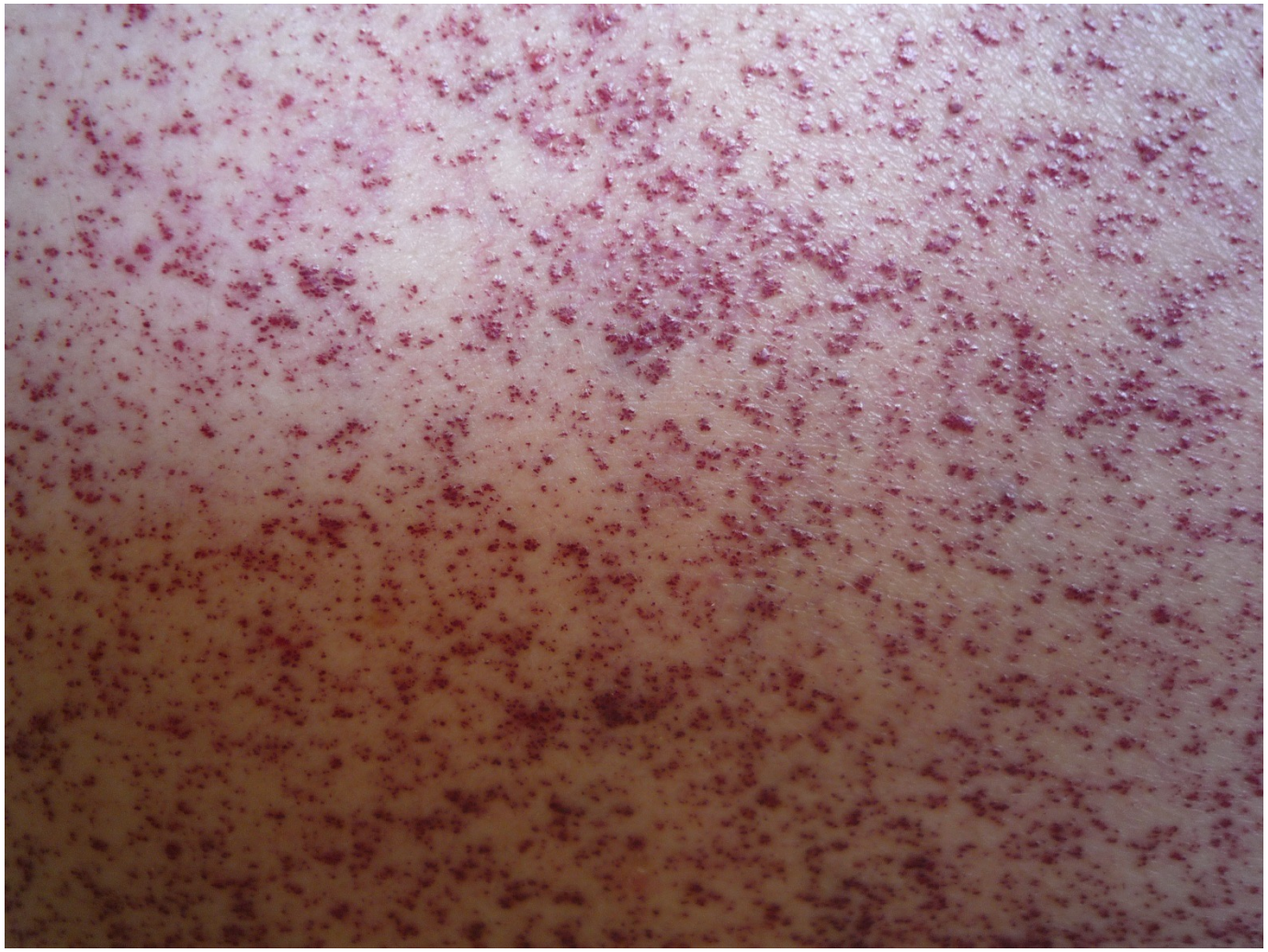


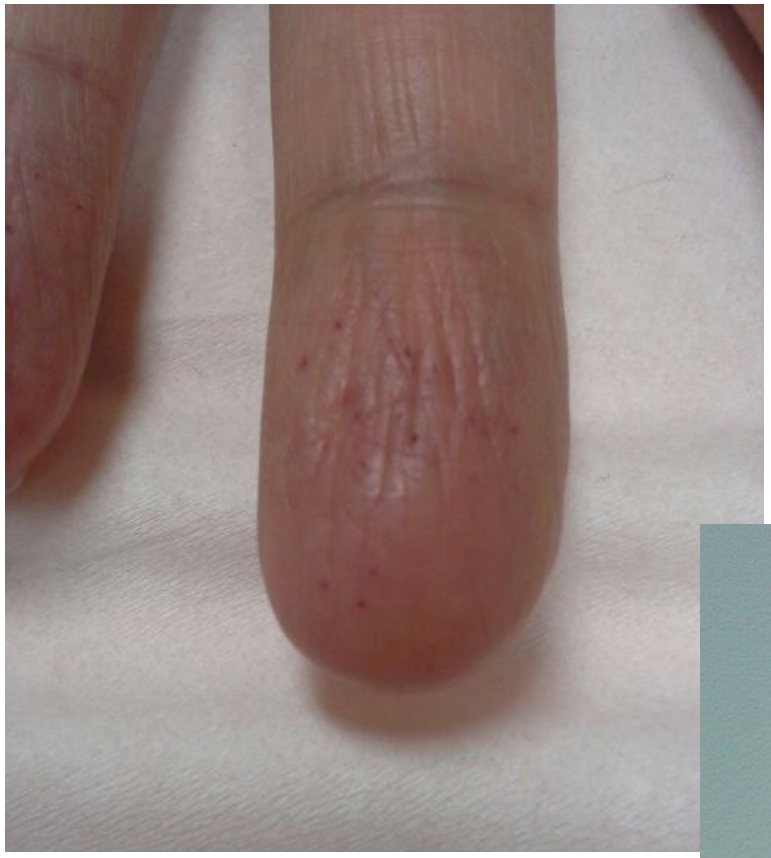
Heat intolerance++++

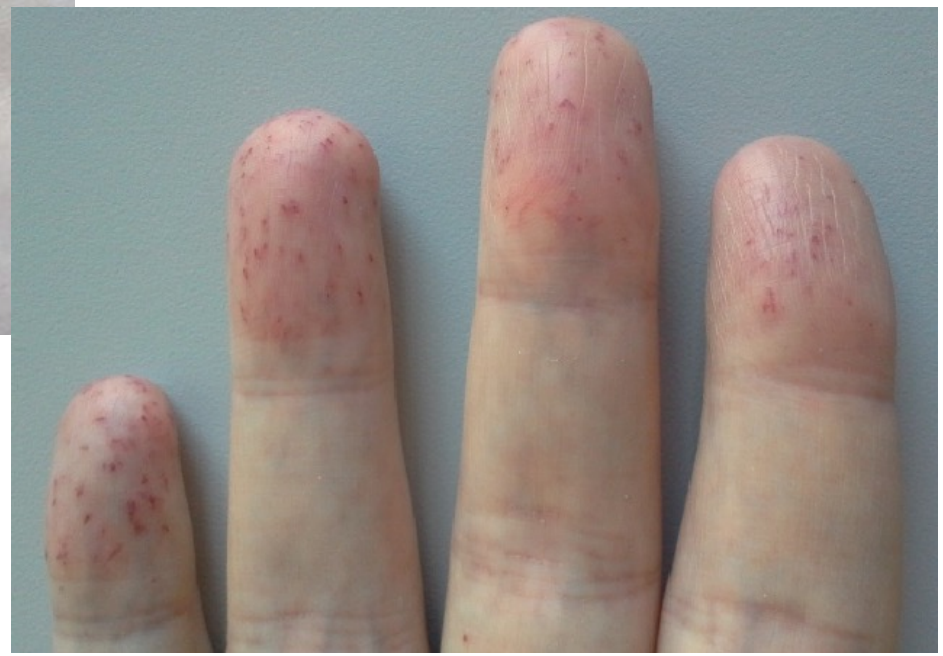
GI symptoms (pain, bloating)

Lanet DA et al. Initial symptoms in young pediatric patients with classic pathogenic Variants in the GLA gene, poster WORLD 2022

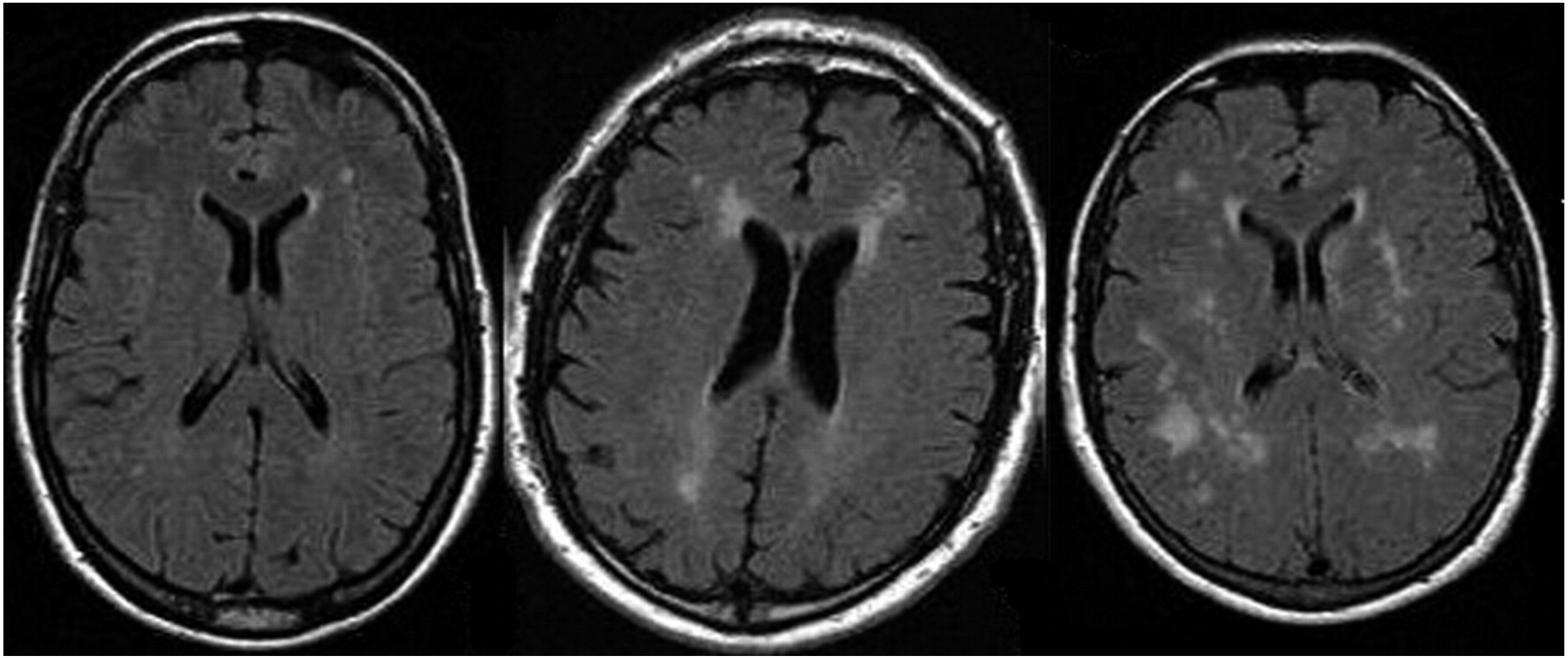






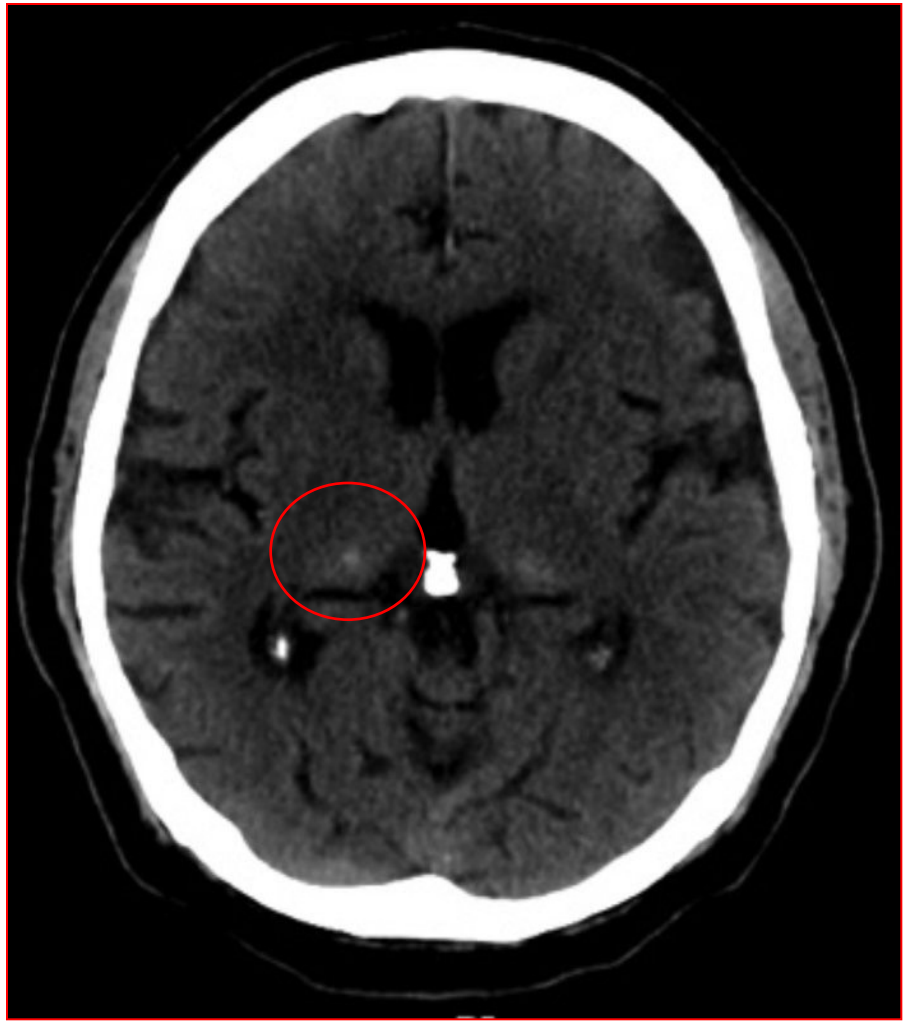


Fredeau L, et al. Br J Dermatol 2020.

