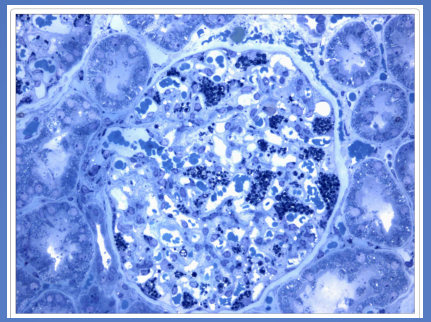
The Canadian Society of Nephrology wishes to thank the following sponsors for their unrestricted educational grant

Dr. West is currently Professor, Division of Nephrology Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada, past President Canadian Society of Nephrology, Director Nova Scotia Fabry Disease Clinic and Chair of the Scientific Committee of Canadian Fabry Disease Initiative Registry, a multicentre outcomes study of Fabry disease. He received his MD from Queen's University, Kingston, Ontario and did post graduate training at Dalhousie University and the University of Toronto.

Fabry Disease: not so rare, just hard to recognize

March 10, 2021



From Germain OJRD 2010

Dr. Michael L. West

Division of Nephrology, Department of Medicine

Dalhousie University

Halifax NS

DALHOUSIE UNIVERSITY *Inspiring Minds*

cfdi CANADIAN FABRY DISEASE INITIATIVE

CENTRE FOR GENOMICS ENHANCED MEDICINE

Disclosures

Dr. West has received research funding, speaker's fees and/or consultant fees from the following:

Amicus
AvroBio
Idorsia
Protalix
Sanofi-Genzyme
Takeda

Dr. West shares IP in Fabry gene therapy and Fabry cardiac biomarkers.

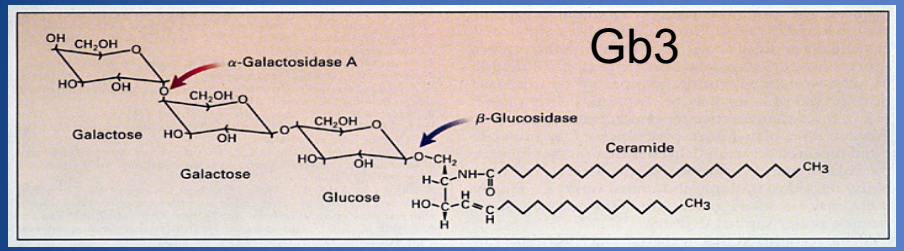
Objectives

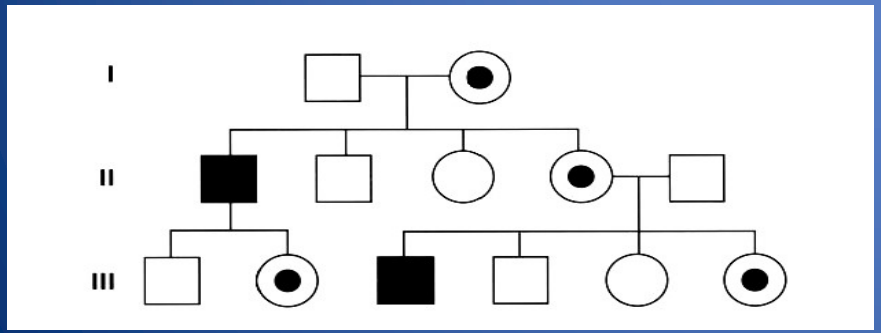
Participants will be able to

- identify the signs and symptoms of FD
- recognize the importance of earlier diagnosis
- recall screening methods for FD
- describe specific therapies for FD

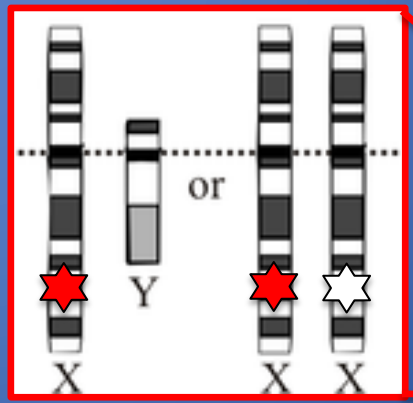
(Anderson)-Fabry Disease

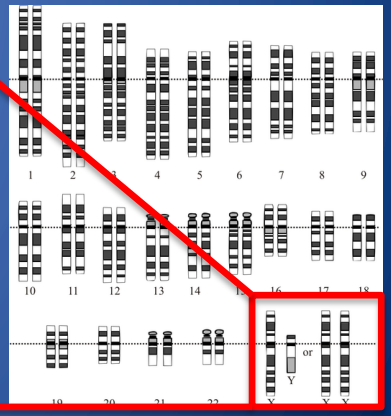
- inborn error of glycosphingolipid metabolism due to decreased activity of lysosomal enzyme α-galactosidase A (α-gal)

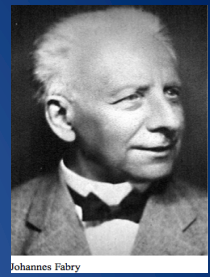


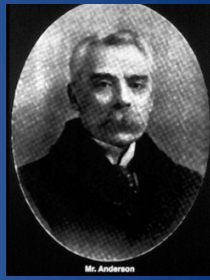


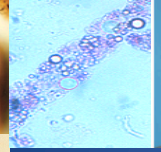
- GLA gene Xq22 region
- 1000+ mutations

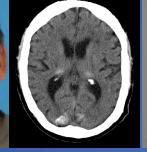
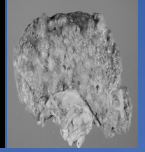




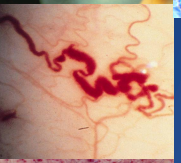
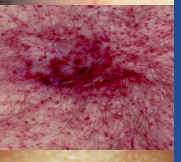
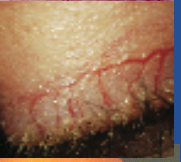
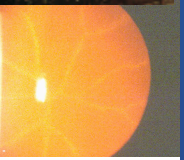
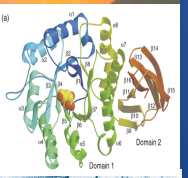
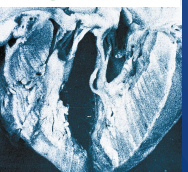

Johannes Fabry


Mr. Anderson

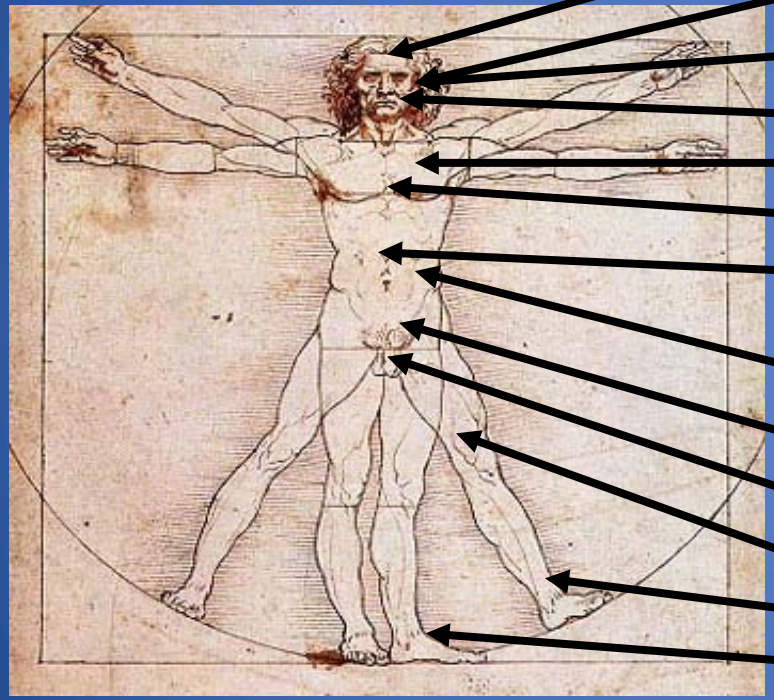



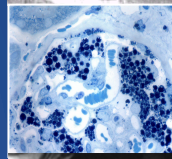
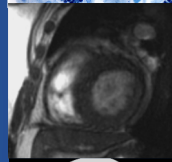
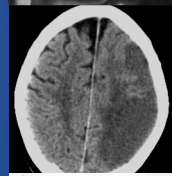
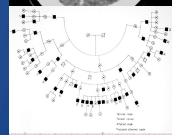
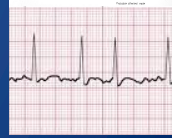
Fabry Disease - Clinical Features