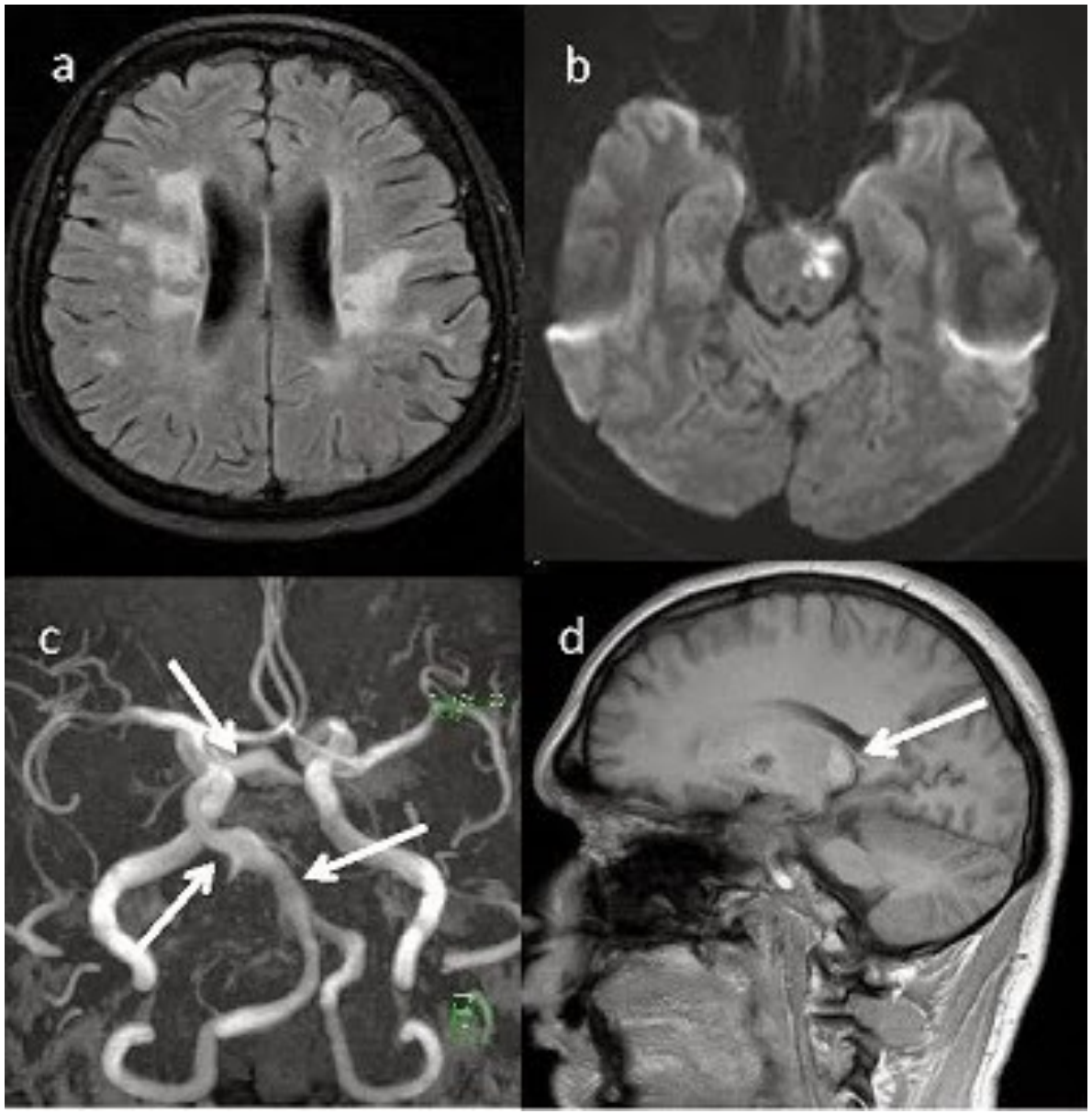


Gavazzi, Radiology 2006

Aspecific white matter lesions
with no clear neurological impact

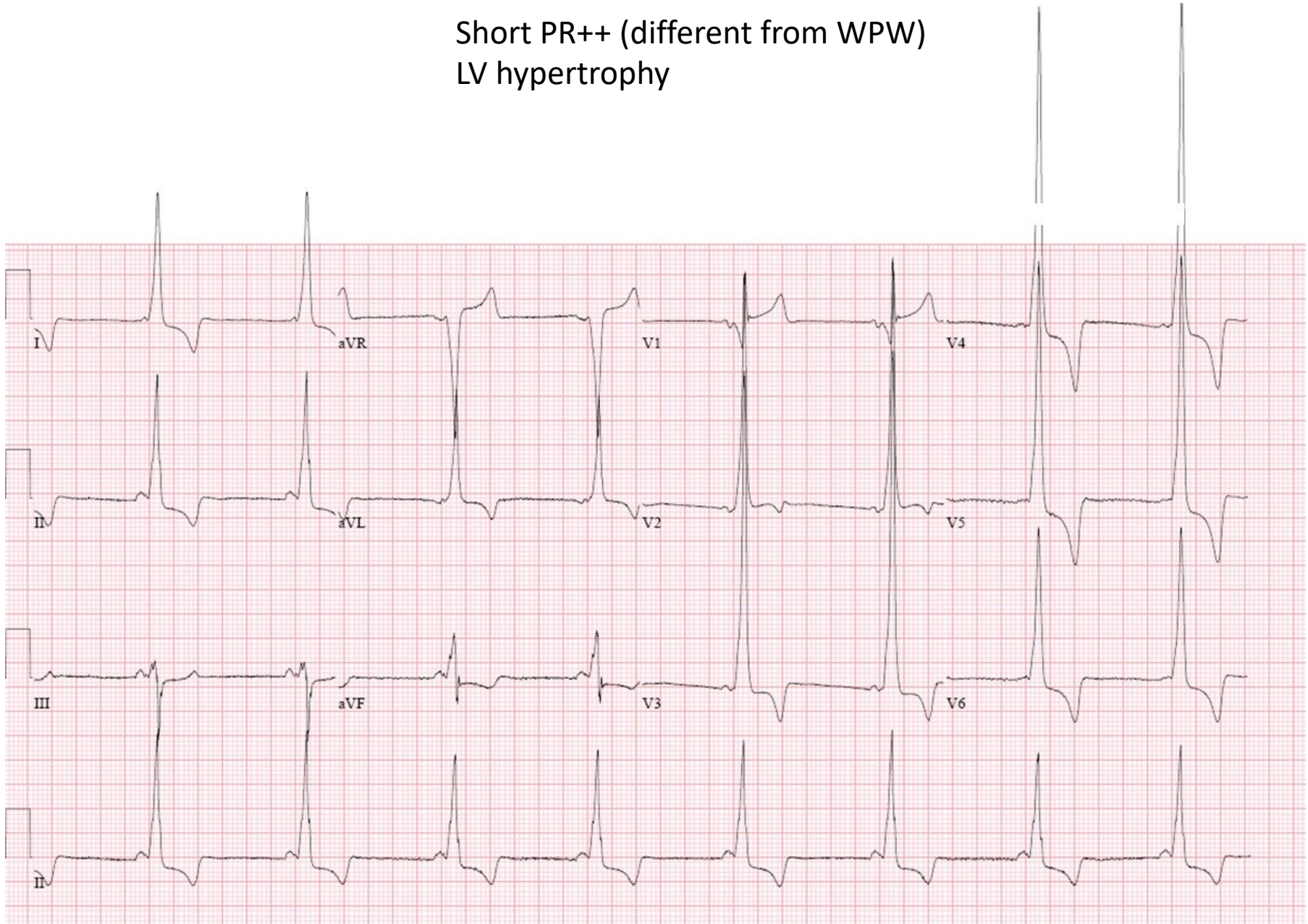


T1 hypersignal in pulvinar
Matias-Guiu, Neurologia 2014

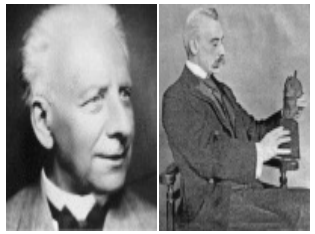


Fazekas, Stroke 2015

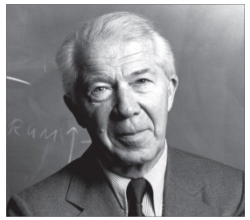
Short PR++ (different from WPW)
LV hypertrophy



J. Fabry W. Anderson



C. De Duve



K. Hashimoto

R. Brady

First descriptions of atypical presentation = late onset = cardiac variant = non classic Fabry disease

1898 — **1950'** — **1965** — **1960-70** — **1990'**

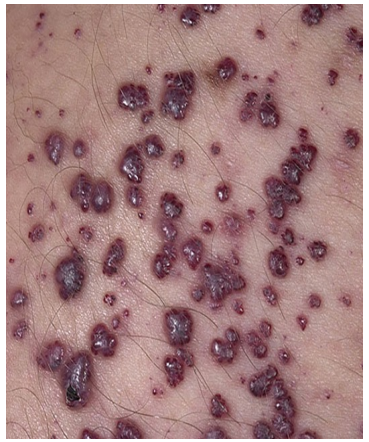
Angiokeratoma corporis diffusum

Lysosome

Fabry = lysosomal

α-Gal A defect

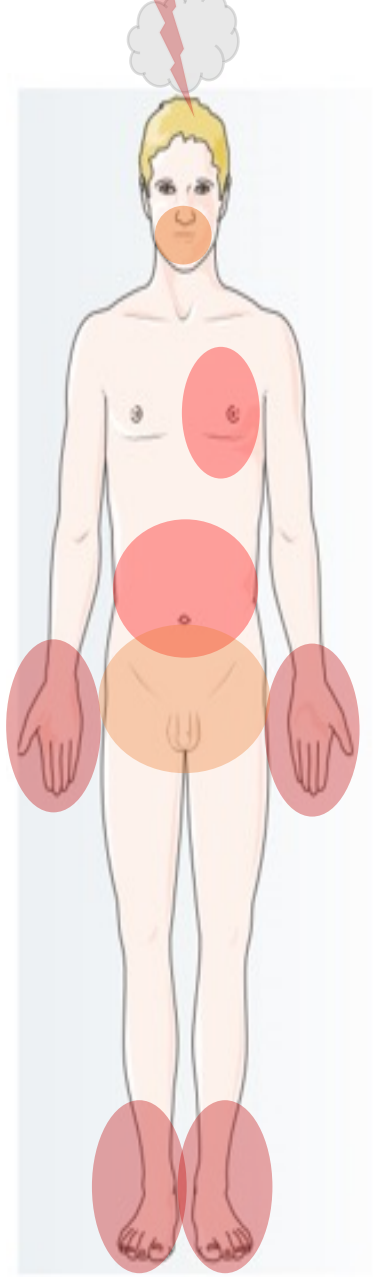
GLA gene



Non classic Fabry disease

- Residual **α-Galactosidase A** enzymatic activity ≠ 0
- Predominant, almost exclusive cardiac disease

(W. Von Scheidt et al. 1991)

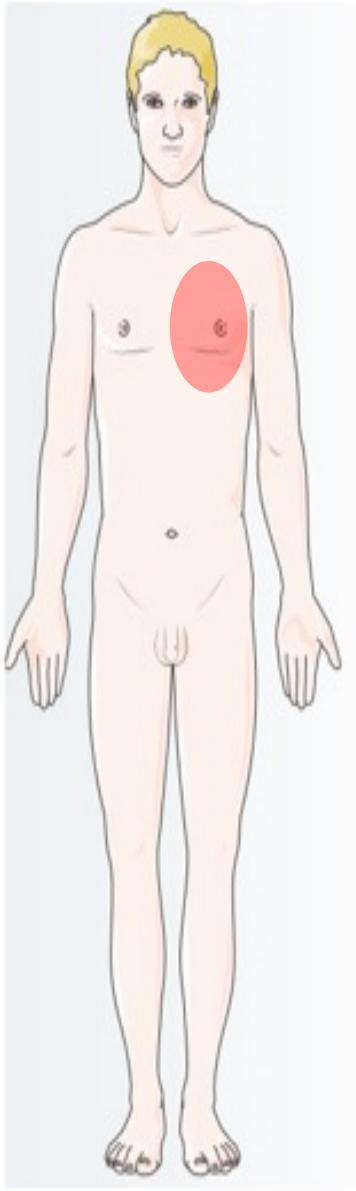


Genetic : Nonsense or missense mutations

aGal activity < 1%

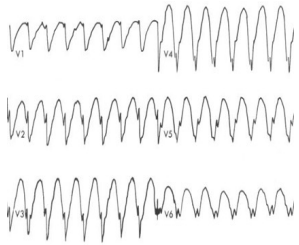
LysoGb3: high, very high

1 < 10



Deafness
Vertigo

Hypertrophic cardiomyopathy, arrhythmia



Genetic : Mostly missense mutations

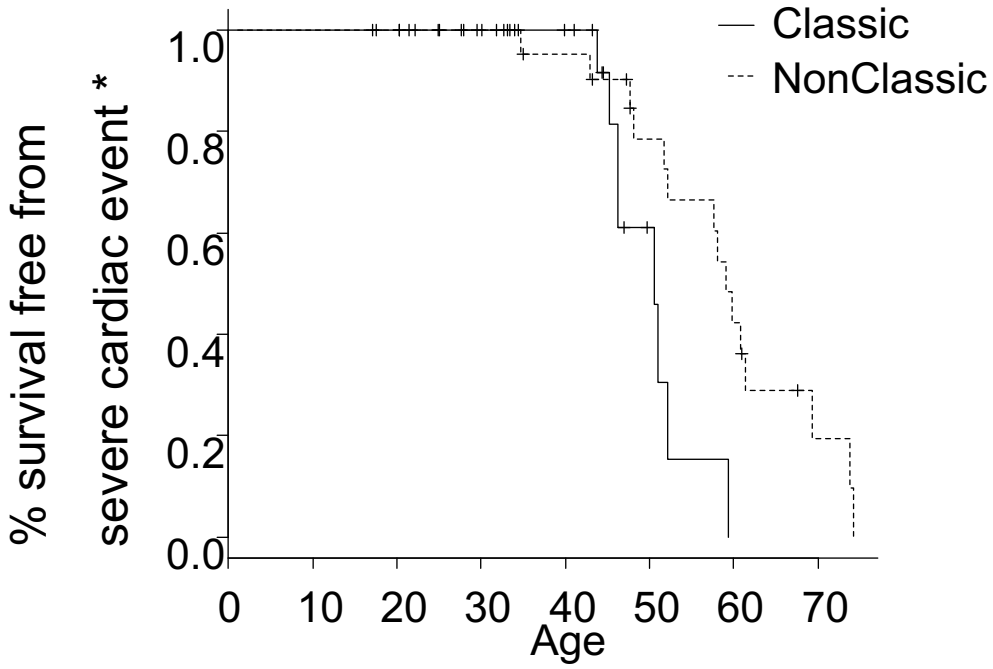
aGal activity > 1%

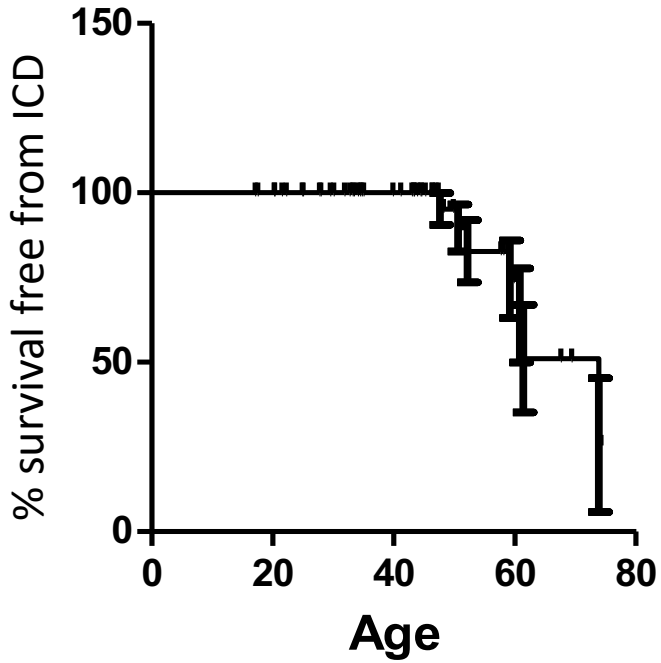
LysoGb3 intermediate

Classic Fabry Disease

Non-Classic Fabry Disease

Cardiac involvement





*severe cardiac event = IVS > 17mm, LVef <50%, Implantable cardiac device (ICD), angor, cardiac transplant)

⇒ Classic vs Non-classic; p= 0,012

⇒ More than half of the Fabry males patients need an ICD after 60.

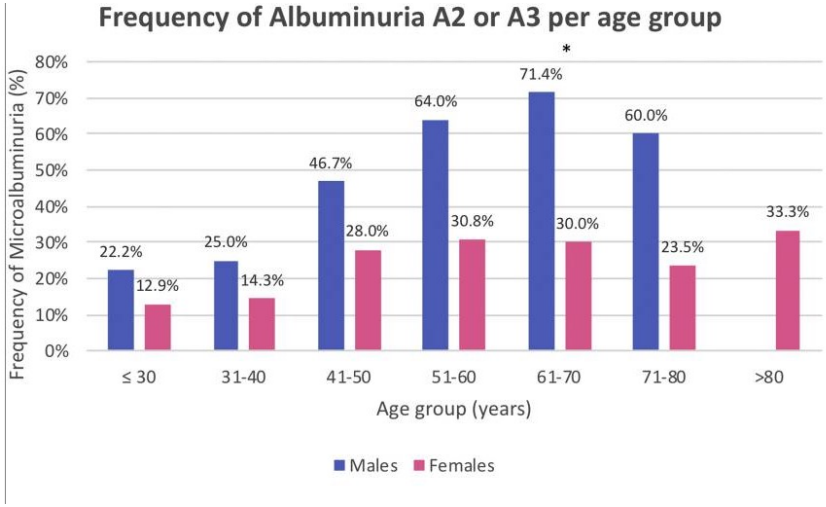
Mauhin W et al, PLoS One 2020

EXAMPLE OF F113L LATE-ONSET PORTUGUESE VARIANT

AZEVEDO ET AL. MOL GENET METAB 2020

N= 120 (females 73 / males 47)
Mean age +/- SD : 46 y. +/- 18

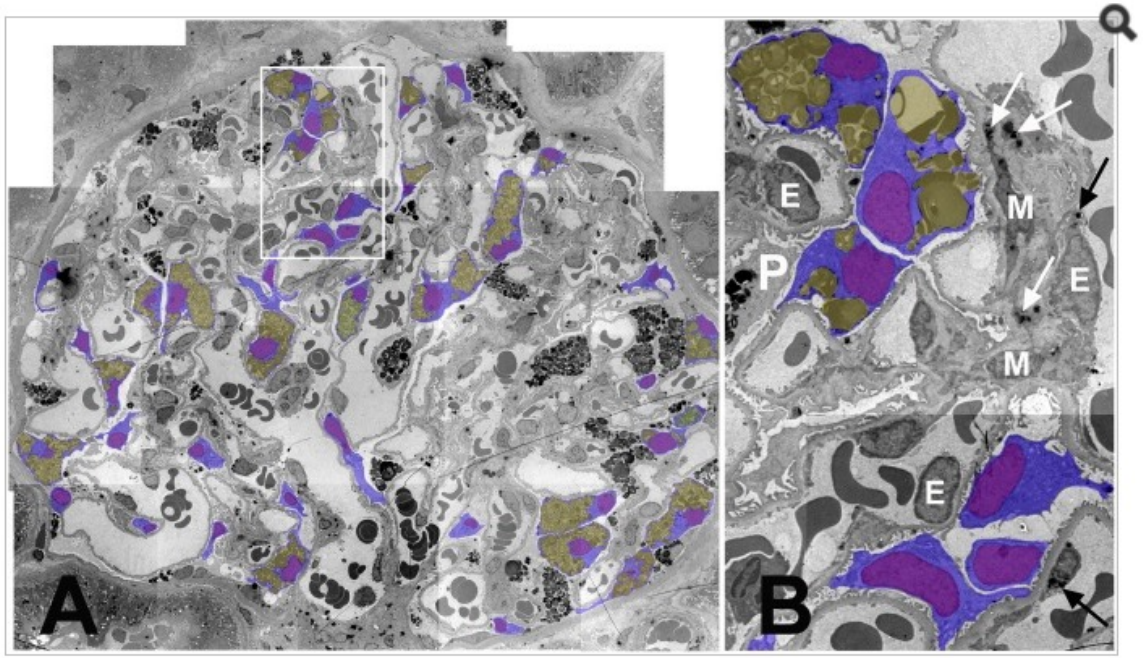
Renal manifestations	
Albuminuria A2 (30-300mg/24 h) (%)	31 (26.1%)
Albuminuria A3 (> 300 mg/24 h) (%)	12 (10.1%)
Albuminuria A2 or A3 (≥ 30 mg/24 h) (%)	43 (36.1%)
Chronic kidney disease stages	
G1 (eGFR ≥ 90 mL/min/1.73m^2) (%)	79 (66.4%)
G2 (eGFR 60-89 mL/min/1.73m^2) (%)	31 (26.1%)
G3a (eGFR 45-59 mL/min/1.73m^2) (%)	6 (5.0%)
G3b (eGFR 30-44 mL/min/1.73m^2) (%)	1 (0.8%)
G4 (eGFR 15-29 mL/min/1.73m^2) (%)	1 (0.8%)
G5 (eGFR < 15 mL/min/1.73 m^2) (%)	1 (0.8%)
Chronic kidney disease stage ≥ G3 (%)	9 (7.6%)
Comorbidities	
Hypertension (%)	38 (31.7%)
Diabetes *mellitus* (%)	15 (12.5%)



albuminuria ≥30 mg/ 24 h was also found in 24.1% of the normotensive non-diabetic patients, with a trend for a male predominance (35.7% vs. 17.6%, p= 0,07)

WHAT ABOUT WOMEN?

- **X-INACTIVATION = LYONISATION**



Mosaicism of podocyte Fabry phenotype in a glomerulus from a female patient with Fabry disease.

(**A**) Montage image of a glomerulus (~3,000×). Podocyte bodies with visible nuclei are colored blue, podocyte nuclei purple, and GL-3 inclusions yellow. The white rectangle is magnified in B. (**B**) Magnified view of three podocyte profiles without (at the bottom) and three other podocyte profiles with GL-3 inclusions (on the top). Arrows show GL-3 inclusions in mesangial (M) cells (black) and endothelial (E) cells. P is a podocyte profile with no visible nucleus on this section.