Vitruvian Man Leonardo DaVinci



- stroke, TIA
- hearing loss, tinnitus
- psychiatric, eye disease
- abnormal facial appearance
- dyspnea, cough
- heart failure, dysrhythmias
- abdominal pain, cramps, diarrhea, weight loss, nausea
- kidney failure
- angiokeratomas
- infertility
- aches and pains, osteopenia
- Acroparathesia
- edema, pseudoclubbing

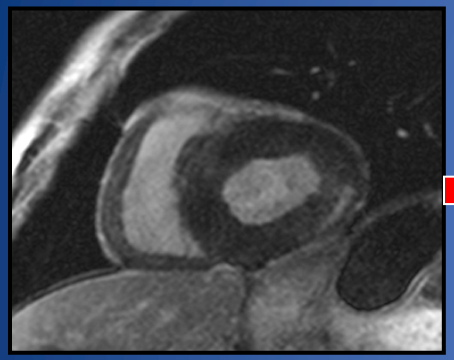
Samiy Survey Ophth 2008;53:416; Sodi Br J Ophth 2007;91:210; https://www.fabrycommunity.com/en/Healthcare/About/Diagnosing/Ophthalmologists.aspx; Michaud J Ophthalmology 2013.doi.org/10.1155/2013/207573; Ries Genet Med 2006;8(2):96; Alroy JASN 2002 13:S134; Sanofi-Genzyme; own pictures.

Phenotypes

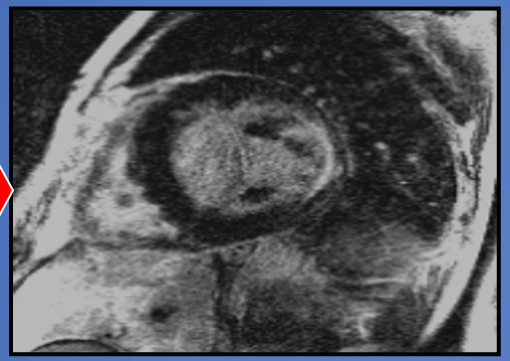
	Type I Classic		Type II Variant
	Male X*Y	**Female X*X**	
Onset	Early-childhood		Late-middle aged adult
Severity	Moderate to severe	Mild to severe	Mild to moderate
Organ involvement	All systems		Cardiac, renal; other organs limited
Mutations	Majority e.g. A143P		Select few e.g. N215S
A-gal activity	<5%	5-100%	5-30%
Gb3 deposits	Extensive, all cell types		Limited, cardiomyocytes, podocytes

Fabry Cardiomyopathy

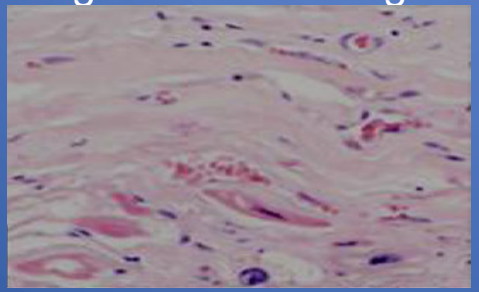
50% of patients display fibrosis assessed by late enhancement cMRI Moon *et al* Eur Heart J 2003



midmyocardial fibrosis + LVH



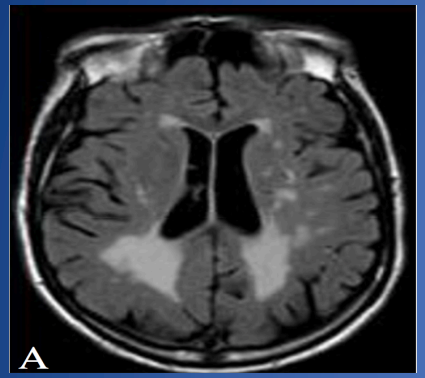
transmural fibrosis + regional LV-thinning



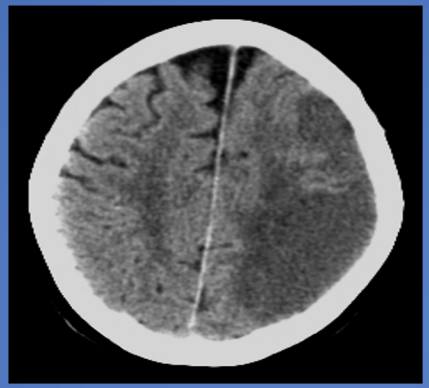
Courtesy of Dr F Weidemann Wuertzburg Takenaka et al J Cardiol 2008;108:50

- decr HR variability, incr PR
- arrhythmias-SV, V, tachy, brady, WPW
- sudden cardiac death
- HCM, prominent papillary muscle, MVP
- diastolic HF
- chest pain: small vessel disease
- hypertension
- abnormal coronary microvascular function

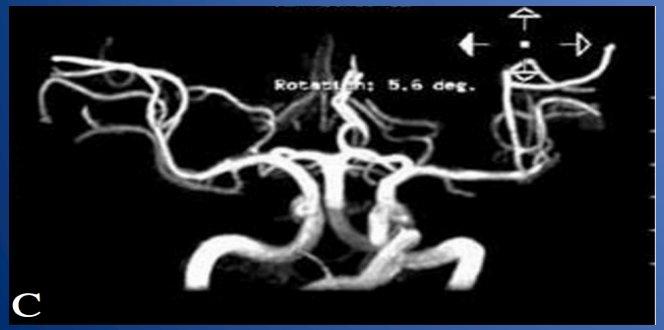
Fabry Neurologic Disease



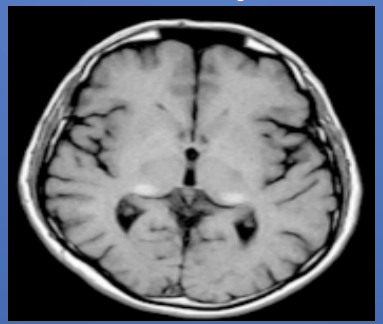
White matter lesions



Stroke < 55 yrs



Dolichoectasia



Pulvinar sign

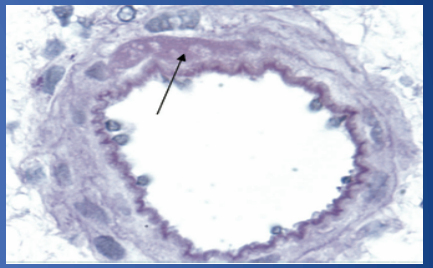
- sensory peripheral neuropathy - acroparesthesiae
- hearing loss, tinnitus, vertigo
- autonomic neuropathy, hypo/hyperhidrosis
- neuro-ophthalmologic disease
- distal ischemic myopathy
- cognitive impairment

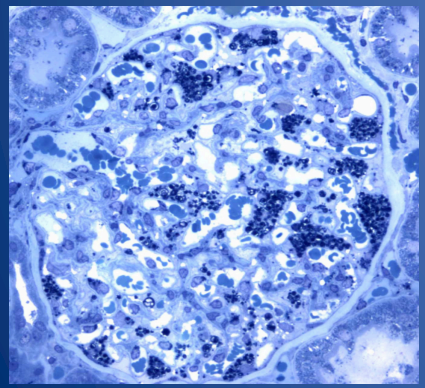
Germain OJRD 2010;5:30;
Fellgiebel Lancet Neurol 2006;5:791

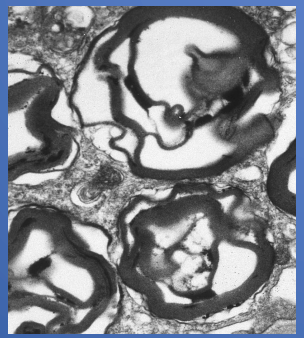
Fabry Nephropathy

- Gb3 deposits in podocytes, all kidney cells
- pathologic changes before abnormal GFR, albuminuria
- deposits early in both males, females
- why do so few women progress to ESRD?
- why do males and females start dialysis at same mean age?