Statistically 50% cells with enzymatic defect

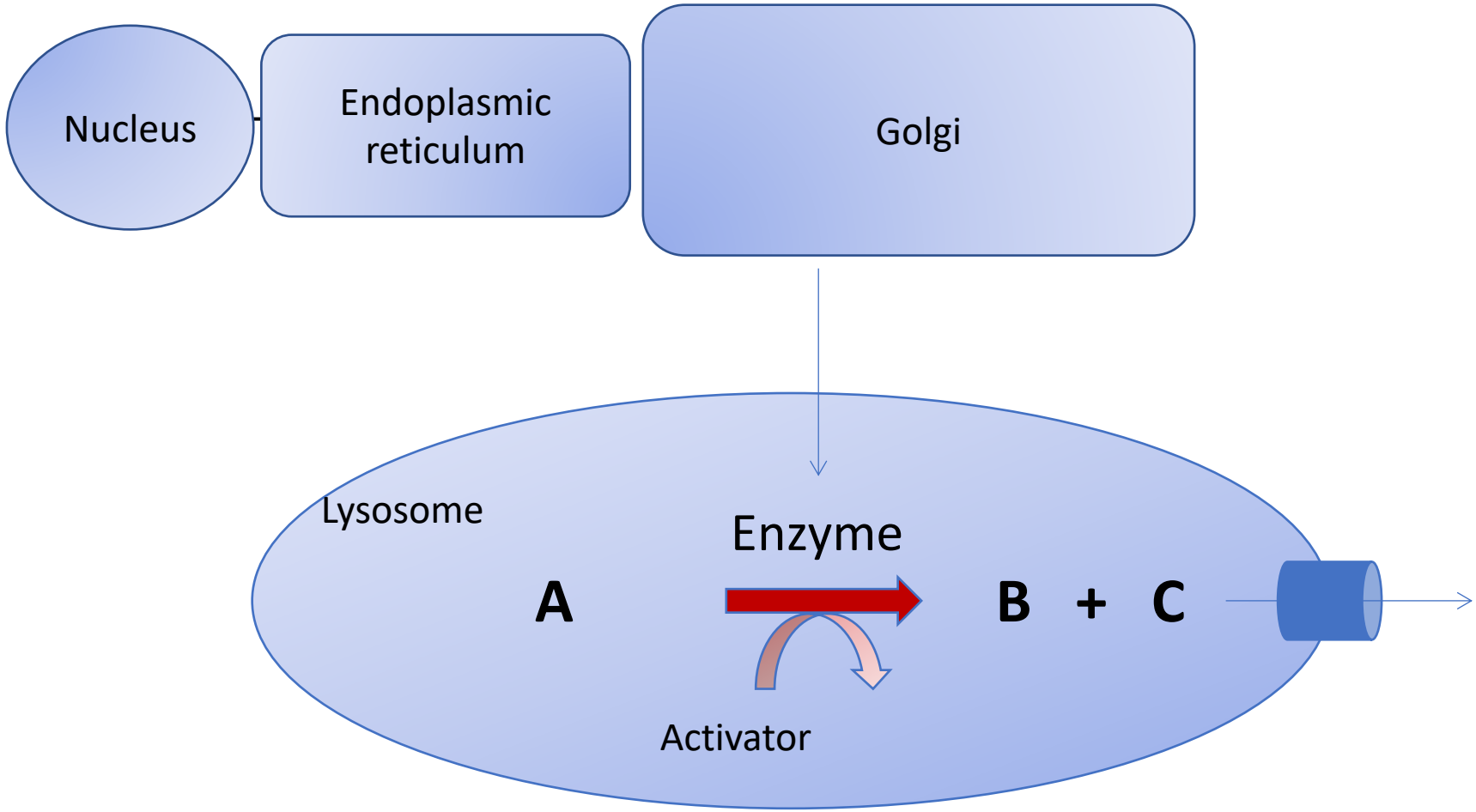
No cross correction between cells ! (Beck et Cox, Mol Genet Metab Reports, 2020)

Random mosaicism?

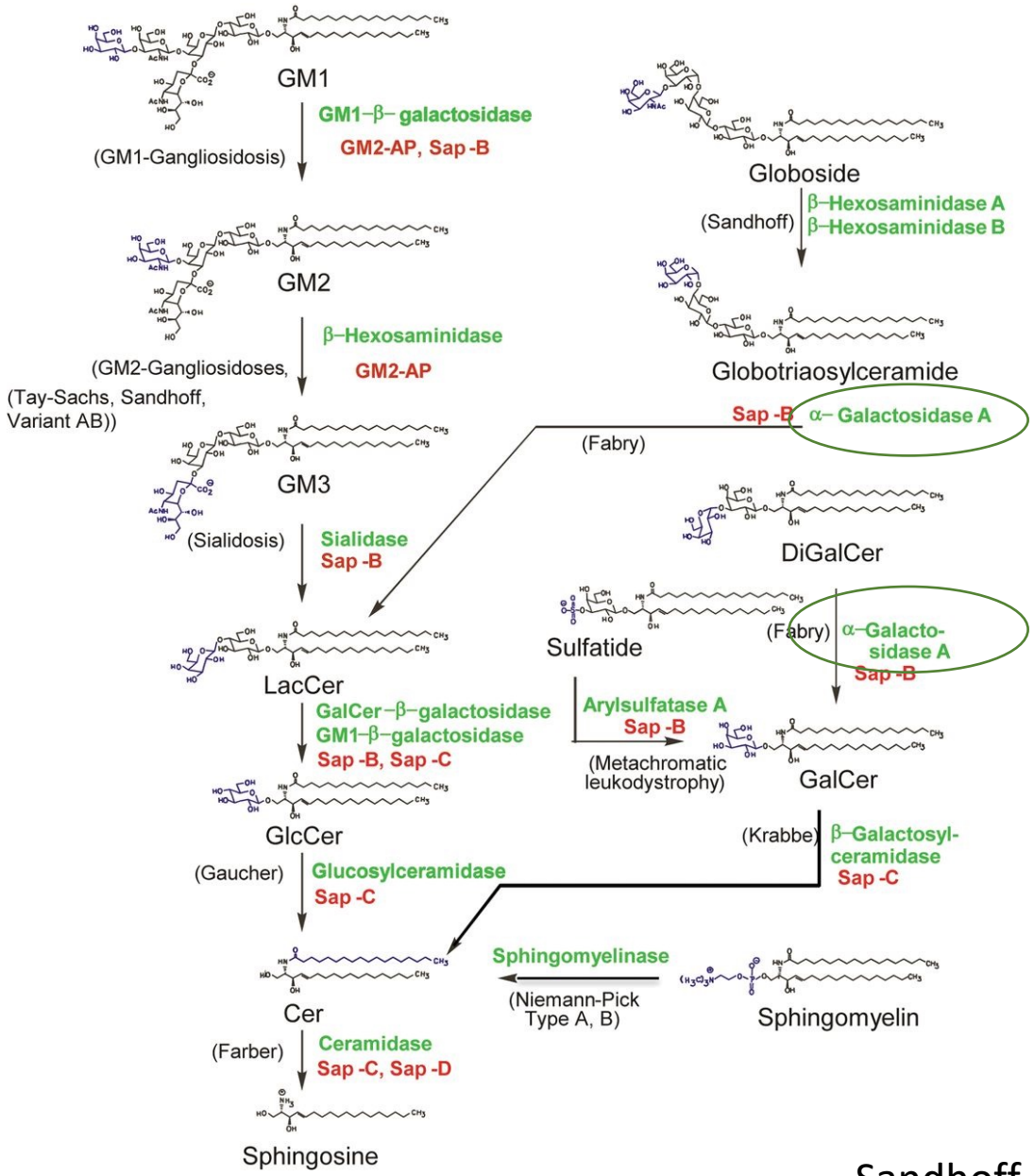
Women can have severe Fabry disease

Mauer, PLoSOne 2014

FABRY DISEASE PATHOPHYSIOLOGY PART I



Sphingolipidosis : defect in sphingolipids catabolism



Sandhoff, 2013

Sphingolipids??

- Lipids with backbone of sphingoid bases
- > 300 different structures
- 3 categories:
  - Cerebrosides
  - Globosides
  - Gangliosides

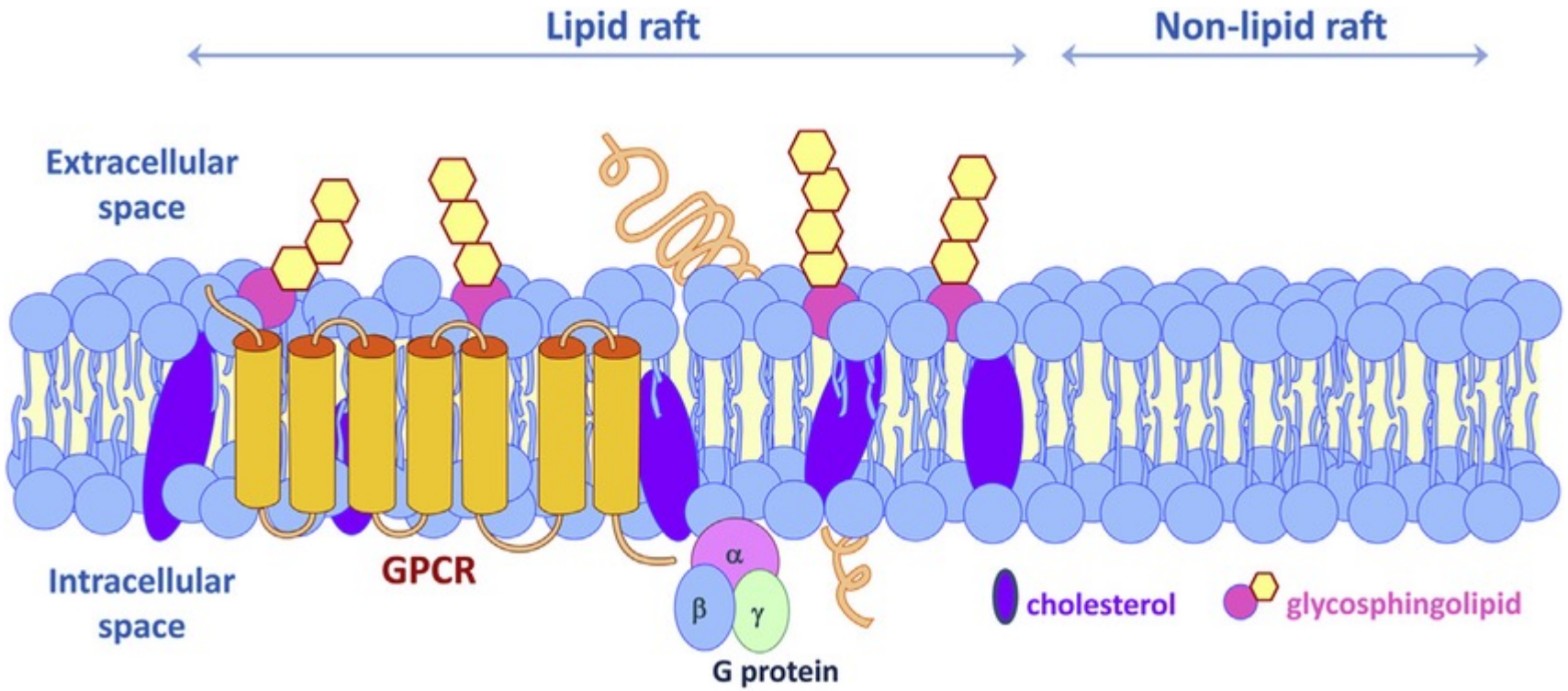
- Essential to structure the plasmic membrane
- Play a role in the cellular specialisation

⇒ Structural role/ mechanic
⇒ Immunological role
⇒ Hormonal receptor

- Cerebrosides => myelin

Globotriaosylceramide = Gb3 = GL3 = CD77 = Pk Ag

Preferentially within the lipid rafts



B Lymphocyte : CD77 = differentiation marker for the germinal center/ associated to CD19

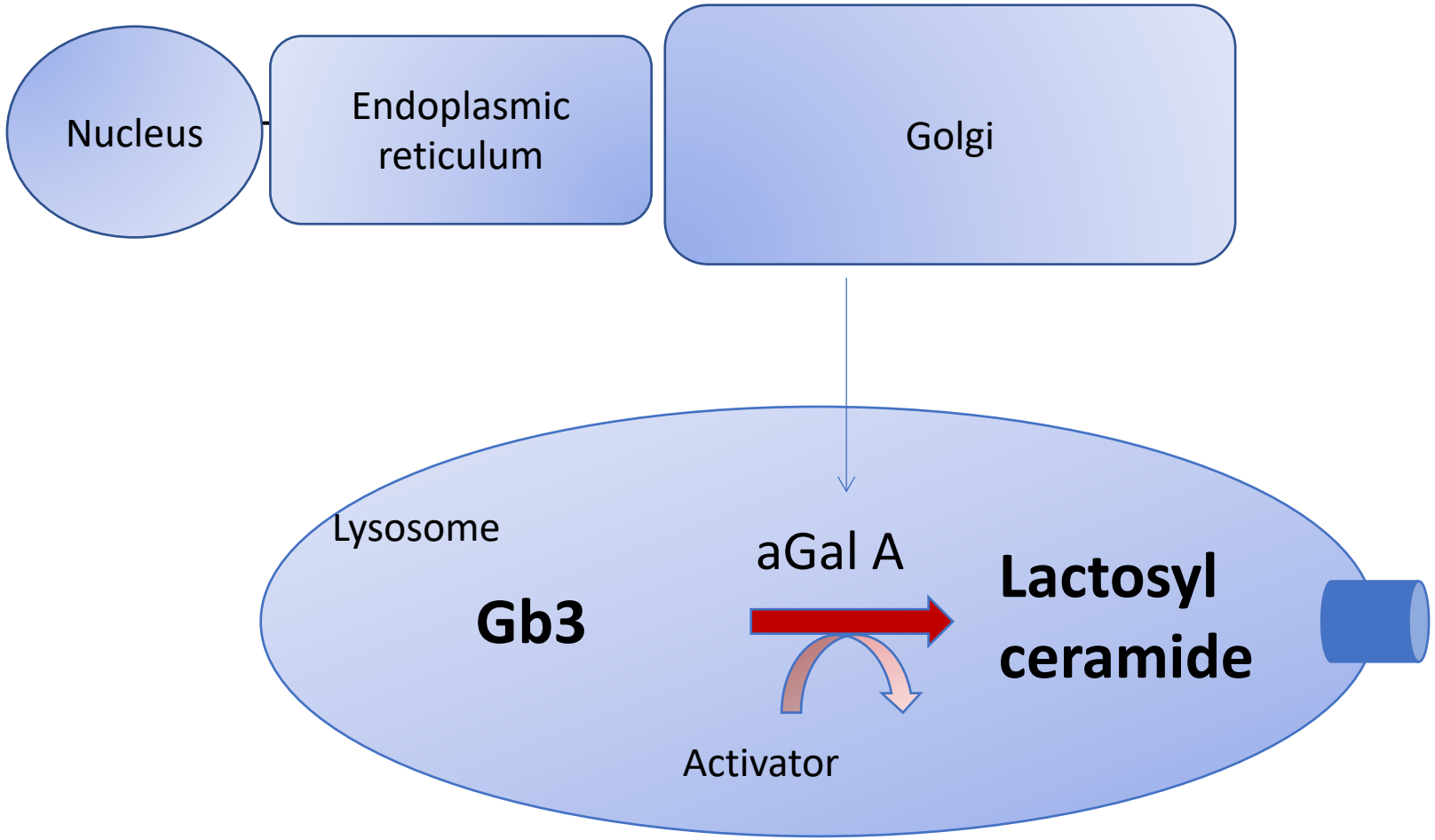
P^k Ag in P0-Pk blood group

On endothelial and renal cells: target/ binding site for **shigatoxins**

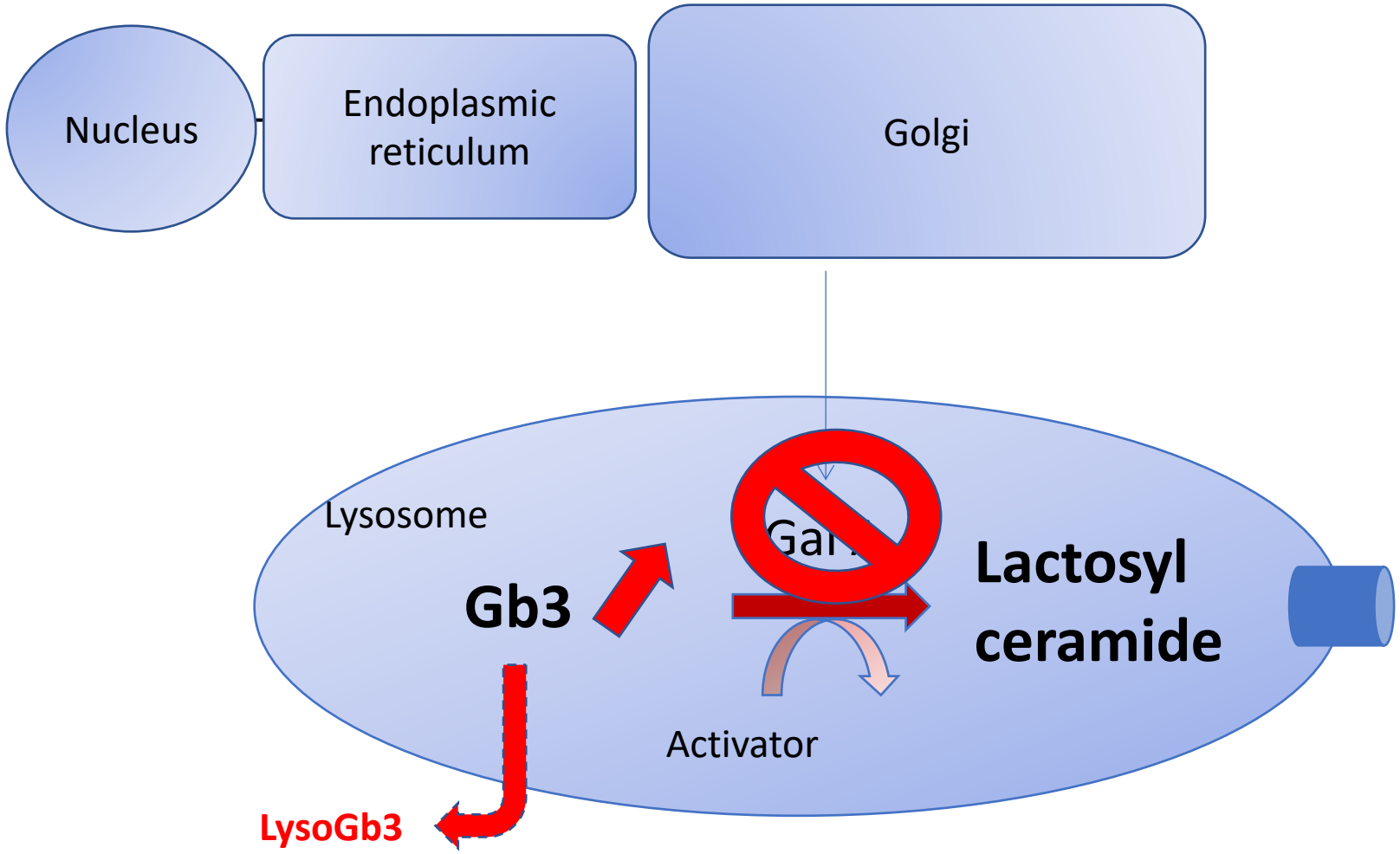
CD4 T cells : first non covalent binding site for **HIV**

From Villar et al., Methods in Cell biology, Dec 2016

FABRY DISEASE PATHOPHYSIOLOGY PART I



FABRY DISEASE PATHOPHYSIOLOGY PART I



lysoGb3 = deacetylated form of Gb3 = soluble = specifically elevated in Fabry disease
Higher in classic phenotype compared to non-classic