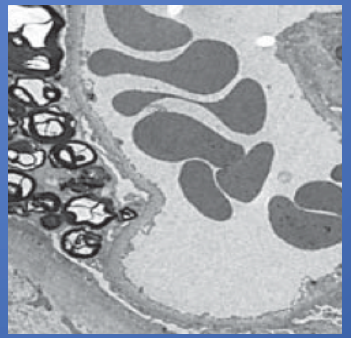
Vascular sclerosis



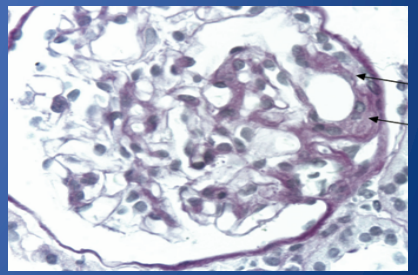




Foot process effacement



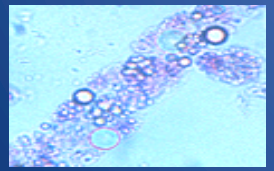
FSGS

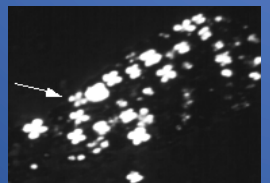


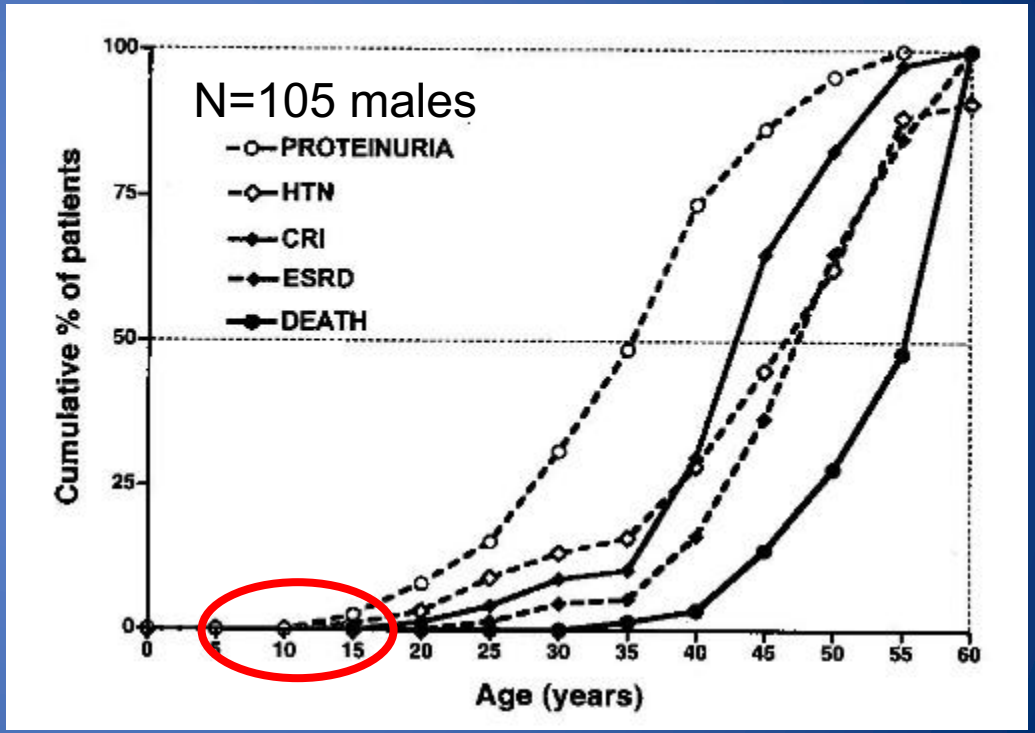
Germain OJRD 2020;5:30; Atlas of Renal Pathology.
http://www.ajkd.org/pb/assets/raw/Health%20Advance/journals/yajkd/atlas37_4.htm; Tondel et al Am J Kidney Dis 2008;51:767; Tondel

Fabry Renal Disease

- progressive since in utero
- isolated proteinuria, hematuria, lipiduria without proteinuria
- CKD 30's
- dialysis mean age 42
  (Thadhani et al Kid Intern 2002;61:249)
- hypertension late

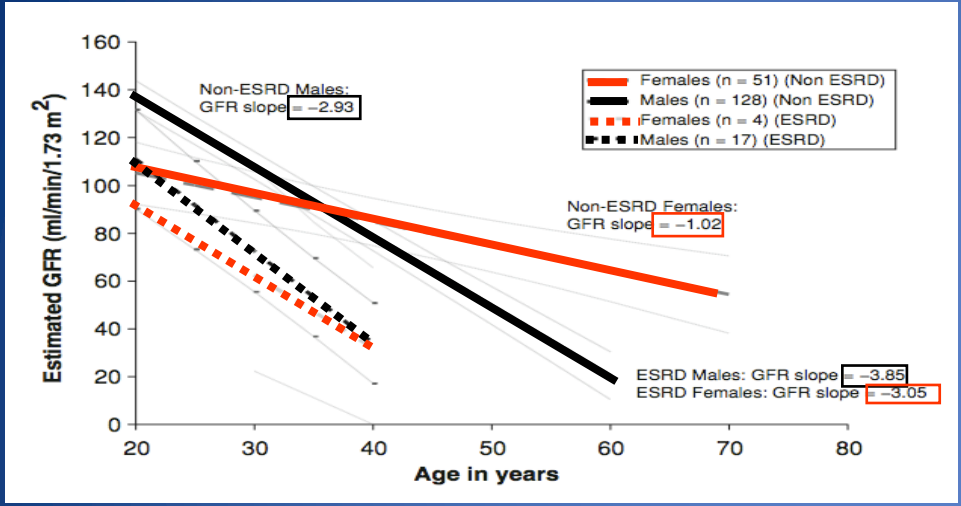


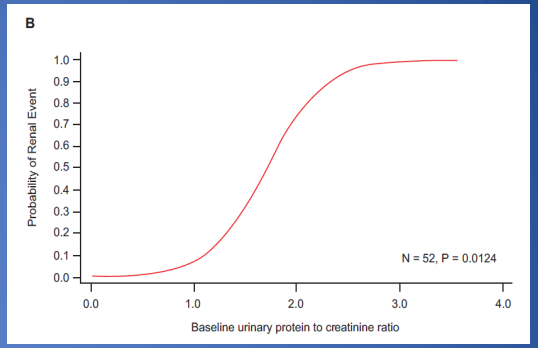




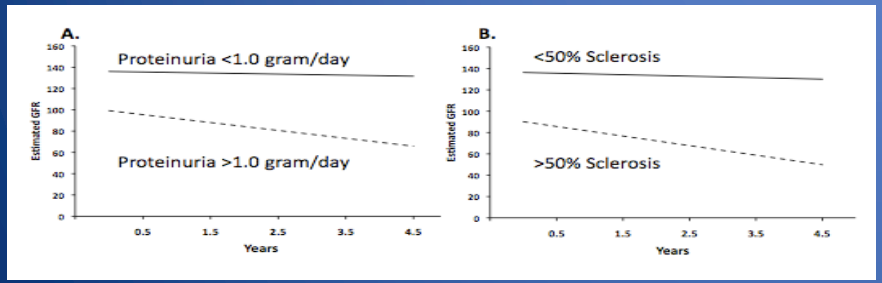
Branton et al Medicine 2002;81:122

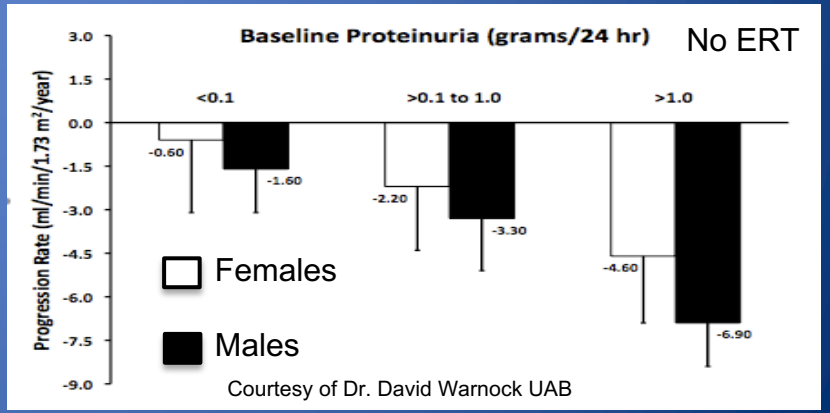
Natural History Fabry Nephropathy: M vs.F





Courtesy of Dr. David Warnock UAB

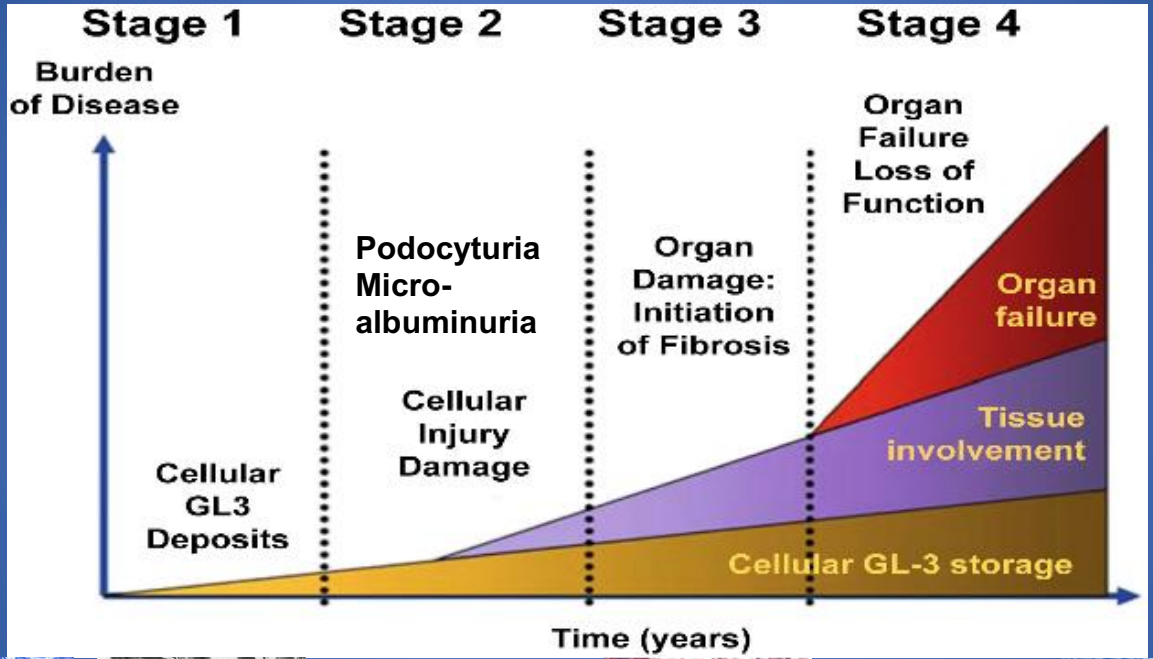


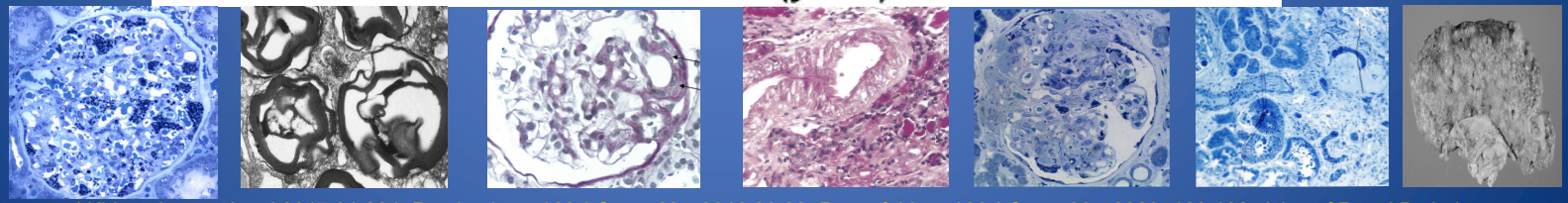


Courtesy of Dr. David Warnock UAB

Schiffmann et al Nephrol Dial Transplant 2009;24:2102; Adapted from Schiffmann et al Nephrol Dial Transplant 2009;24(7):2102; Adapted from Germain et al J Am Soc Nephrol 2007;18: 1547; ERT enzyme replacement therapy

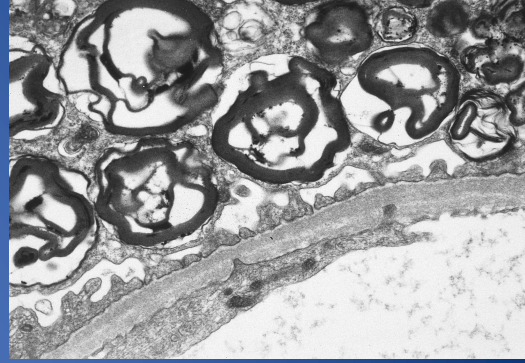
Progression of Fabry Nephropathy





adapted from Schiffmann et al Kidney International 2017;91:284; Rombach et al Mol Genet Met 2010;99:99; Rozenfeld et al Mol Genet Met 2020: 129:132; Atlas of Renal Pathology. http://www.ajkd.org/pb/assets/raw/Health%20Advance/journals/yajkd/atlas37_4.htm; Germain OJRD 2020;5:30; Tondel et al Am J Kidney Dis 2008;51:767

Role of Renal Biopsy



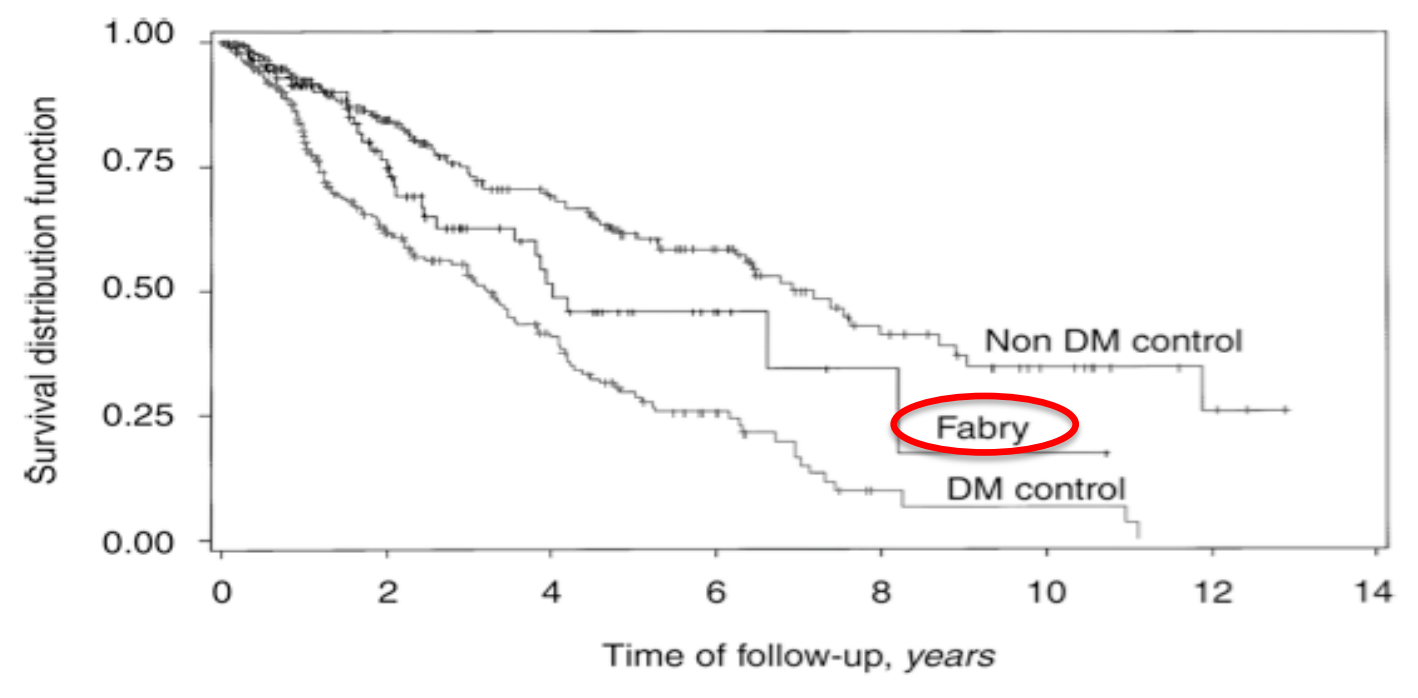
- Confirm Fabry nephropathy
- Especially in women
- Issue of concurrent renal disease: DM, SLE, ANCA+, IgA-N, MCD, MGN, other GNs
- Confirm pathogenicity of GVUS
- Monitor effect of Rx

Atlas of Renal Pathology. http://www.ajkd.org/pb/assets/raw/Health%20Advance/journals/yajkd/atlas37_4.htm

Factors influencing outcomes

- Age
- Gender
- Phenotype
- GLA mutation
- Residual enzyme activity
- Other-VDR polymorphisms, IL-6
- Treatment, timing, ? ERT dose