HOW TO DIAGNOSE FABRY DISEASE

- **In males**
  - **Alpha-galactosidase enzymatic activity** necessarily decreased (<1% of normal range in classic; < 5% in non-classic phenotype)
  - LysoGb3 mildly (non-classic) to highly (classic) elevated
  - Genotyping GLA gene : be carreful of Variant of Unknown Significance (VUS)

- **In females**
  - Alpha-galactosidase enzymatic activity possibly decreased = reflect of X-inactivation bias
    ⇒ Usually normal!
  - LysoGb3 normal to elevated

  ⇒ **Genotyping GLA gene** : be carreful of Variant of Unknown Significance

- Biopsy +++ : zebra bodies, Gb3 inclusions
  - If atypical presentation : proteinuria > 3 g/d (nephrotic syndrome is unusual in FD), kidney disease without proteinuria, renal disease in non-classic patient
  - If unknown genetic variant or VUS

EPIDEMIOLOGY

- **Screening on clinical criteria 1980 – 1996 (classic phenotype)** = 1/117 000 (Meikle, 1999)

- **Systematic newborn screening programs**
  - Italy: 1/4600 births (Spada, 2006)
  - Illinois: 1/8454 births (Burton, 2017)
  - Missouri: 1/3277 births (Hopkins, 2018)

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Minireview

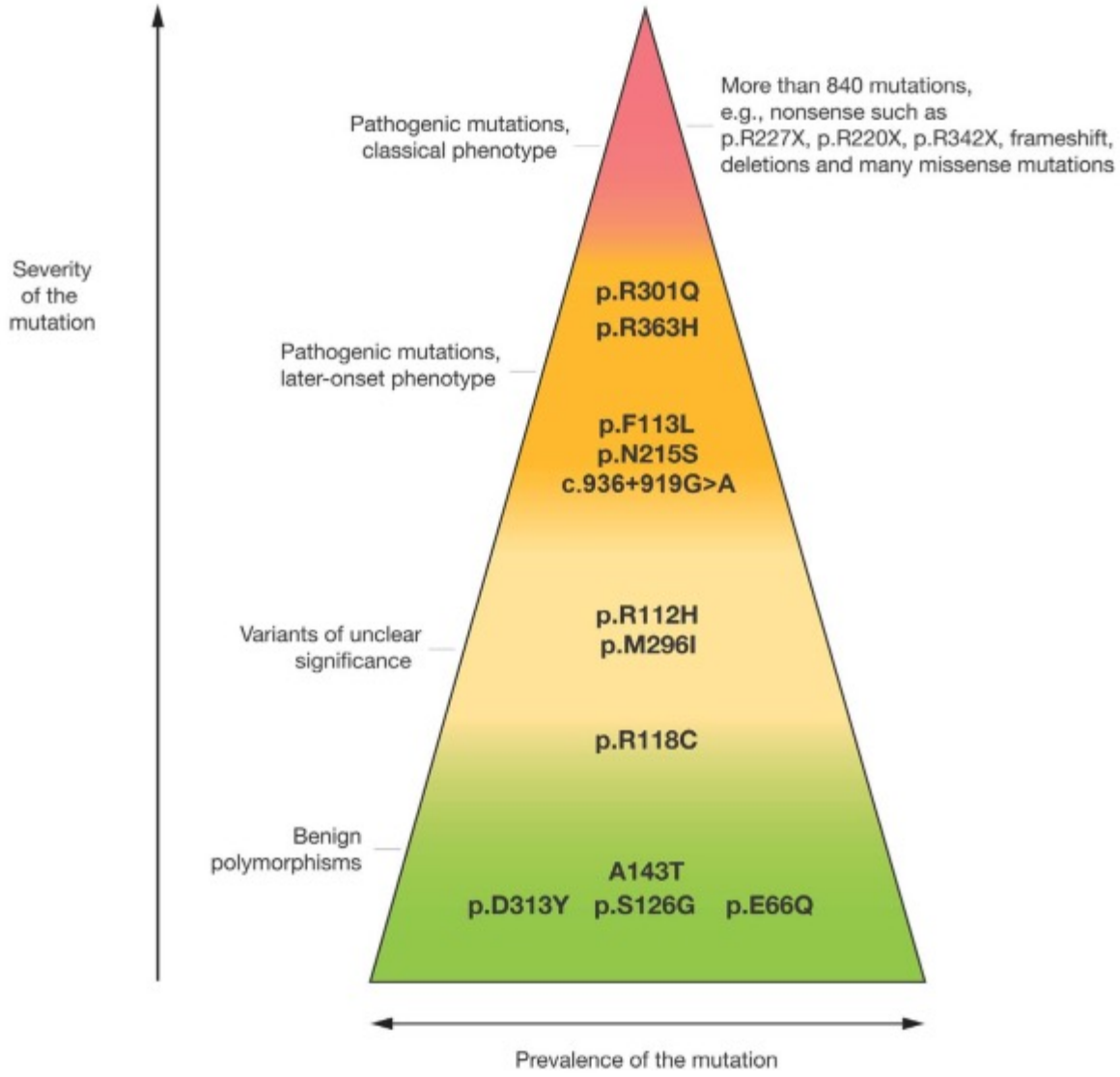
Fabry disease revisited: Management and treatment recommendations for adult patients

Alberto Ortiz[a,*], Dominique P. Germain[b], Robert J. Desnick[c], Juan Politei[d], Michael Mauer[e], Alessandro Burlina[f], Christine Eng[g], Robert J. Hopkin[h], Dawn Laney[i], Aleš Linhart[j], Stephen Waldek[k], Eric Wallace[l], Frank Weidemann[m], William R. Wilcox[i]

Background:

- Diagnosis: Genetic > Enzymatic
- Newborn screenings (Matern, 2015)
  - Classic: 1/22570 males
  - Non-classic: 1/1390 males
  - Variant of Unknown Significance (VUS)

- VUS in males: need to have low aGal enzyme activity + organ disease (familial or personal = biopsy)



Variant of Unknown Significance = VUS

Table 1 Prevalence of previously unrecognised Fabry Disease in males by screening specialty clinics

Clinic type/study	Studies (n)	Males screened (n)	Overall positive n (%)	Revised by phenotype: Pathogenic: Total n (%)	Pathogenic: Classic n (%)	Pathogenic: Later-onset n (%)	Pathogenic: Type 1:type 2 ratio	Benign: Benign n (%)	Benign: % of all variants
Haemodialysis									
Linthorst *et al*, 2010 (Enzyme and DNA data)	12	7182	24 (0.33)						
Linthorst *et al*, 2010 (DNA only)*†	11	6618	24 (0.36)	21 (0.32)	13 (0.20)	8 (0.12)	3:2	3 (0.05)	12.5
Additional studies, 2009–2017	16	17 336	77 (0.44)	29 (0.17)	20 (0.12)	9 (0.05)	2:1	48 (0.28)	62.3
Combined data, 1995–2017*	27	23 954	101 (0.42)	50 (0.21)	33 (0.14)	17 (0.07)	2:1	51 (0.21)	50.5
Caucasian*	18	14 398	68 (0.47)	35 (0.24)	25 (0.17)	10 (0.07)	5:2	33 (0.23)	48.5
Asian	9	9556	33 (0.35)	15 (0.16)	8 (0.08)	7 (0.07)	1:1	18 (0.19)	54.5
Renal transplantation									
Linthorst *et al*, 2010 (Enzyme and DNA data)	2	1584	6 (0.38)						
Linthorst *et al*, 2010 (DNA only)	2	1584	6 (0.38)	5 (0.32)	3 (0.19)	2 (0.13)	3:2	1 (0.06)	16.7
Additional studies, 2009–2017	1	447	5 (1.12)	0 (0.00)	–	–	–	5 (1.12)	100.0
Combined data, 1995–2017	3	2031	11 (0.54)	5 (0.25)	3 (0.15	2 (0.10)	3:2	6 (0.30)	54.5
Caucasian	3	2031	11 (0.54)	5 (0.25)	3 (0.15)	2 (0.10)	3:2	6 (0.30)	54.5
Asian	0	–	–	–	–	–	–	–	–
Cardiac: LVH and HCM									
Linthorst *et al*, 2010 (Enzyme and DNA data)	3	711	19 (2.67)						
Linthorst *et al*, 2010 (DNA only)	3	711	19 (2.67)	15 (2.11)	3 (0.42)	12 (1.69)	1:4	4 (0.56)	21.1
Additional studies, 2009–2017‡	13	3343	30 (0.90)	23 (0.69)	6 (0.18)	17 (0.51)	1:3	7 (0.21)	23.3
Combined data, 1995–2017‡	16	4054	49 (1.21)	38 (0.94)	9 (0.22)	29 (0.72)	1:3	11 (0.27)	22.5
Caucasian‡	13	2909	37 (1.27)	29 (1.00)	9 (0.31)	20 (0.69)	1:2	8 (0.28)	21.6
Asian	3	1145	12 (1.05)	9 (0.79)	0 (0)	9 (0.79)	0:1	3 (0.26)	25.0
Stroke									
Linthorst *et al*, 2010 (Enzyme and DNA data)	2	496	21 (4.23)						
Linthorst *et al*, 2010 (DNA only)*	1	64	0	–	–	–	–	–	–
Additional studies, 2009–2017	15	3840	26 (0.68)	5 (0.13)	3 (0.08)	2 (0.05)	3:2	21 (0.55)	80.8
Combined data, 1995–2017*	16	3904	26 (0.67)	5 (0.13)	3 (0.08)	2 (0.05)	3:2	21 (0.54)	80.8
Caucasian*	13	2773	16 (0.58)	5 (0.18)	3 (0.11)	2 (0.07)	3:2	11 (0.40)	68.8
Asian	3	1131	10 (0.88)	0 (0.00)	–	–	–	10 (0.88)	100.0

Renal transplant or haemodialysis ≈ 0,2%

Hypertrophic cardiomyopathy ≈ 1%

Cryptogenic stroke ≈ 0,1%

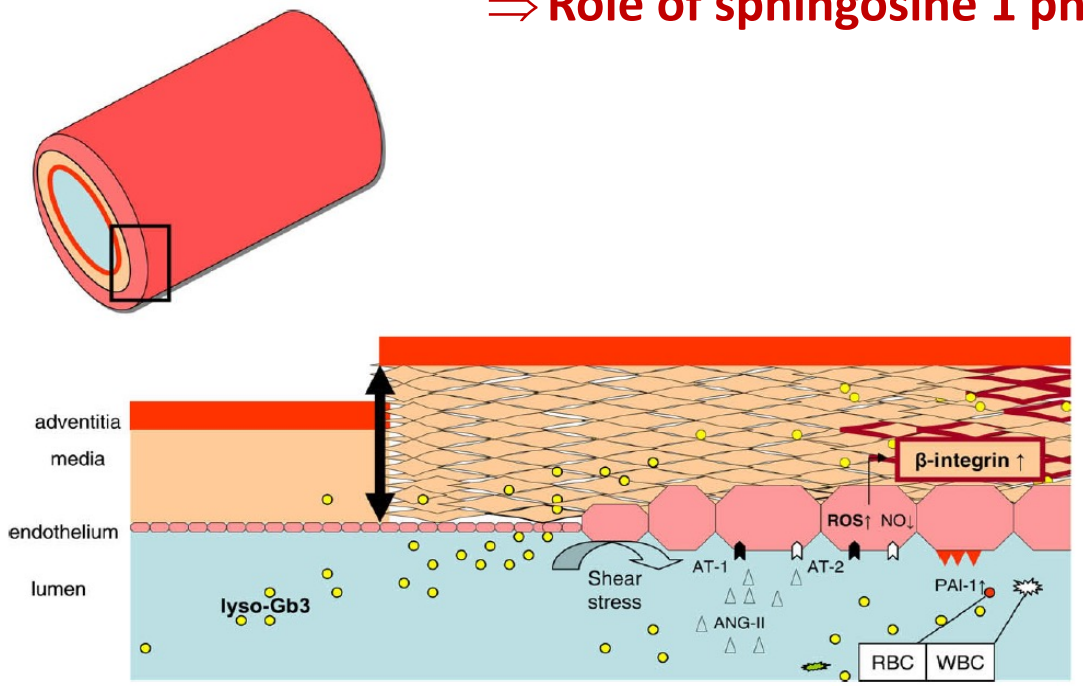
Doheny et al., J Med Genet 2018

FABRY DISEASE PATHOPHYSIOLOGY PART II

Hypothesis

⇒ Role of lysoGb3

⇒ Role of sphingosine 1 phosphate



Cellular proliferation of muscular cells in the media

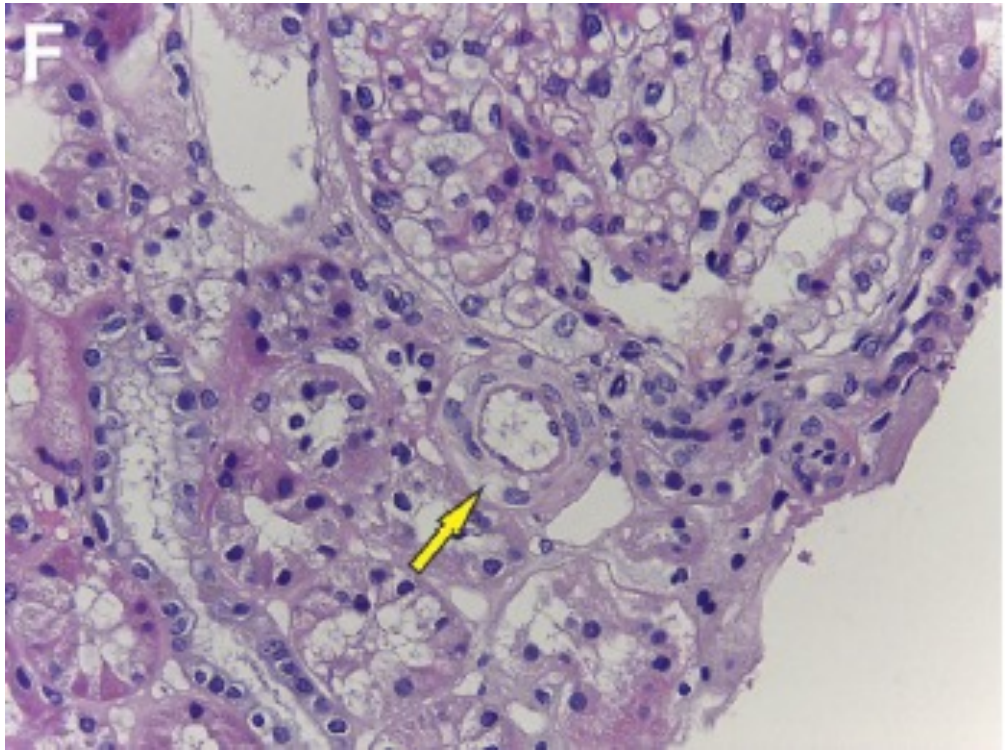
AT-1/2 : angiotensin receptors ; ANG-II : angiotensine II ; PAI-1 : plasminogen activator inhibitor I ; NO : Nitric oxid ; RBC : red blood cell ; ROS : *reactive oxygene species* ; S1P: sphingosine 1 phosphate; WBC : white blood cell

Adapted from de Rombach et al, Mol Genet Metab, 2010
Brakch et al., Eur Heart J, 2010

Pathogenesis of Fabry nephropathy: The pathways leading to fibrosis

Paula Adriana Rozenfeld[a,*], María de los Angeles Bolla[b], Pedro Quieto[c], Antonio Pisani[d], Sandro Feriozzi[e], Pablo Neuman[f], Constanza Bondar[a]

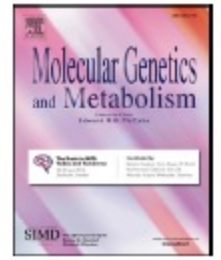
- N= 15 treatment-naive Fabry patients (7 females/ 8 males)
- Median age 43 y. (23-64)
- Classic 11 / Non classic 4

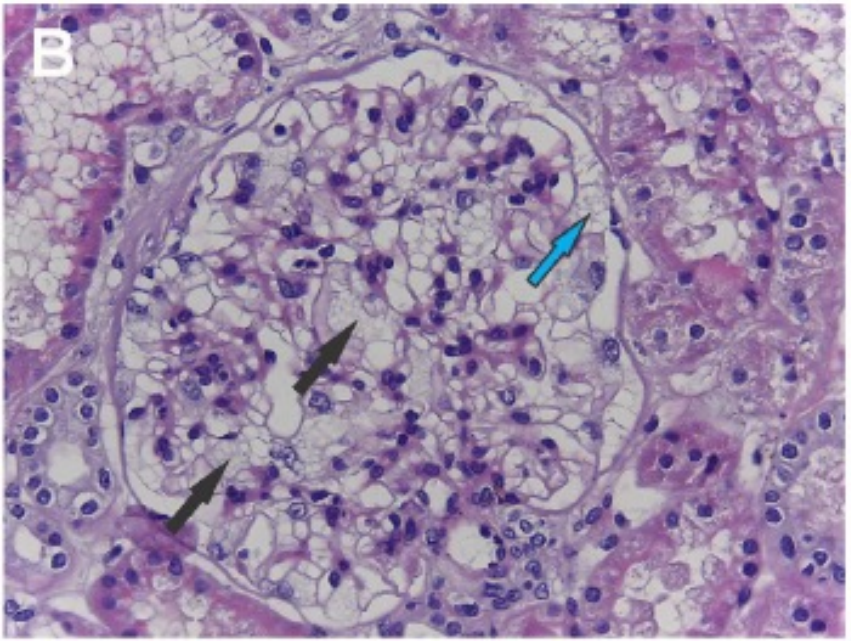


Thickening of the arteriolar walls

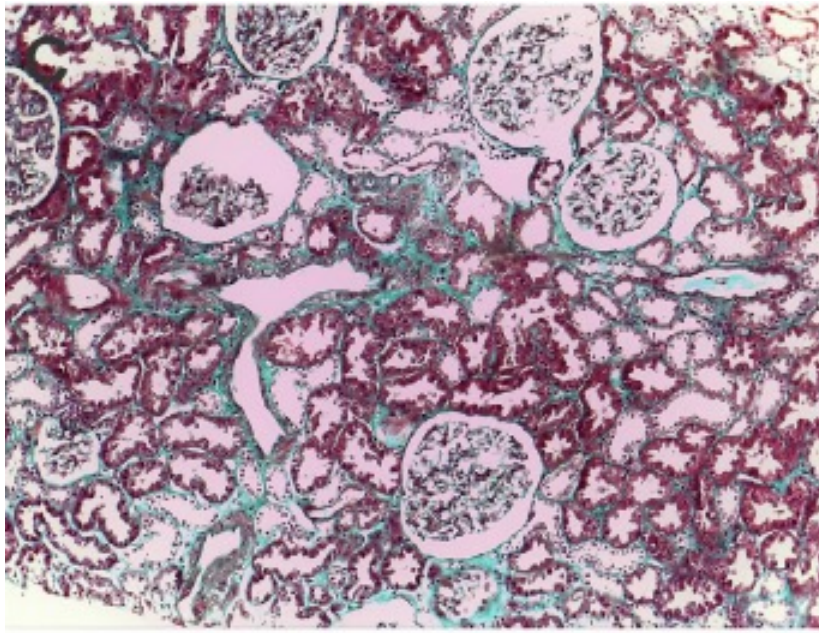
Pathogenesis of Fabry nephropathy: The pathways leading to fibrosis

Paula Adriana Rozenfeld[a,*], María de los Angeles Bolla[b], Pedro Quieto[c], Antonio Pisani[d], Sandro Feriozzi[e], Pablo Neuman[f], Constanza Bondar[a]

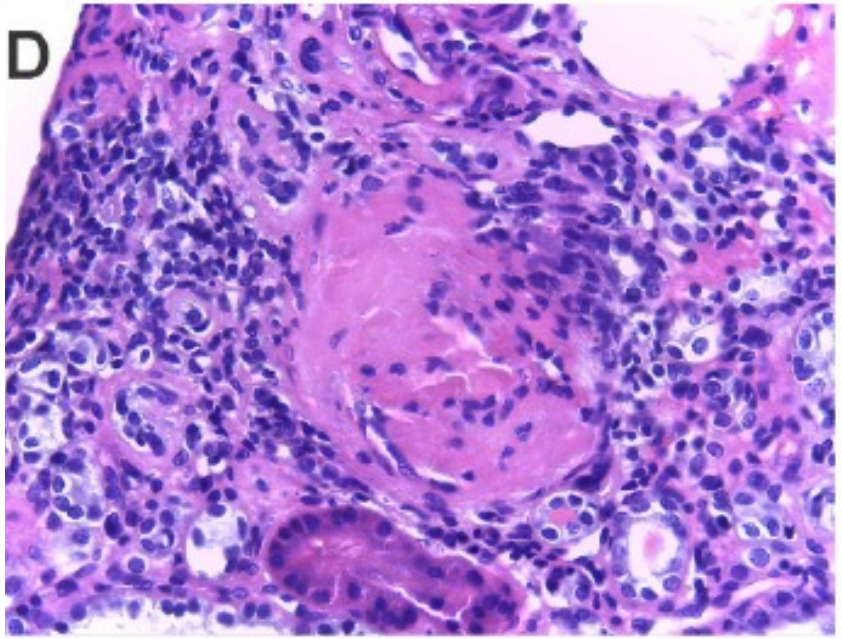




Black arrows: mesangial cells vacuolization
Blue arrow: podocyte vacuolization



Interstitial fibrosis



Global glomerular sclerosis and interstitial
inflammatory lymphocyte infiltration

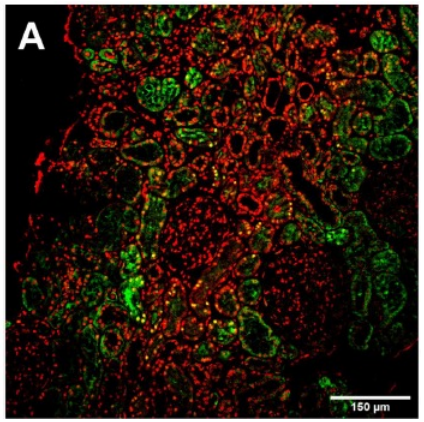
LysoGb3

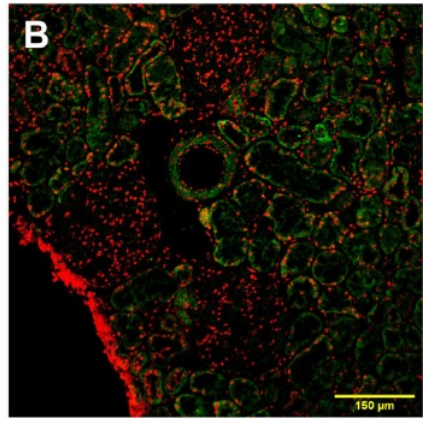
?

Proximal tubular cell

TGF beta

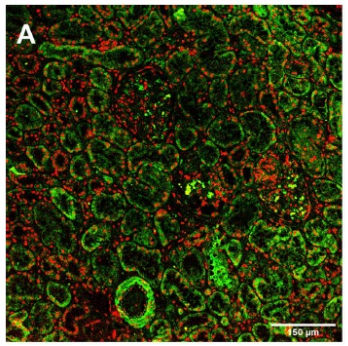
TGF-β1 staining in proximal tubular cells but not in glomeruli





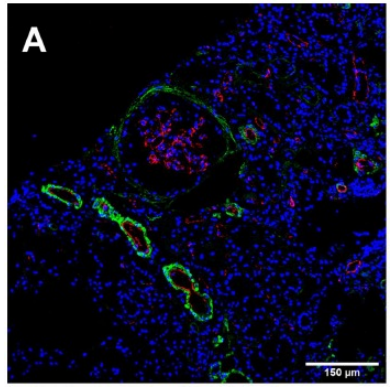
FGF-2

FGF2 was found in 75% of tubular, mesangial and endothelial cells



Myofibroblasts

Myofibroblasts surrounding peritubular and periglomerular capillaries

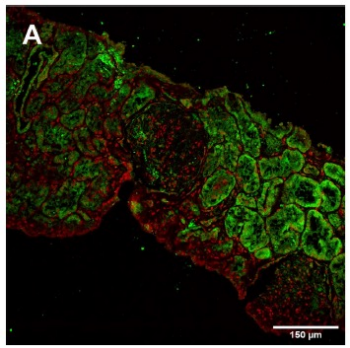


Green : αSMA (myofibroblasts)
Red : CD31 (Endothelial cells)

VEGF

Apoptosis

Anti-caspase 3 staining



FIBROSIS

Glomerulosclerosis
Interstitial fibrosis

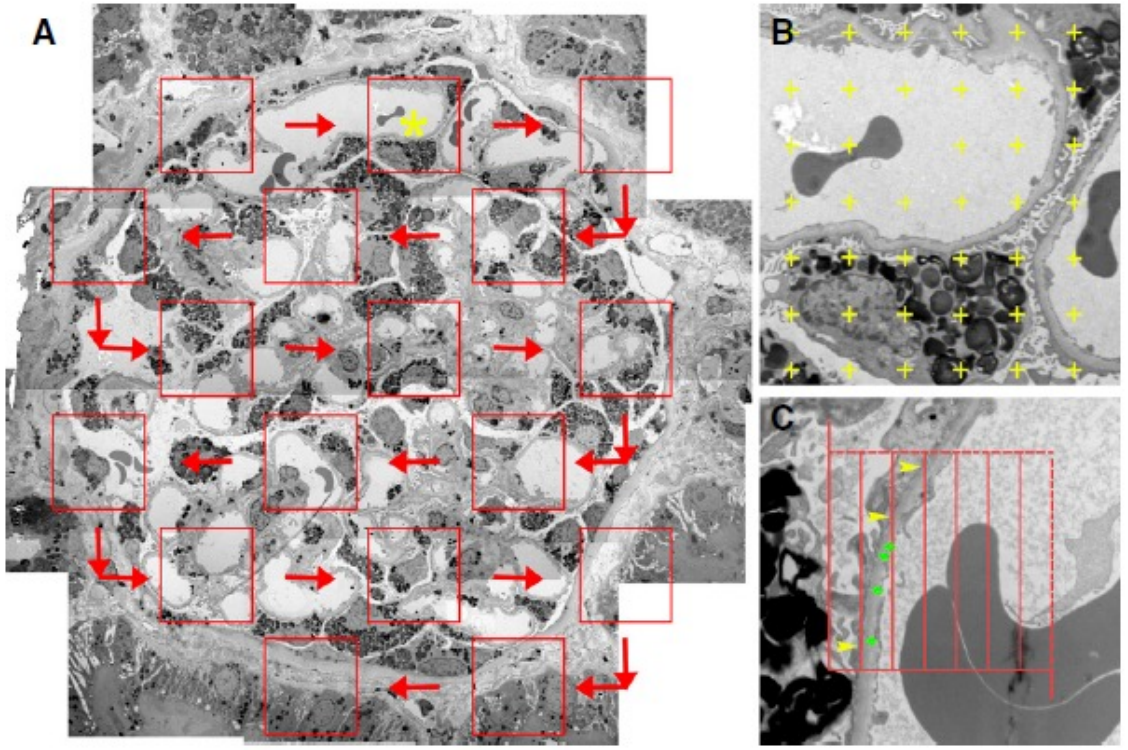
Rozenfeld et al, Mol Genet Metab

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

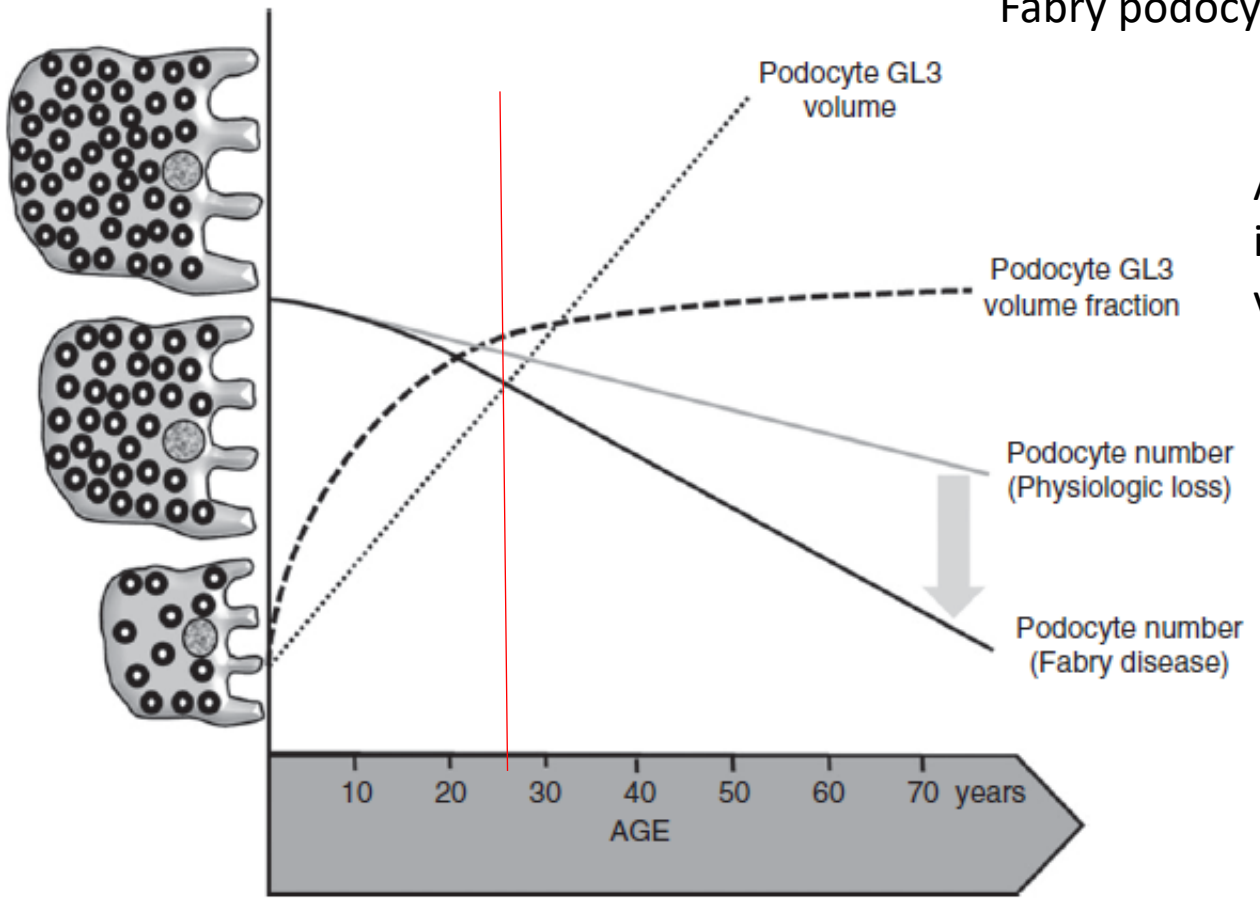
Behzad Najafian,[1] Camilla Tøndel,[2,3] Einar Svarstad,[3] Marie-Claire Gubler,[4] João-Paulo Oliveira,[5,6] and Michael Mauer[7,8]

JASN 31: 865–875, 2020

- N = 55 untreated males
- 4 to 60 y. (median age 26 Y.)
- Kidney biopsy for clinical trial
- Classic phenotype 80% (?)
  - Any patient with eGFR < 60ml/min/1,73m²
  - Numerous clinical and genetic missing data



GL3 volume and podocyte volume increase with age
Fabry podocyte = 4 times bigger than non Fabry podocyte



At 27 y. of age, the relative volume of GL3 inclusions reach a plateau at 63% of the cell volume

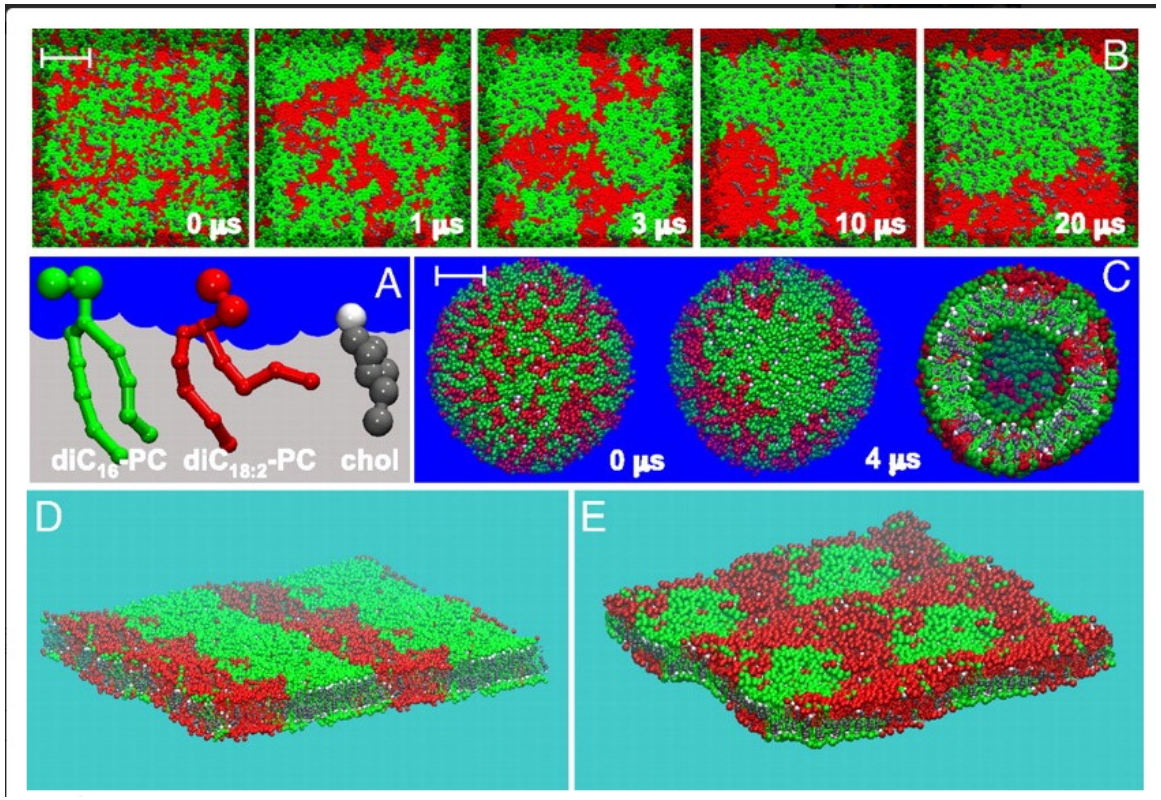
Independent prognostic factor associated with podocyte loss
- GL3 volume ($p<0,001$)
- Residual enzymatic activity ($p=0,001$)

⇒ Early treatment would theoretically be better

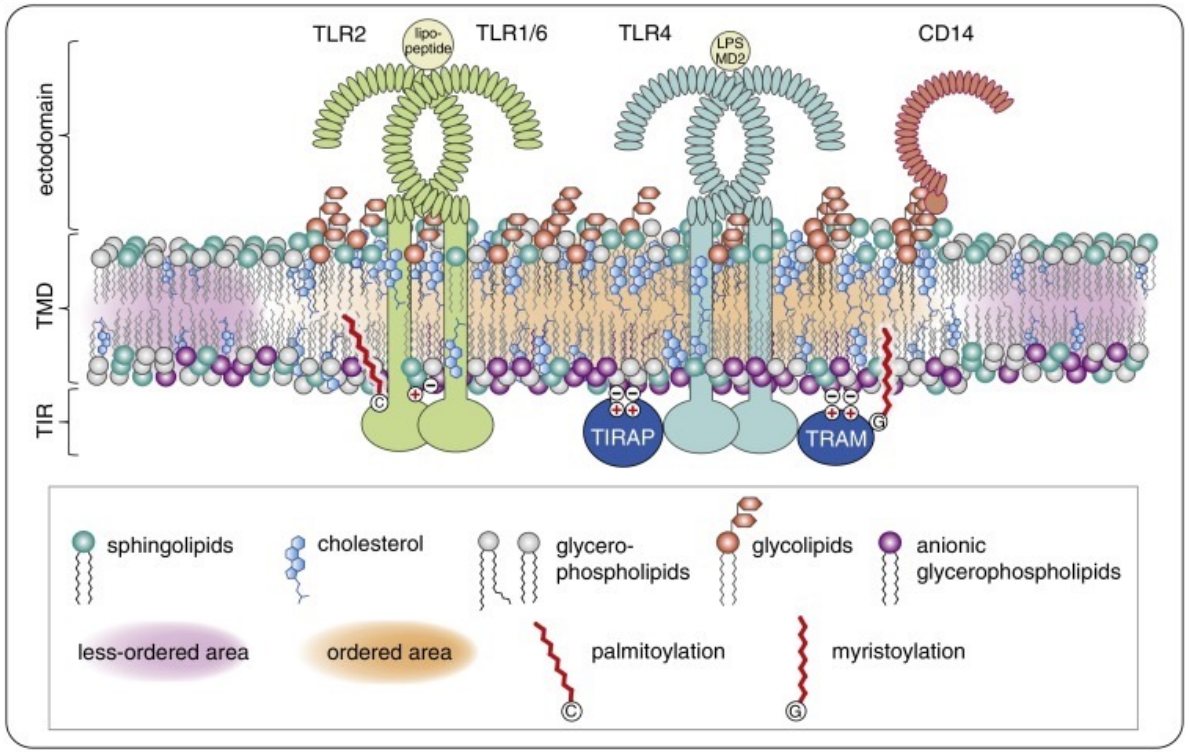
Figure 4. Visual depiction of proposed relationships between age and podocyte parameters in Fabry patients and normal controls. Relationships between aging and podocyte GL3 volume (dotted line), podocyte GL3 volume fraction (dashed line), and podocyte loss in Fabry disease (black bold line). The gray line represents physiologic podocyte loss with aging. Initially, the rate of GL3 accumulation is greater than the rate of podocyte enlargement, this leading to increasing podocyte GL3 volume fraction with increasing age up to 25–30 years of age. Thereafter, podocyte GL3 volume fraction plateaus while GL3 accumulation continues in parallel with podocyte enlargement, and this is associated with podocyte loss from aging aggravated by additional podocyte loss from Fabry disease.