Survival on Dialysis USRDS 1995-98



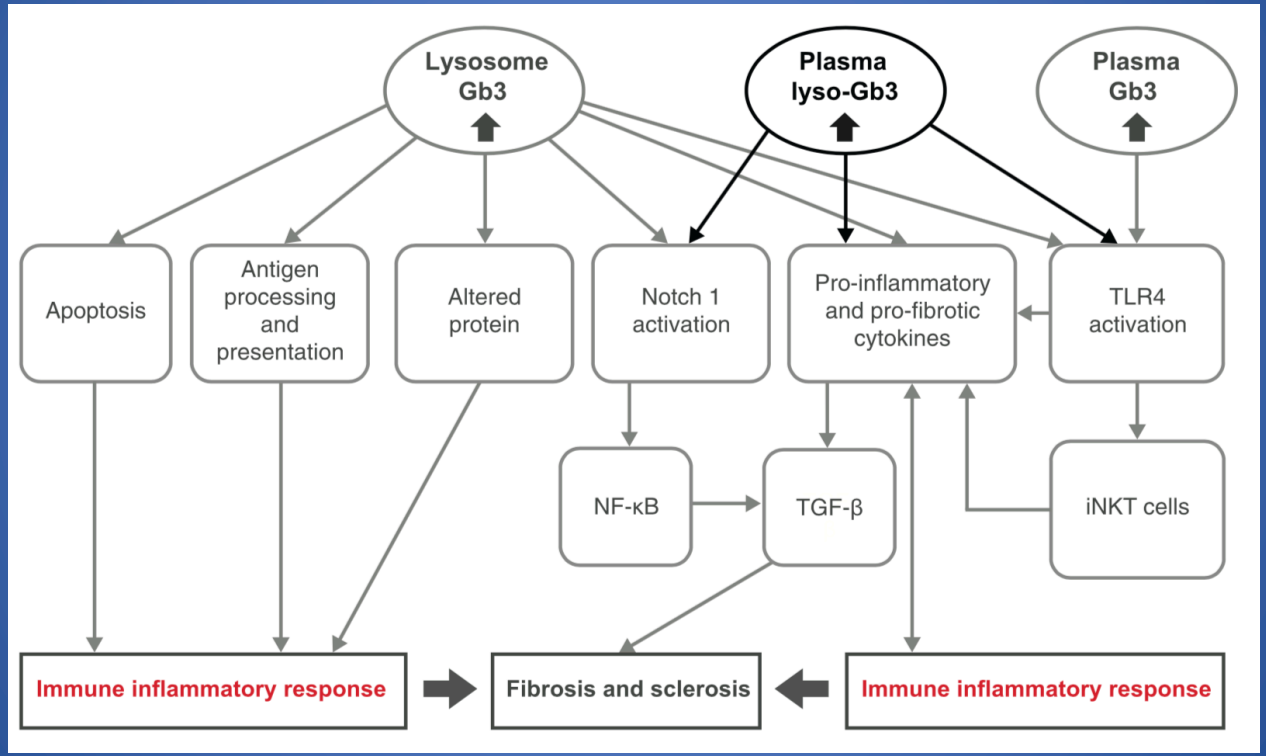
Thadhani et al Kidney Int 2002;61:249

Fabry Disease - Pathophysiology

- accumulation of glycosphingolipids in plasma, lysosomes of tissues e.g. *Gb3 ;* increased lysoGb3
- small vessel vasculopathy
- apoptosis increased by oxidative stress
- increased thrombosis, inflammation, fibrosis
- increased circulating myeloperoxidase
- other lysosomal functions altered-autophagy, cell regulation, stress response, signaling

Rombach et al Mol Genet Met 2010;99:99; Rozenfeld et al Mol Genet Met 2020: 129:132; Atlas of Renal Pathology. http://www.ajkd.org/pb/assets/raw/Health%20Advance/journals/yajkd/atlas37_4.htm

Fabry Disease - Pathophysiology



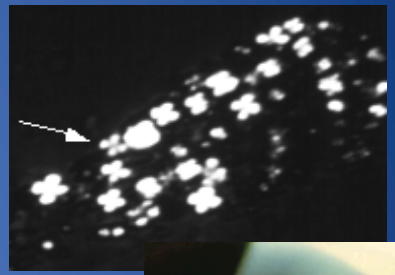
Rozenfeld, Feriozzi, Mol Genet Metab 2017;122:19

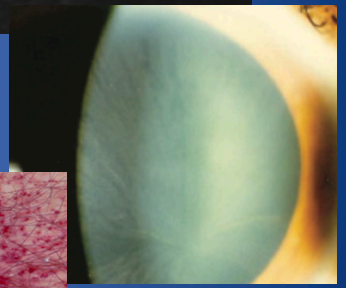
Diagnosis of Fabry disease

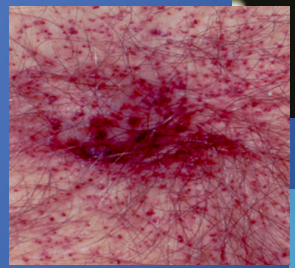
- low α-galactosidase activity
- GLA gene mutation
- increased urine Gb3, plasma lysoGb3
- females mosaics, a-gal low/normal, DNA analysis
- + family history; new mutations 5% no family history
- biopsy kidney

Think of Fabry disease when

- Unexplained chronic kidney disease
- Lipiduria in the absence of proteinuria
- LVH, arrhythmias
- Chest pain w negative cardiac catheterization
- Stroke/TIA under 55 years
- Myalgias, arthralgias
- Irritable bowel symptoms
- Sensory peripheral neuropathy
- Angiokeratomas/facial dysmorphism