Sphingolipids structure the lipid rafts

- Toll like receptors
- Receptors and inflammatory cascade (IL1b, TNFa…)



Risselada and Marrinck, PNAS 2008

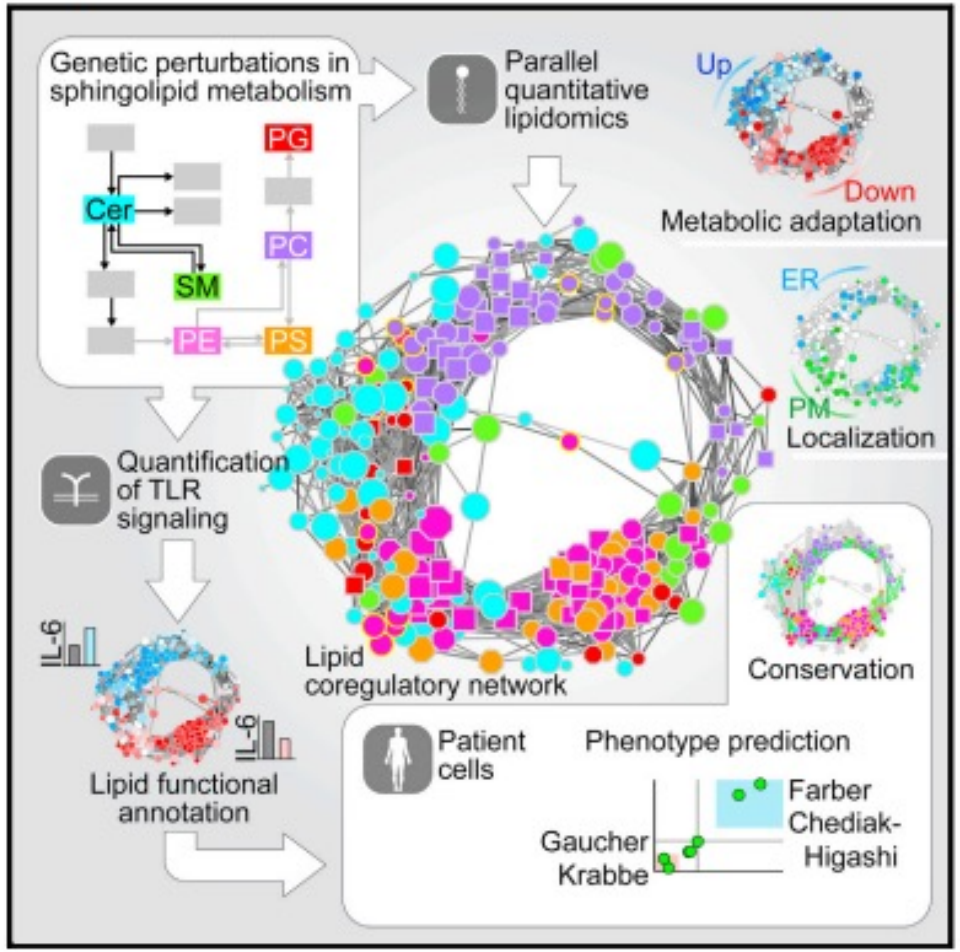


Villar et al., Methods in cell biol, 2016
Köberlin et al., Cell, 2015

Cell

A Conserved Circular Network of Coregulated Lipids Modulates Innate Immune Responses

Graphical Abstract



Authors

Marielle S. Köberlin, Berend Snijder, Leonhard X. Heinz, ..., Gregory I. Vladimer, Anne-Claude Gavin, Giulio Superti-Furga

Correspondence

gsuperti@cemm.oeaw.ac.at

In Brief

Combining lipidomics with genetic perturbations in immune cells reveals the logic of inter-lipid regulatory structure and enables the functional assignment of lipids to different steps of Toll-like receptor signaling. Moreover, quantitative lipidomics alone can predict the inflammatory response of patient-derived cells.

Excess of Gb 3 → **Disturbances in lipid-rafts structure** → **« uncoupling » of eNOS**

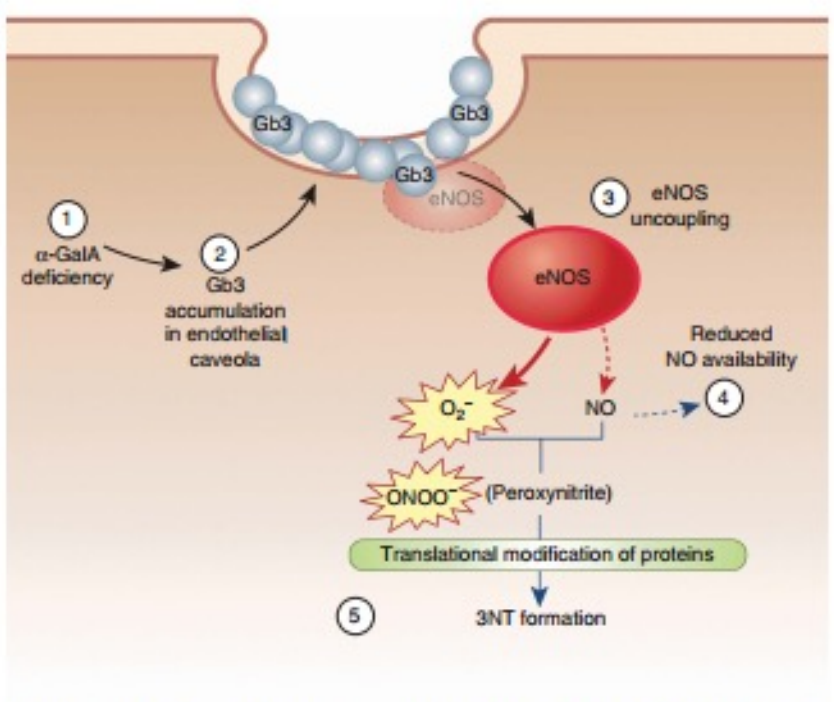


Figure 1 | Putative mechanism linking α-galactosidase A (α-GalA) deficiency and endothelial nitric oxide synthase uncoupling. Following α-GalA deficiency globotriaosylceramide (Gb3) accumulates within caveolae of endothelial cells. As a consequence, endothelial nitric oxide synthase (eNOS) is uncoupled, resulting in superoxide (O_2^-) production; NO is consumed to form peroxynitrite ($ONOO^-$), which leads to the formation of 3-nitrotyrosine (3NT).

Joly, Kidney Int 2014

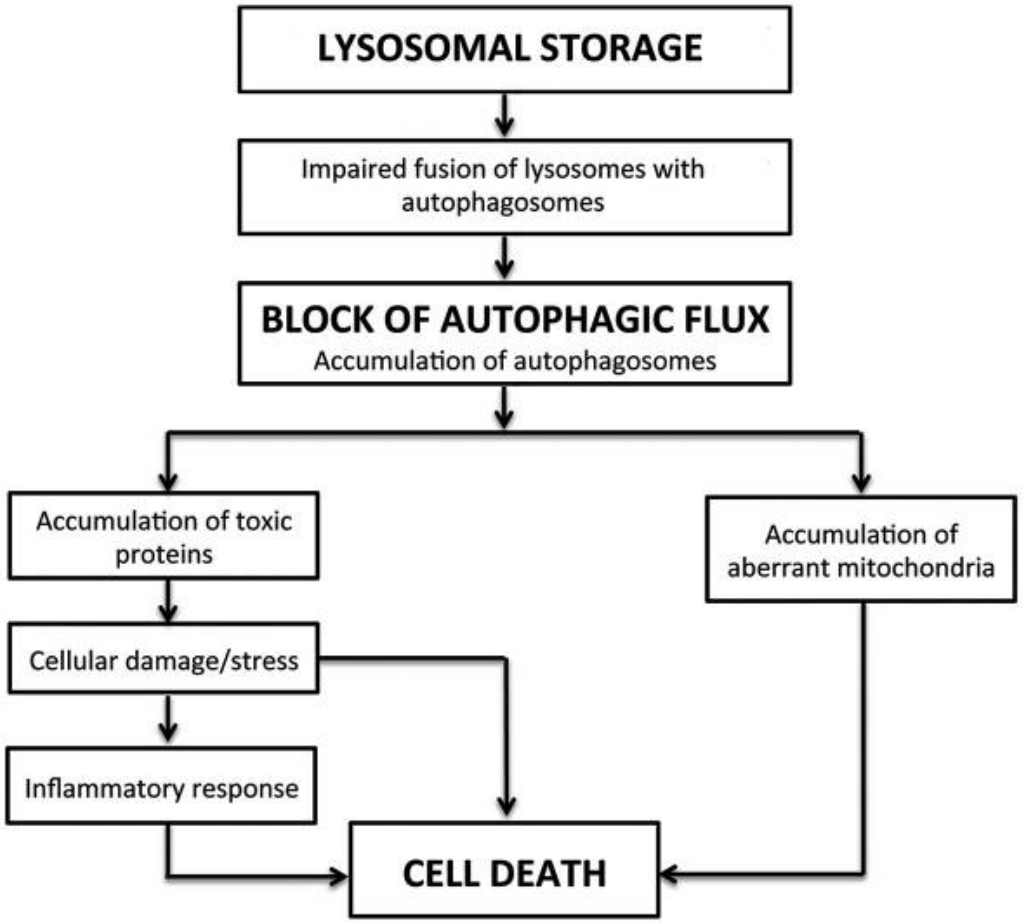
Peroxydated coumpounds such as 3NT
= Oxydative stress

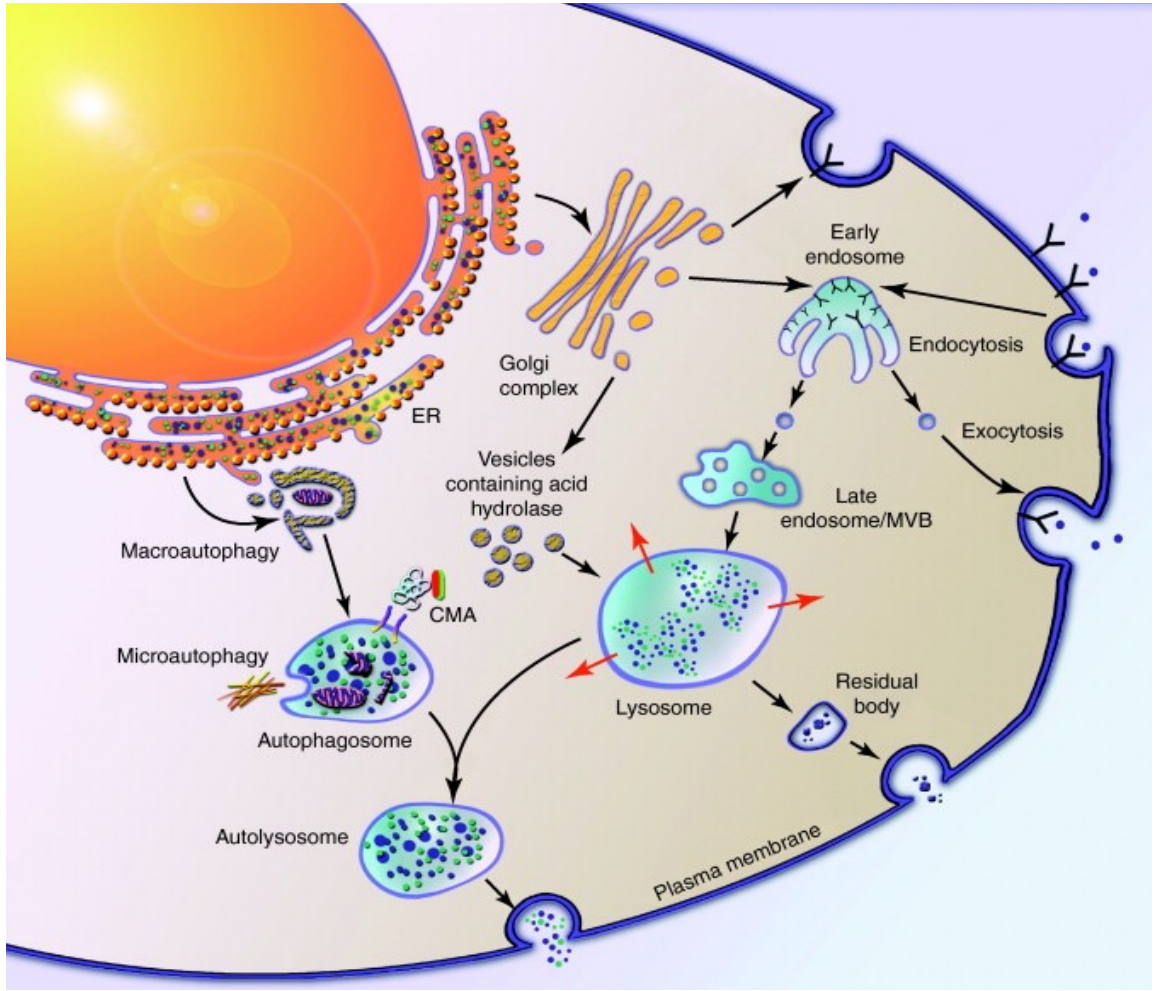
3NT = 3 NitroTyrosine

Enough to cause the fabry vasculopathy ?
Shu et al, Kidney int, 2014

eNOS gene polymorphism (Marin-Medina, 2016)

AUTOPHAGY





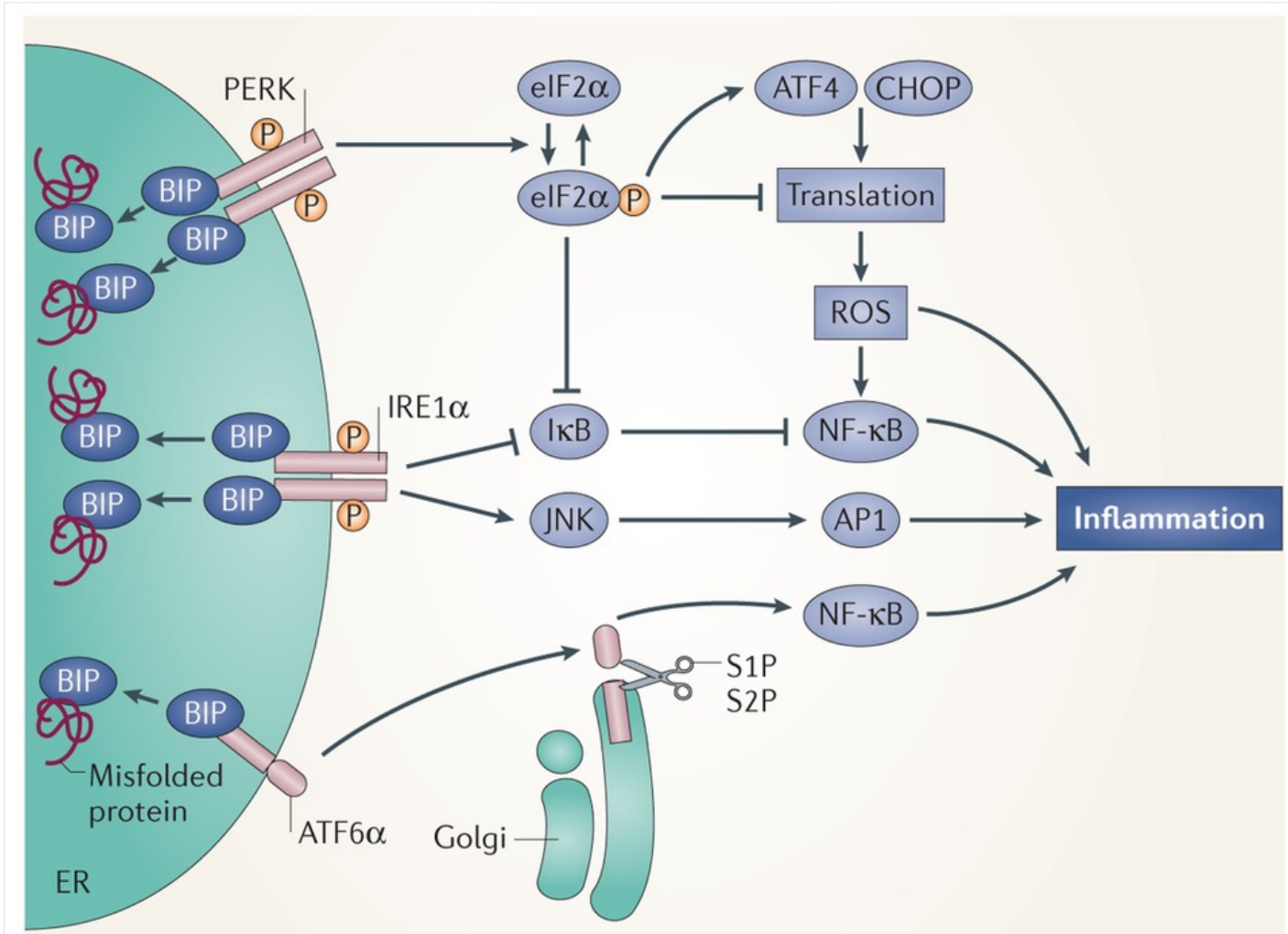
Lieberman et al., Autophagy, 2012
Chévrier et al., Autophagy, 2010