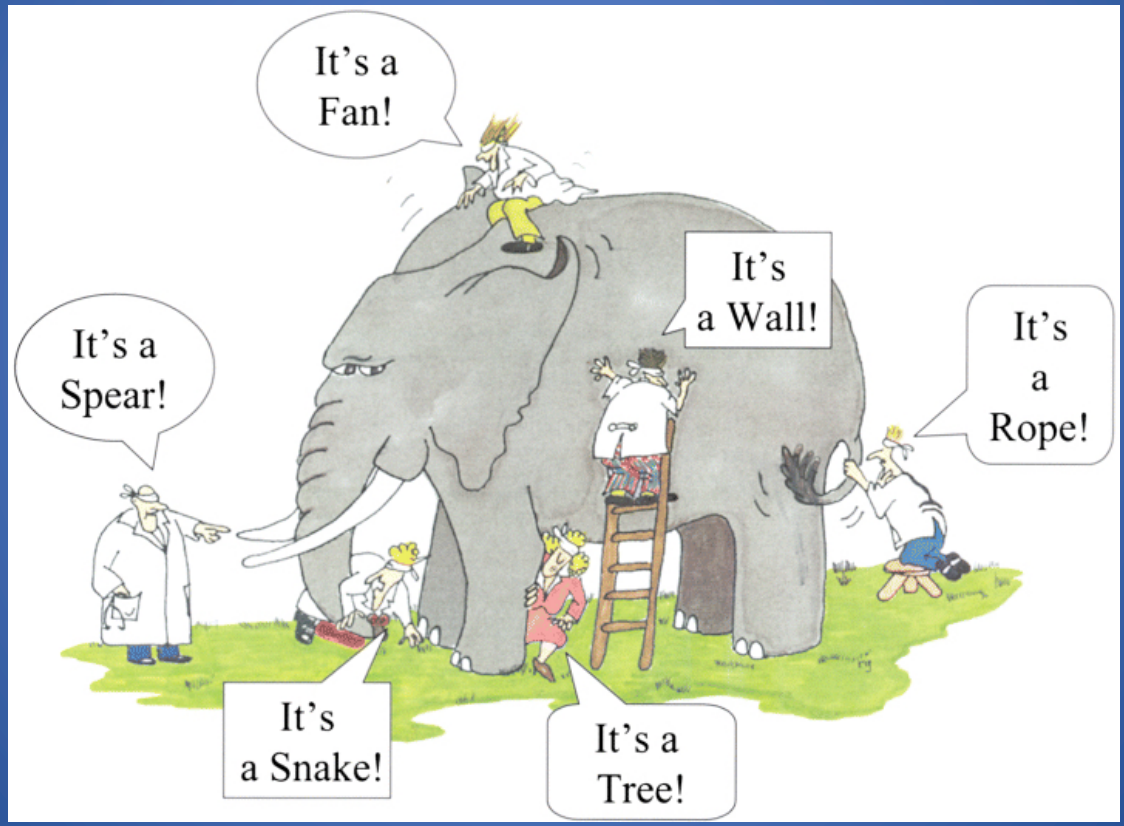




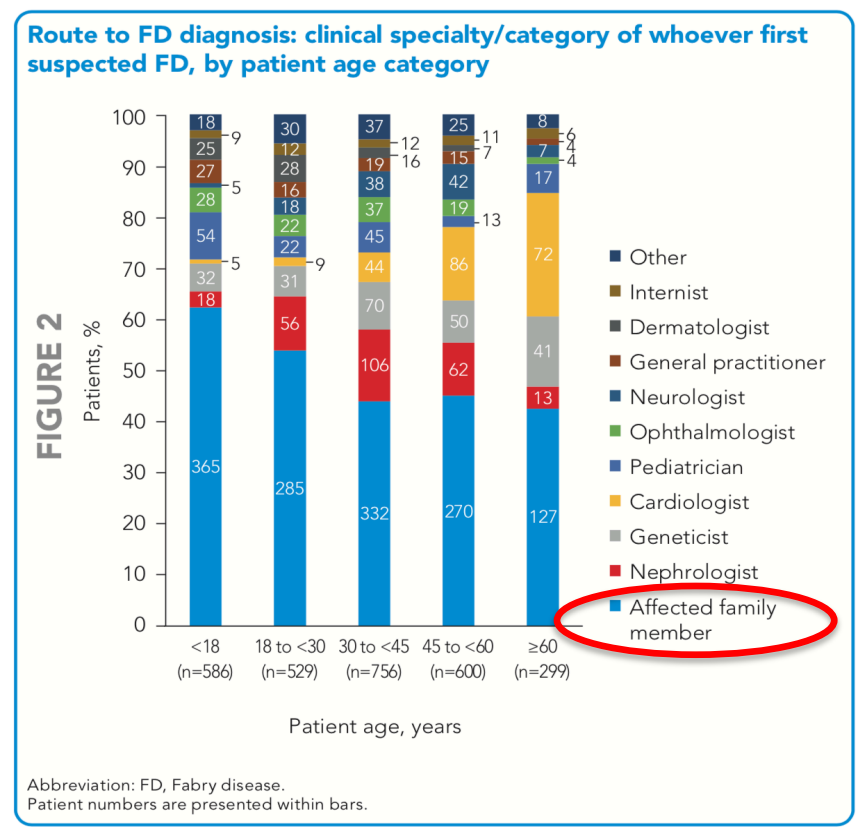
Why is Fabry disease difficult to recognize?

- relatively rare
- not often taught in medical school
- family history may be negative-new mutation, adoption, divorce etc.
- shares clinical features with far more common conditions
- phenotype varies widely, even within families, males vs. females, late onset variant disease
- medical specialization, sub-specialization

6 blind wo/men and the elephant



Who diagnoses FD?



Ramaswami et al FOS poster presented at WORLD meeting, Orlando FLA USA Feb 11, 2020

Fabry disease is an old disease in Canada

ANGIOKERATOMA CORPORIS DIFFUSUM UNIVERSALE (FABRY'S DISEASE) IN TWO BROTHERS*

J. E. Bethune, M.D., F.R.C.P.(C),† P. L. Landrigan, M.D.,‡ and C. D. Chipman, M.D., F.R.C.P.(C)§

HALIFAX, NOVA SCOTIA

ANGIOKERATOMA corporis diffusum universale, or Fabry's disease, was regarded as a dermatologic curiosity until a description by Ruiter and Pompen[1] from the Netherlands in 1939 suggested

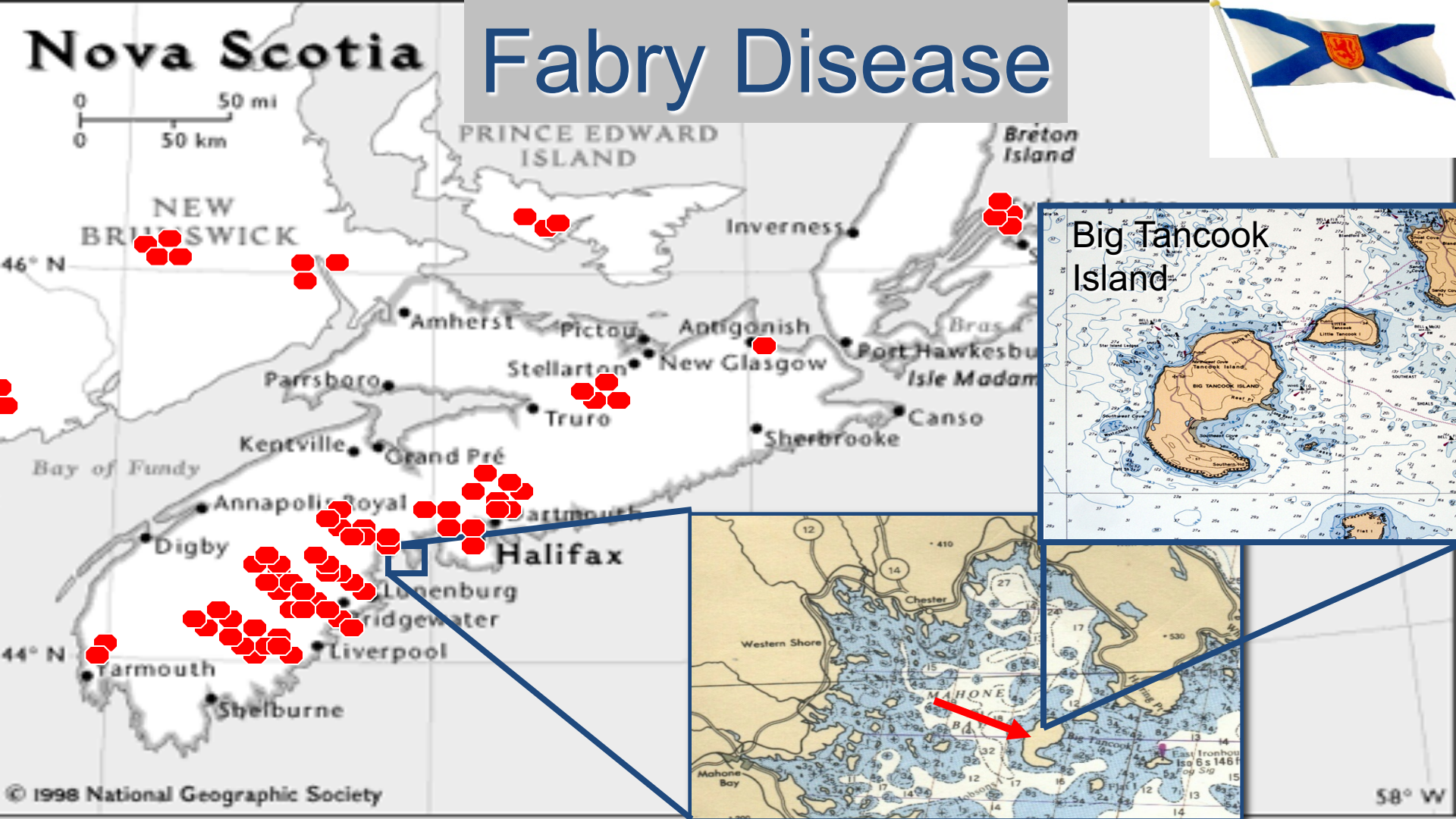
It is apparent from a review of the cases reported that a characteristic clinical pattern of progressive disease develops. At about the time of puberty in males, skin lesions that are only slowly progressive