MISFOLDED PROTEINS AND ER STRESS

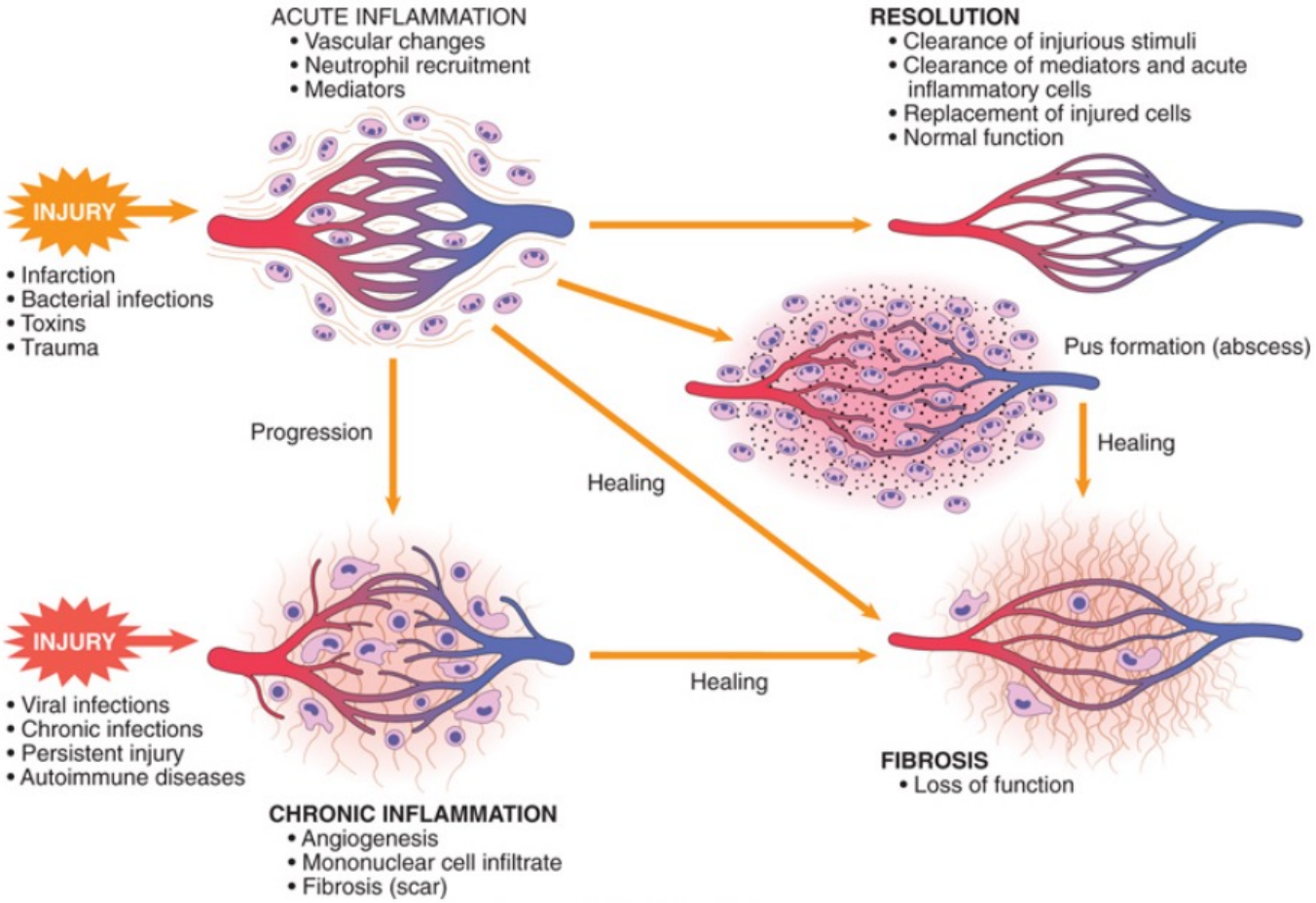
The impact of the endoplasmic reticulum protein-folding environment on cancer development

Miao Wang & Randal J. Kaufman

Nature Reviews Cancer **14**, 581–597 (2014) | doi:10.1038/nrc3800



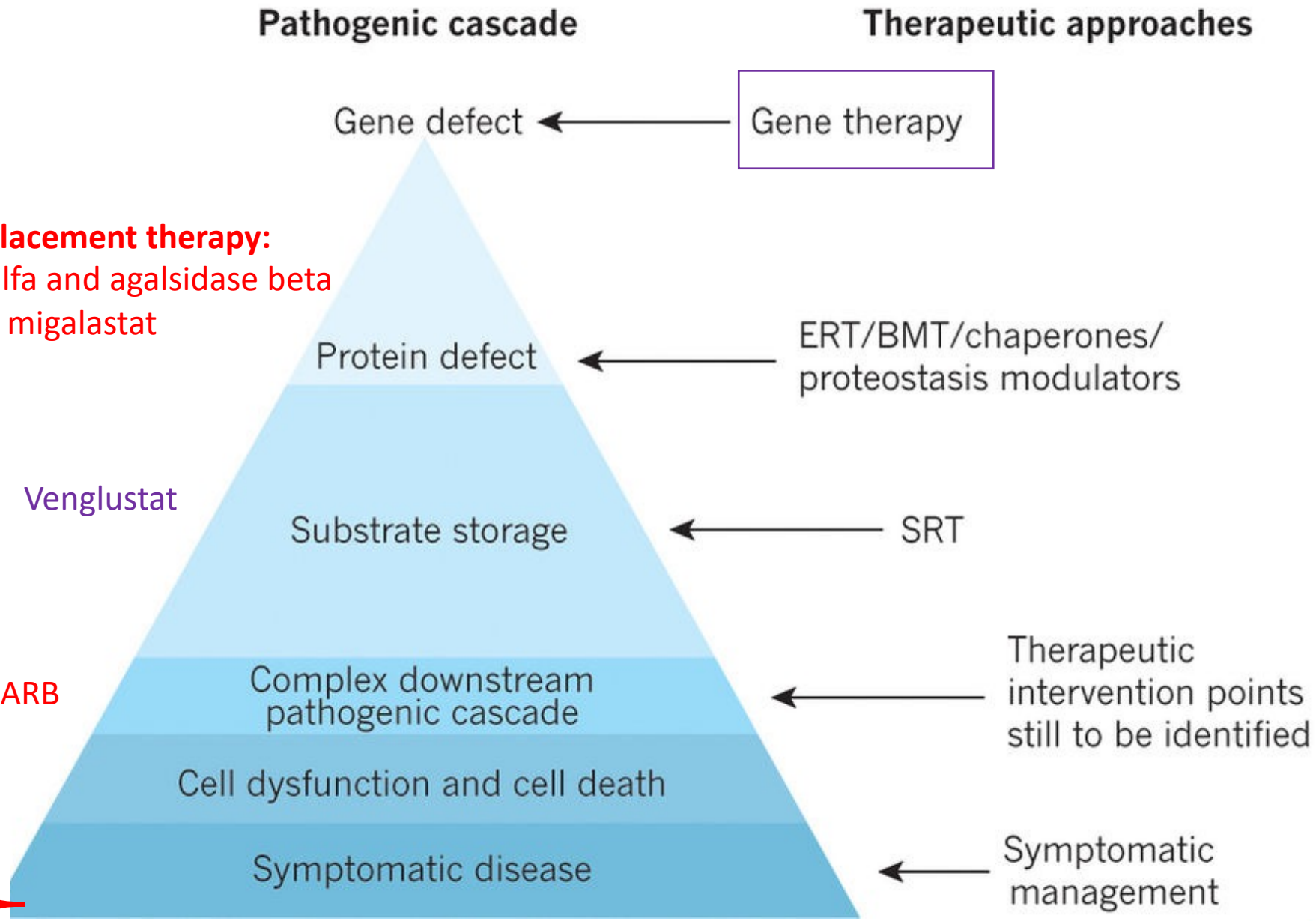
Chronic inflammation leads to fibrosis and loss of function



- Epithelial-mesenchymal transition of tubular epithelial cells due to Gb3 and lysoGb3 (Jeon 2015)
- Cardiac fibrosis (Weidemann, 2013)

TREATMENT

Enzyme replacement therapy:
agalsidase alfa and agalsidase beta
Chaperone: migalastat



Venglustat

ACEi or ARB

Neuropathic painkillers
Anticoagulant, cardiac device…
Preventive care (tobacco, etc…)
Supportive psychological care

Adapted from Platt, Nature 2014

ENZYME REPLACEMENT THERAPY: AGALSIDASE ALFA OR AGALSIDASE BETA

	agalsidase alfa	agalsidase beta
Marketing	Replagal®	Fabrazyme®
Pharmaceutical	Shire-Takeda	Genzyme-Sanofi
Product.	Human fibroblast	Chinese Hamster Ovary
	Intravenous infusion	
Dose /14d.	0.2 mg/kg	1 mg/kg
Patients	All Fabry patients	

Differences in terms of glycosylation sites

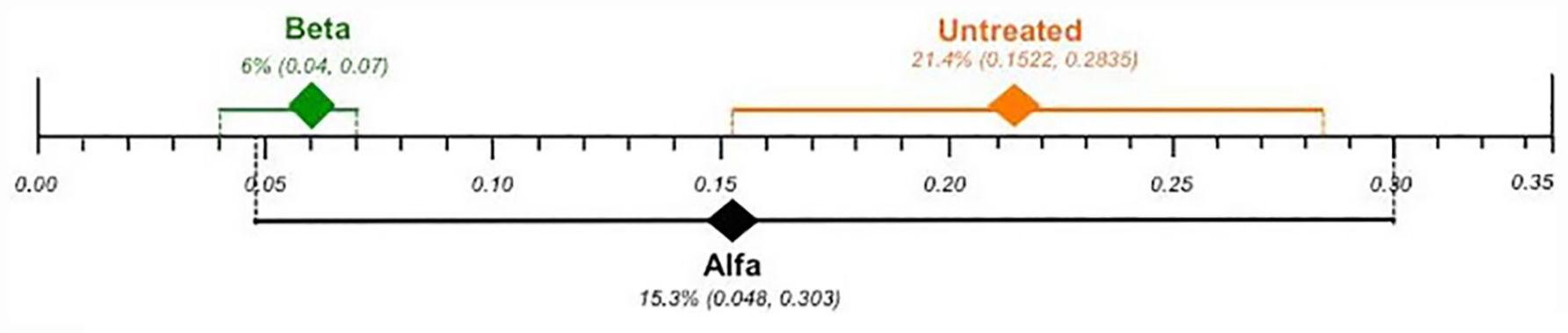
Immunogenicity: Inhibitory anti-agalsidase antibodies in patients with no residual enzyme activity (males with classic phenotype)

The dose matters: to date, preference for higher dose of ERT

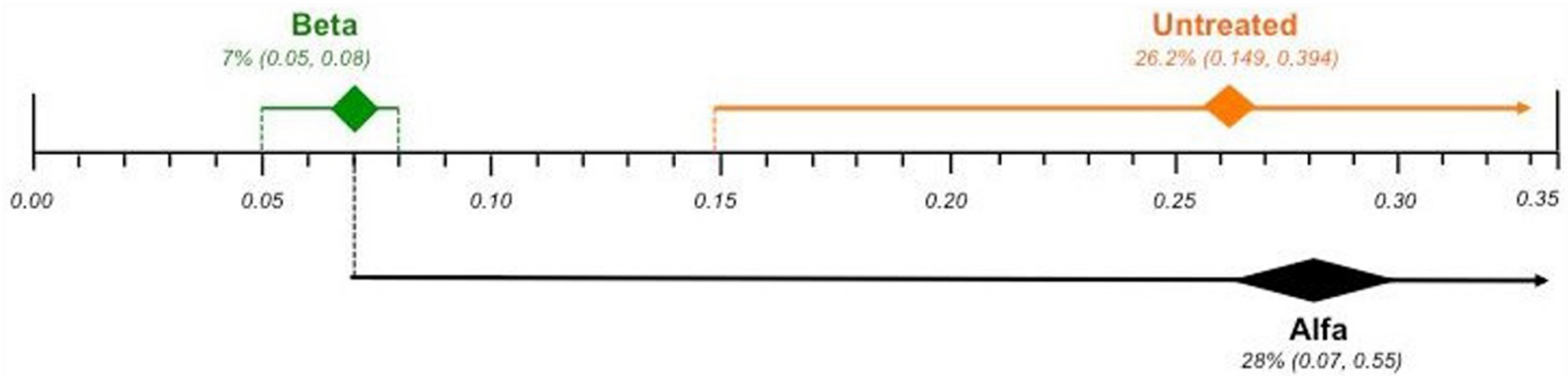
Enzyme replacement therapy for Anderson-Fabry disease: A complementary overview of a Cochrane publication through a linear regression and a pooled analysis of proportions from cohort studies

Regina El Dib[1,2]*, Huda Gomaa[3], Alberto Ortiz[4], Juan Politei[5], Anil Kapoor[2], Fellype Barreto[6]

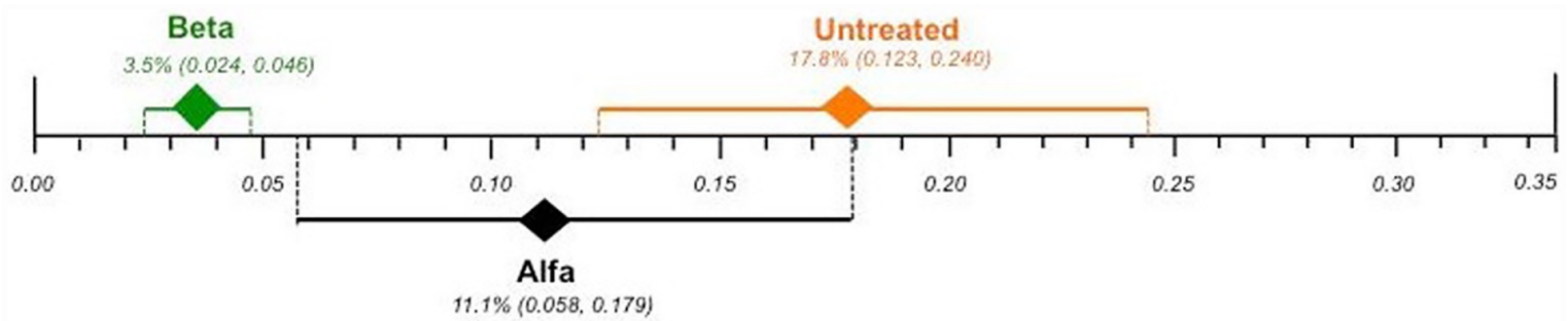
PLoS One 2017



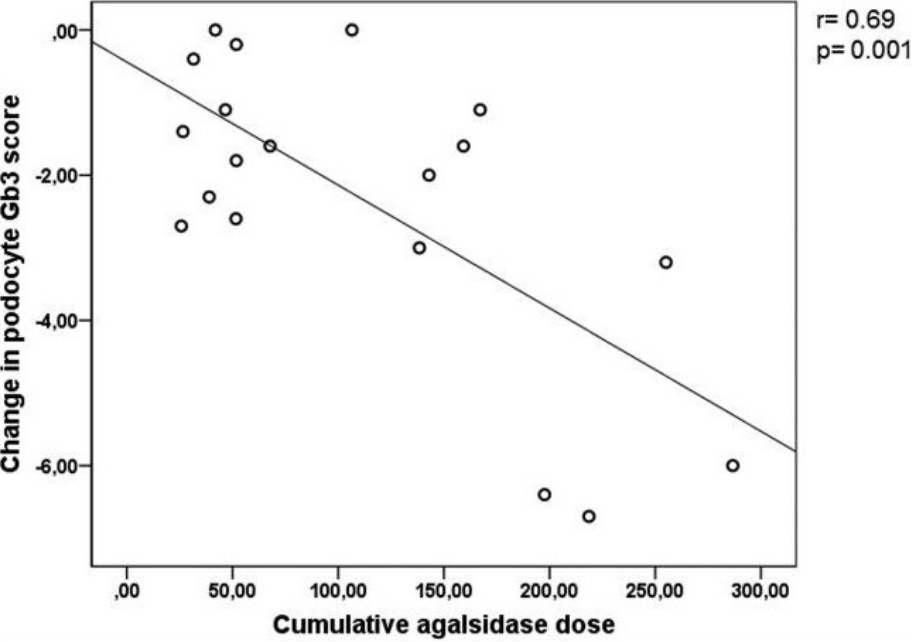
Renal events: end stage kidney disease needing dialysis; or kidney transplantation;



Cardiovascular events: myocardial infarction; needing cardiovascular devices; severe arrhythmia; or congestive heart failure;



Cerebrovascular events: stroke; or transitory ischemic attack.



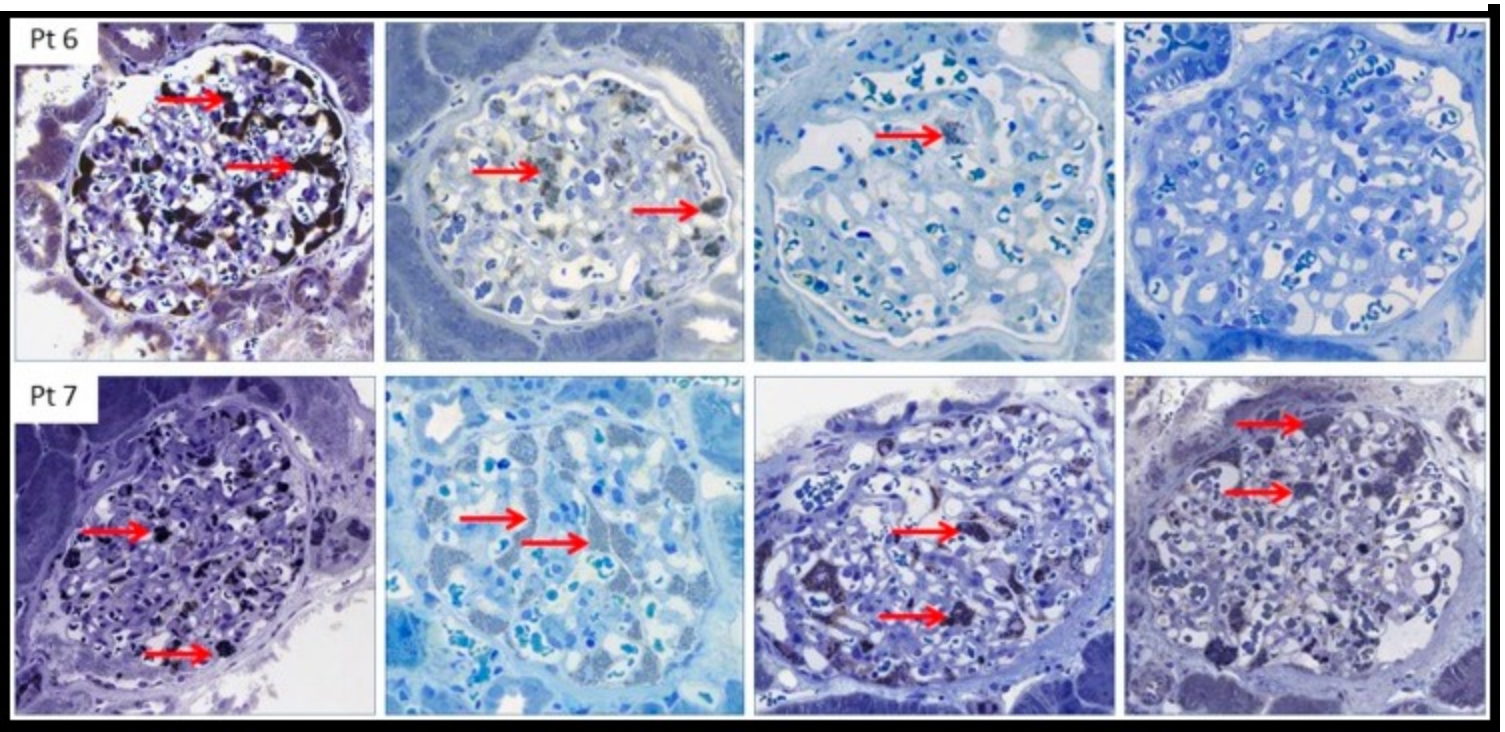
Clin J Am Soc Nephrol. 2017 Sep 7; 12(9): 1470–1479.
Published online 2017 Jun 16. doi: 10.2215/CJN.01820217
PMCID: PMC5586567
PMID: 28625968

Long-Term Dose-Dependent Agalsidase Effects on Kidney Histology in Fabry Disease

Rannveig Skrunes,[✉*†] Camilla Tøndel,[†‡] Sabine Leh,[†§] Kristin Kampevold Larsen,[§] Gunnar Houge,[‖] Einar Skulstad Davidsen,[¶] Carla Hollak,[**††] André B.P. van Kuilenburg,[‡‡] Frédéric M. Vaz,[‡‡] and Einar Svarstad[*†]

N = 20 patients
Males = 12
15 patients started ERT with eGFR > 90 ml/min

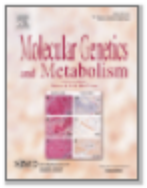
ERT: 2years 3years 7 years 13 years



Cumulative dose effect

Earlier is better

Molecular Genetics and Metabolism
Volume 123, Issue 4, April 2018, Pages 416-427



Minireview

Fabry disease revisited: Management and treatment recommendations for adult patients

Alberto Ortiz [a], Dominique P. Germain [b], Robert J. Desnick [c], Juan Politei [d], Michael Mauer [e], Alessandro Burlina [f], Christine Eng [g], Robert J. Hopkin [h], Dawn Laney [i], Aleš Linhart [j], Stephen Waldek [k], Eric Wallace [l], Frank Weidemann [m], William R. Wilcox [i]

Given the biochemical similarity of the products, the five-fold difference in the labeled doses (and related difference in infusion duration), and the need for effective early treatment to prevent or mitigate disease progression, the choice of ERT formulation should be based on the dose necessary to optimize clinical outcomes

FUTURE:

ORIGINAL ARTICLE | Open Access

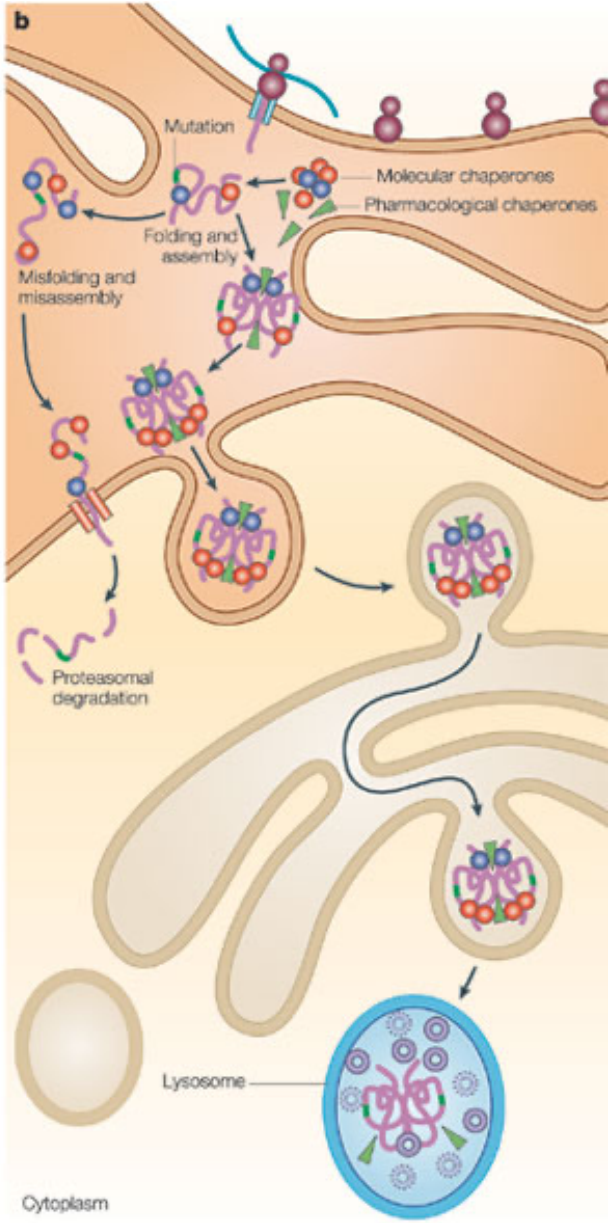
Pegunigalsidase alfa, a novel PEGylated enzyme replacement therapy for Fabry disease, provides sustained plasma concentrations and favorable pharmacodynamics: A 1-year Phase 1/2 clinical trial

Raphael Schiffmann, Ozlem Goker-Alpan, Myrl Holida, Pilar Giraldo, Laura Barisoni, Robert B. Colvin, Charles J. Jennette, Gustavo Maegawa, Simeon A. Boyadjiev, Derlis Gonzalez ... See all authors

- Pegunigalsidase alfa, Chiesi Therapeutics
- Expectations:
  - Better pharmacodynamics
  - Less immunogenicity
  - Monthly infusion
- Ongoing clinical trial

CHAPERONE THERAPY:

- Migalastat = Galafold®, Amicus Therapeutics®
- Oral: 123mg/ 48h away from meals (2h before and after!)
- Only available for « amenable » GLA variants
- Amenable variant if enzymatic activity in transfected-HEK model is increased > 1,2 fold or > 3 % with 10µM migalastat compared to without
- https://www.galafoldamenabilitytable.com/hcp
- Only 30-50% of patients
  - Missense mutations
  - Often associated with non classic phenotype



Mc Cafferty and Scott, Drugs, 2019

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Fabry's Disease with the Pharmacologic Chaperone Migalastat

D.P. Germain, D.A. Hughes, K. Nicholls, D.G. Bichet, R. Giugliani, W.R. Wilcox, C. Feliciani, S.P. Shankar, F. Ezgu, H. Amartino, D. Bratkovic, U. Feldt-Rasmussen, K. Nedd, U. Sharaf El Din, C.M. Lourenco, M. Banikazemi, J. Charrow, M. Dasouki, D. Finegold, P. Giraldo, O. Goker-Alpan, N. Longo, C.R. Scott, R. Torra, A. Tuffaha, A. Jovanovic, S. Waldek, S. Packman, E. Ludington, C. Viereck, J. Kirk, J. Yu, E.R. Benjamin, F. Johnson, D.J. Lockhart, N. Skuban, J. Castelli, J. Barth, C. Barlow, and R. Schiffmann

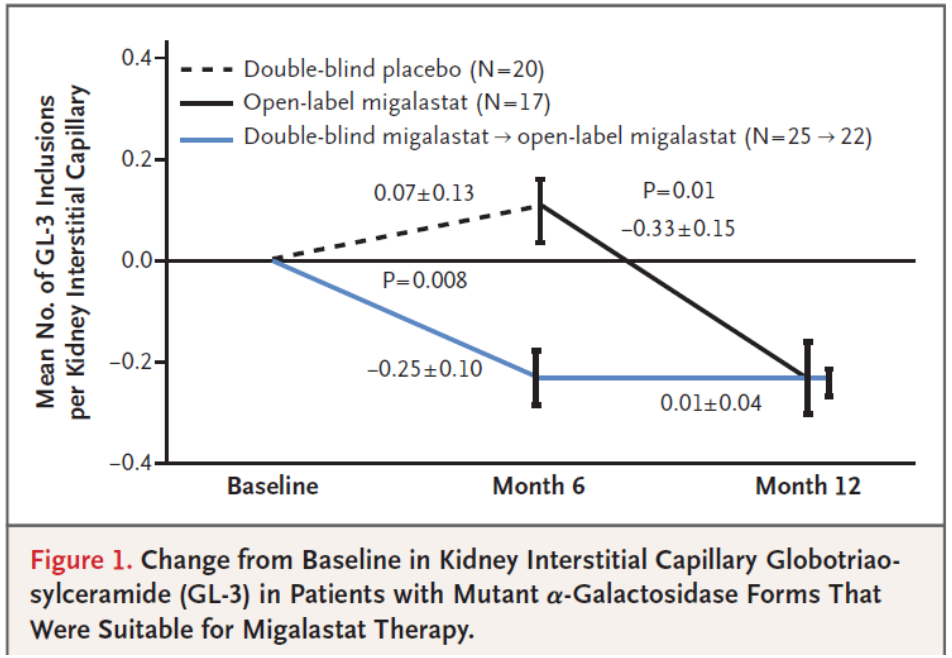


Figure 1. Change from Baseline in Kidney Interstitial Capillary Globotriaosylceramide (GL-3) in Patients with Mutant α-Galactosidase Forms That Were Suitable for Migalastat Therapy.

Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study

Hughes DA et al, J Med Genet 2017

Table 5 Echocardiography-derived changes in patients with amenable mutations

Parameter	Baseline mean	Change from baseline to month 18 (95% CI)
Migalastat: LVMi (g/m^2)		
All (n=33) (% abnormal)	95.3 (39)	−6.6 (−11.0 to −2.2)*
LVH† at baseline (9 females and 4 males)	116.7	−8.4 (−15.7 to 2.6)
ERT: LVMi (g/m^2)		
All (n=16) (% abnormal)	92.9 (31)	−2.0 (−11.0 to 7−0)
LVH† at baseline (n=5) (1 female and 4 males)	123.3 (100%)	4.5 (−20.9 to 30.0)

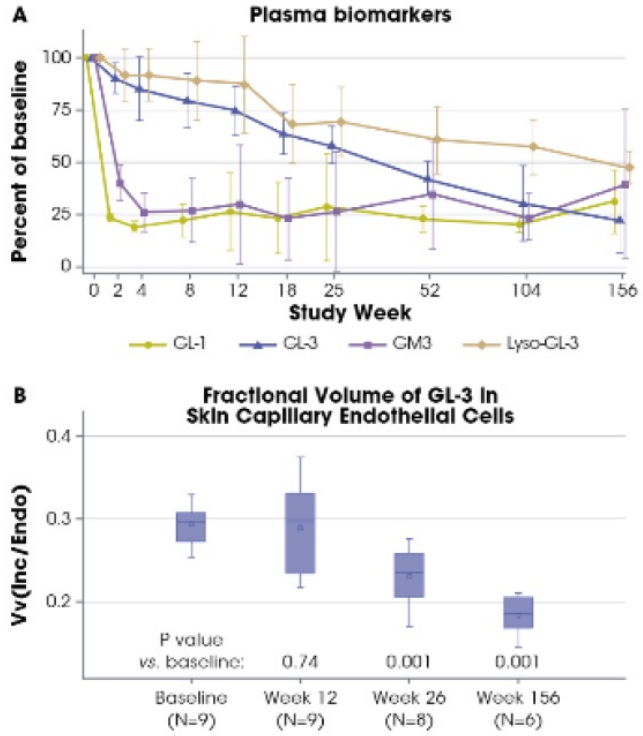
Early warnings concerning eGFR decreases under migalastat (eGFR -6 ml/min/y.) (Lenders et al. Clin pharm Ther 2020)

"the annualized $eGFR_{CKD\text{-}EPI}$ change was minimal (mean: -0.1 and 0.1 mL/min/1.73 m^2 in ERT-naive and ERT-experienced patients, respectively) (…) patients with Fabry disease and amenable GLA variants receiving long-term migalastat treatment (≤8.6 years) maintained renal function irrespective of treatment status, sex, or phenotype" (Bichet et al. Mol genet Metab rep, 2021)

THE FUTURE IS TODAY

- **Oral substrate reduction therapy with venglustat (poster World 2022, Najafian et al)**

Figure 1. Percentage reduction in plasma biomarkers detected using electron microscopy GL-1, GL-3, GM3 and Lyso-GL-3 from baseline (A) and factional volume of GL-3 in skin capillary endothelial cells (B) in male patients with classic FD treated with venglustat for up to three years[6-8]



Phase 3 trial ongoing

- **Gene therapy**

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Showing 1-10 of **18** studies 10 studies per page

Row	Saved	Status	Study Title
1	☐	Enrolling by invitation	Long-Term Follow-up Study of Subjects With **Fabry Disease** Who Received Lentiviral **Gene Therapy** in Study AVRO-RD-01-201
2	☐	Recruiting	An Open-label, Phase 1/2 Trial of **Gene Therapy** 4D-310 in Adult Males With **Fabry Disease**
3	☐	Recruiting	Dose-Ranging Study of ST-920, an AAV2/6 Human Alpha Galactosidase A **Gene Therapy** in Subjects With **Fabry Disease**
4	☐	Recruiting	A **Fabry Disease Gene Therapy** Study
5	☐	Recruiting	A Long Term Follow-Up Study of **Fabry Disease** Subjects Treated With FLT190

QUESTION: WOULD YOU INTRODUCE SPECIFIC THERAPY IN FABRY PATIENTS WITH END-STAGE RENAL FAILURE?

- YES
- NO

QUESTION: WOULD YOU TREAT PATIENTS WITH END-STAGE RENAL FAILURE?

1. Need to protect the heart : cardiovascular is nowadays the leading cause of death in Fabry patients

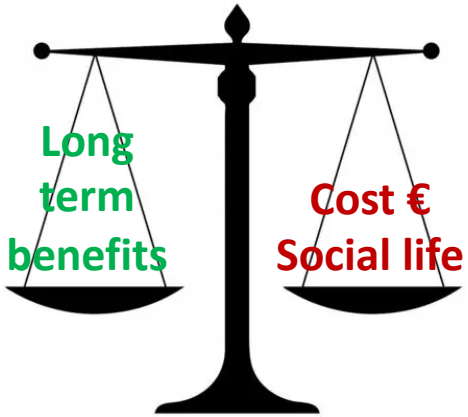
2. No enzymatic cross-correction from renal transplant !

WHO & WHEN PATIENTS SHOULD BE TREATED

- Never an emergency !

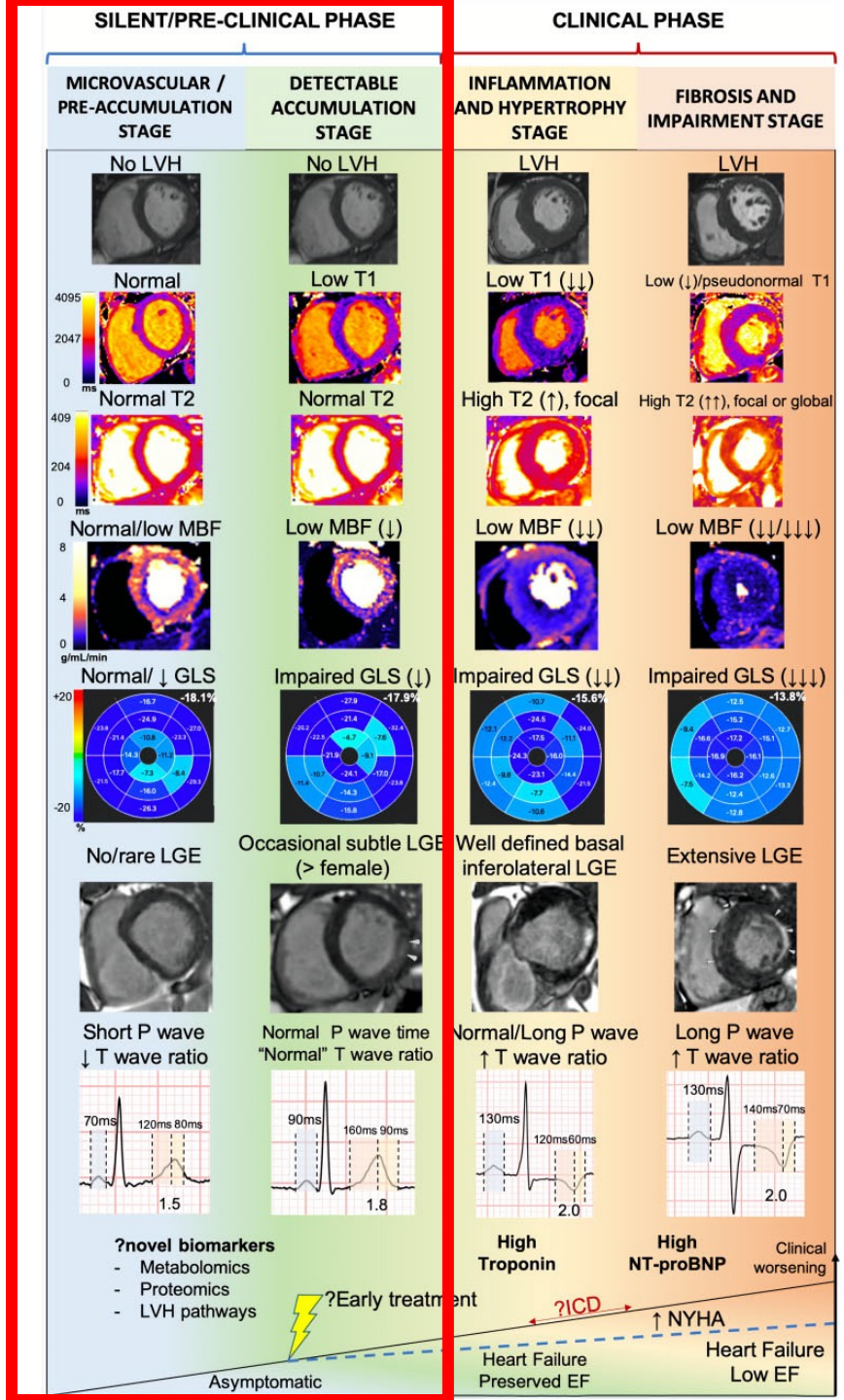
- Need to know the history of the disease
  - Genetic variant : VUS vs non-classic vs classic phenotype
  - Familial history (probable genetic polymorphism)

- Ideal timing = pre-symptomatic
  - Male :
    - Classic patients
      - Systematic treatment = Earlier is better.
      - Social burden of ERT
    - Non-classic patients
      - Ideally start treatment at a presymptomatic stage: cardiac MRI, longitudinal strain in cardiac echography
  - Female:
    - Very difficult to predict the disease
      - Classic variant: proteinuria
      - Non-classic variant: holterECG



MBF: myocardial blood flow

GLS: global longitudinal strain



Augusto JB et al, Eur Heart J. 2020

T1 mapping : normal > hypoT1

T2 mapping : normal > hyperT2

MBF: normal > hyposignal
=> Early microvascular disease?

GLS: normal > decrease => early myocardium/ vascularisation uncoupling?

Gadolinium Enhancement : 0 => extended

P wave : short > normal > prolonged
=> Intra atrial conduction acceleration thanks to sphigolipids deposits then extracellular remodeling

T wave ratio: short > prolonged

DIACONESSES CROIX S' SIMON

GENETIC CONSELING : X-LINKED DISEASE

1 patient = 1 family

Acnowledgements

- **Patients and families**

- **Patient's associations:**
  - **APMF**
  - **VML**

- **CRML**

- **Co-workers**
  - Groupe collaboratif français
- **Collaborators**
  - **Physicians**
  - **Biochemists**
  - **Geneticists**
  - **……**

THANK YOU

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NEXT WEBINARS

19/04/22

<u>Methylmalonic acidemia</u>
Anais Brassier & Manuel Schiff (Paris, France)

03/05/22

<u>Collagenopathies</u>
Roser Torra (Barcelona, Spain)

17/05/22

<u>Reno-vascular hypertension</u>
Jelena Stojanovic (London, UK)

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