Bethune et al NEJM 1961;264:1280

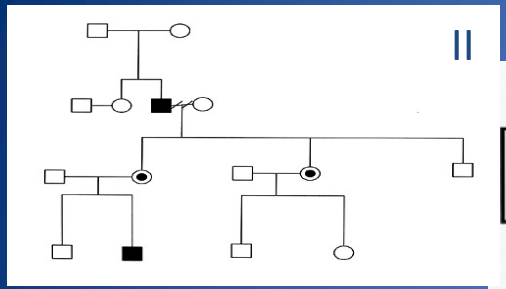
Tancook Island NS

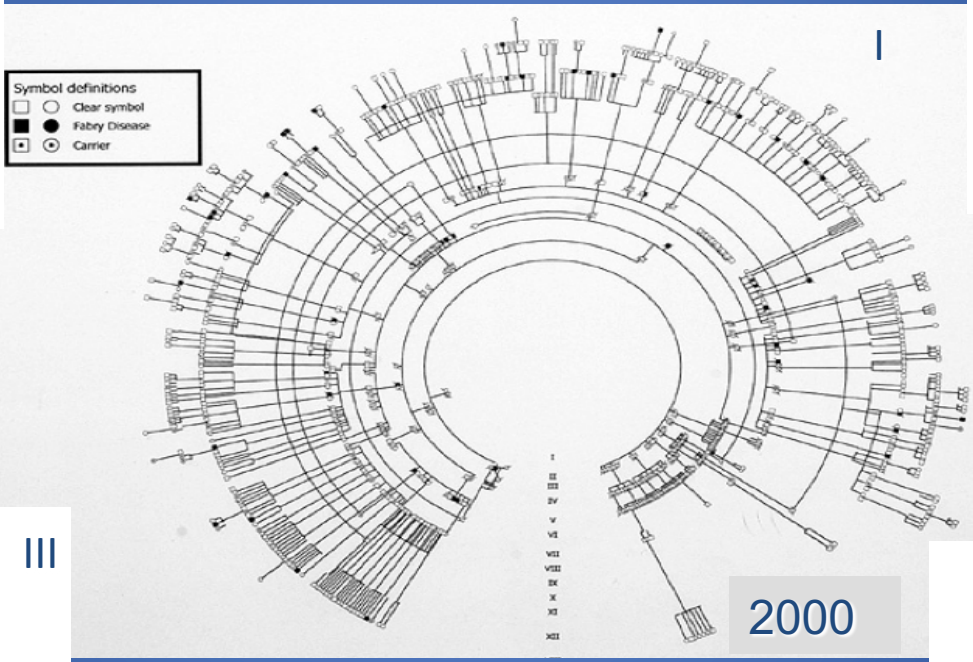
Personal photograph

Fabry Disease

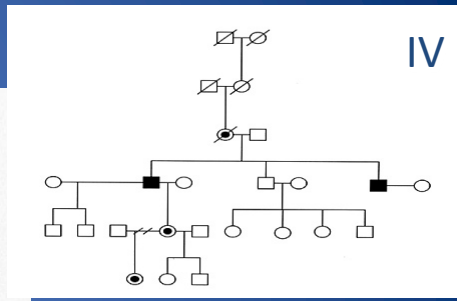


Nova Scotia Fabry Disease Kindreds

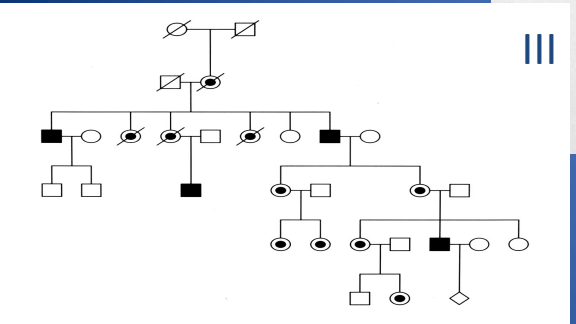


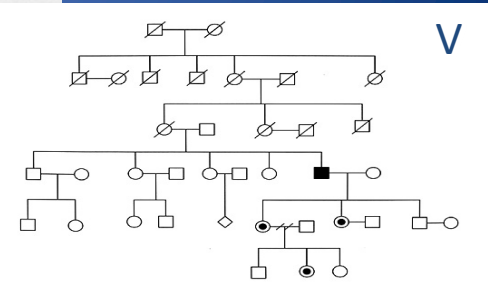


From Dr. P. Camfield, Dr. C. Camfield
Neurology IWK



From Dr. S. Dyack
Medical Genetics IWK





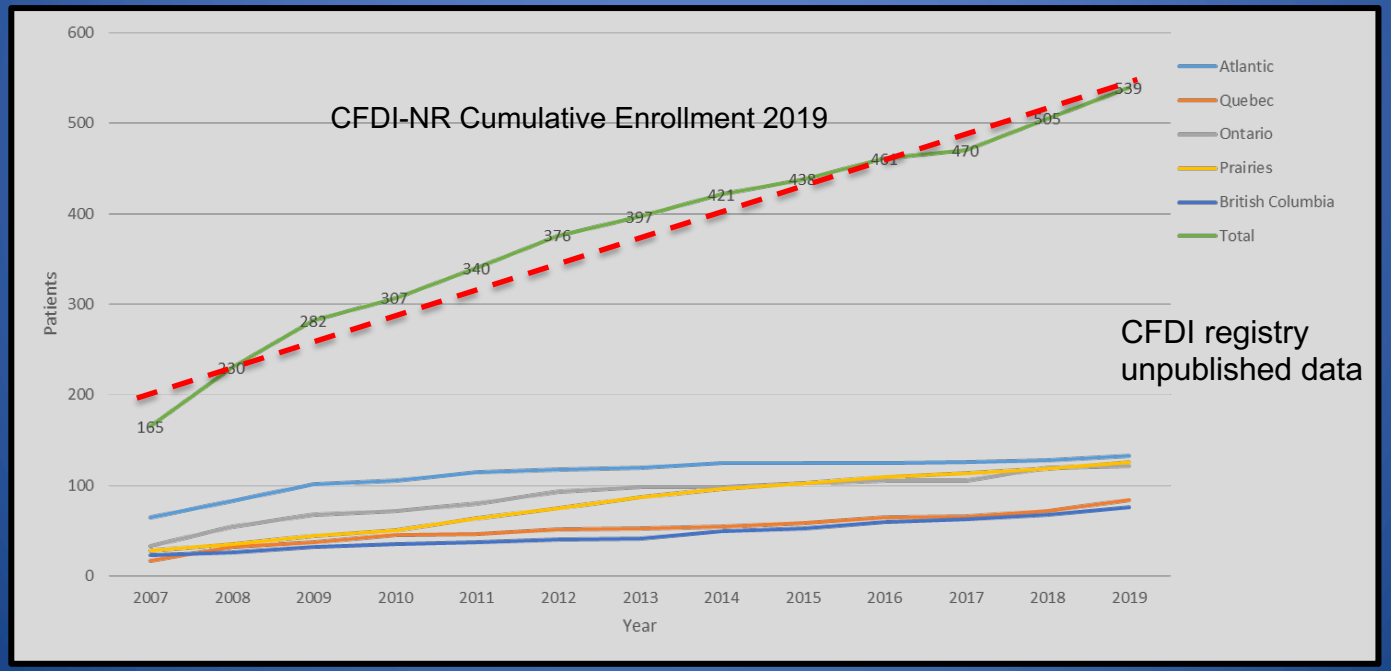
Is Fabry disease a rare disease in Nova Scotia?

- NO!
- Nova Scotia kindred 100+ / 1M ~1/8,000
- A143P Nova Scotia mutation
- large founder effect
- 1/117,000 population
- newborn screening 1/1,600 males Taiwan, 1/4,000 Italy

Meikle PJ et al JAMA 1999, 281:249; Lin et al Circ Cardiovasc Genet 2009;2:450-6;Spada et al Am J Hum Genet 2006;79:31

Is Fabry disease a rare disease in Canada?

- Maybe
- Canada 450+ / 38.4 M ~ 1/85,000

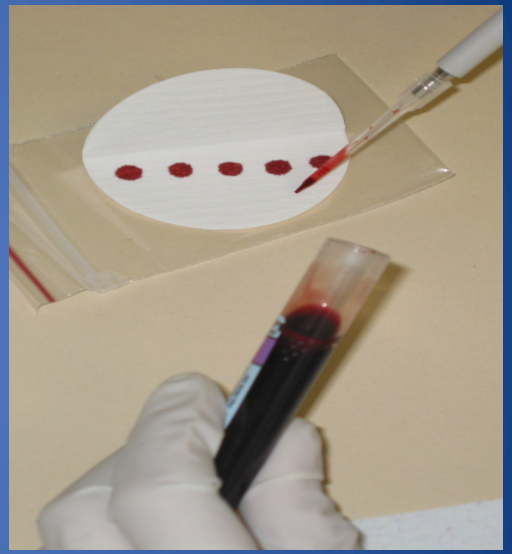


Why screen for Fabry disease?

- diagnostic delay common ~15 years from onset of symptoms to diagnosis (Germain OJRD 2010;5:30)
- 5% patients no positive family history
- treatable disease-specific therapies
- progressive disease so earlier therapy before fibrosis of myocardium or kidney gives better results
- allows genetic counseling, informed reproductive choice
- recommended by 2017 KDIGO FD conference (Schiffmann et al Kid Intern 2017;91:284-93)

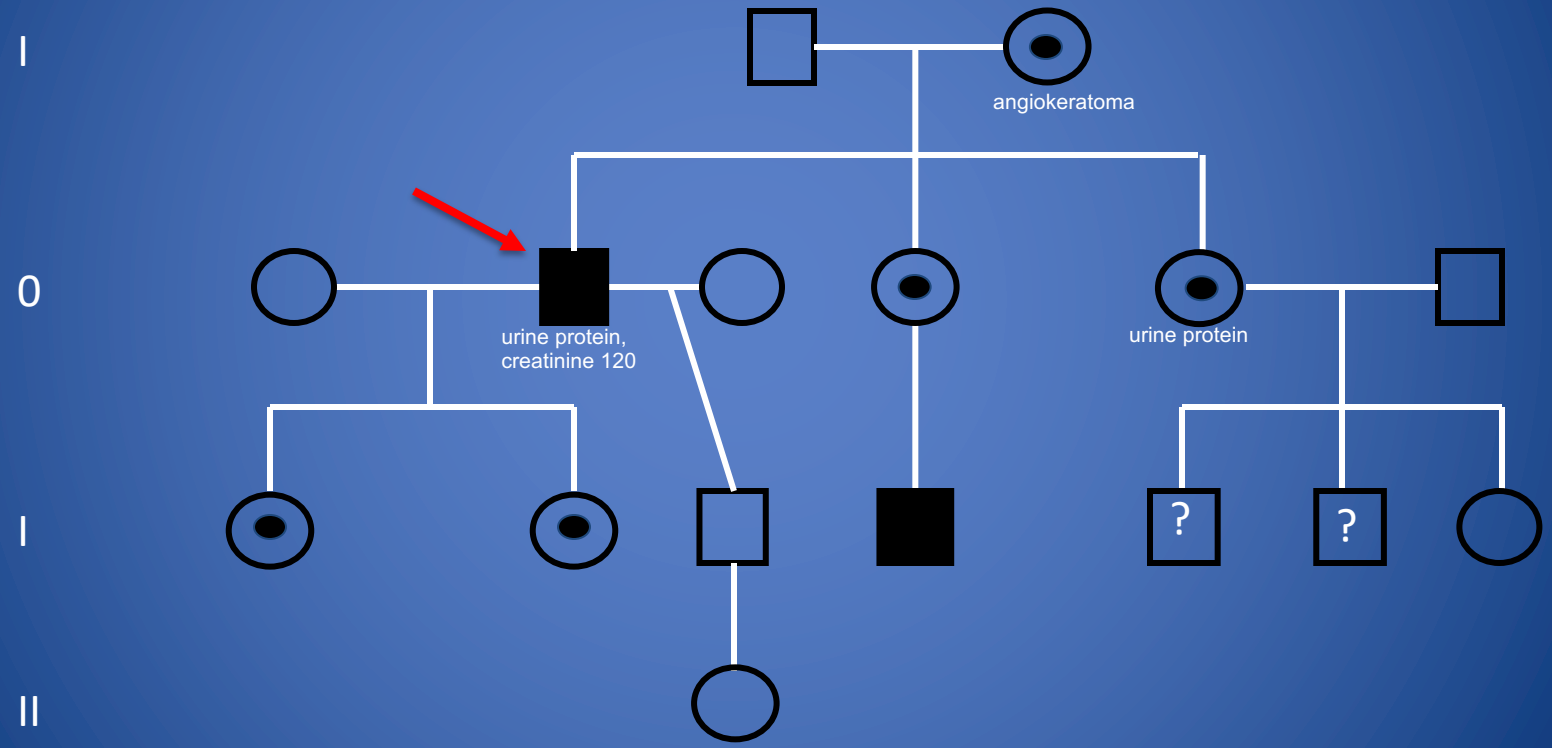
Screening for Fabry disease

- dried blood spot samples
- A-gal activity, Gb3, lysoGb3, GLA mutational analysis
- variety of screening strategies
- cost is decreasing



Chamoles *et al* Clin Chim Acta 2001;308:195; Linthorst *et al* Nephrol Dial Transplant 2003;18:1581. Rombach *et al* Biochim Biophys Acta 2010;1802:74;Auray-Blais et al Clin Chim Acta 2010;411:1906; presenter's picture

Cascade Screening for Fabry disease



can find up to 7 additional relatives from a single proband (Bekri et al Nephron 2005;101:c33)

High Risk Screening

combined data 63 studies FD screening 51,363 patients: 33,943 M, 17,420 F (1995–2017)

	Sex	Studies n	Screened n	Positive n (%)	Pathogenic	Benign
Hemodialysis	M	27	23,954	101 (0.42)	50	51
	F	20	12,866	87 (0.68)	19	68
LVH, HCM	M	16	4,054	49 (1.21)	38	11
	F	12	1,437	22 (1.53)	13	9
Stroke	M	16	3,904	26 (0.67)	5	21
	F	14	2.074	23 (1.11)	3	20

Adapted from Doheny et al J Med Genet 2017;55:261

FD screening in CKD

- 397 CKD patients, 70.3% male, median age 68 y (range: 32–75 y)
  - 153 (38.6%) stage 3 eGFR 30-60 ml/min/1.73m^2
  - 236 (59.6%) stage 4 eGFR 15-30
  - 7 (1.8%) stage 5 eGFR <15
- Increased urinary Gb3 found in 13.6%
- No FD pts found after DNA analysis, α-gal activity done

Auray-Blais et al Clinica Chimica Acta 2020;501:234-40

- 2 FD w pathogenic GLA mutations/72 (2.7%) renal clinic patients in Italy with CKD, proteinuria, albuminuria

Favalli *et al* JACC 2016;68:1068

Problems with Fabry Screening

- polymorphisms D3113Y, R112H, E66Q, P60L, A143T
- genetic variant of unknown significance (GVUS)
- risk of misdiagnosed and mistreatment with costly ERT

Van der Tol et al J Med Genet 2014;51:1-9

Novel strategies for rare disease screening

- CKD w over 500 single gene disorders
- 30% + of CKD pts w genetic condition
- Use of EMR ± machine learning to screen using algorithm with clusters of signs and symptoms
- Use of gene chips to screen for multiple genetic conditions
- phenotypes overlap; NGS/WES can identify misdiagnosis in 10%
- WES can identify causative gene in up to 37%

Bullich et al Kid Intern 2018;94:363-71; Connaughton et al Kid Intern 2019;95:914-28; Groopman et al NEJM 2019;380:142-51; Garcelon et al Kid Intern 2020;97: 676-86; Schonauer et al Genet Med 2020;22:1374-83

Canadian Fabry Treatment Guidelines 2020

- Kidney disease -function 10% < normal or fall 15% fall from prior GFR, proteinuria>500mg/d, renal pathology M; minor: NDI, Fanconi, HBP, proteinuria >300mg/d, hyperfiltration, renal pathology F
- Heart disease – incr WT, LVH, LVMI, arrhythmia, heart block, diastolic CHF, incr LA, VHD, abn tissue doppler, cMRI LE, NT-proBNP
- TIA/strokes, acute hearing loss
- Uncontrolled GI symptoms
- Uncontrolled neuropathic pain

http://www.garrod.ca/wp-content/uploads/Canadian-FD-Treatment-Guidelines-2019.pdf

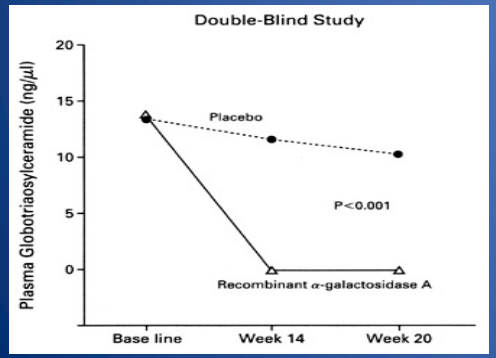
Fabry Disease Treatment 2021

- Control risk factors-high cholesterol, smoking, high blood pressure
- Stroke prevention-ASA, clopidogrel
- Control nerve pain with medications-Gabapentin
- Limit urine protein-ACEinh, ARB, low salt diet, Vitamin D
- Enzyme replacement therapy, chaperone
- Kidney transplant, dialysis
- Multidisciplinary team, regular follow up
- Investigational treatments-gene therapy, Lucerastat, modified ERT

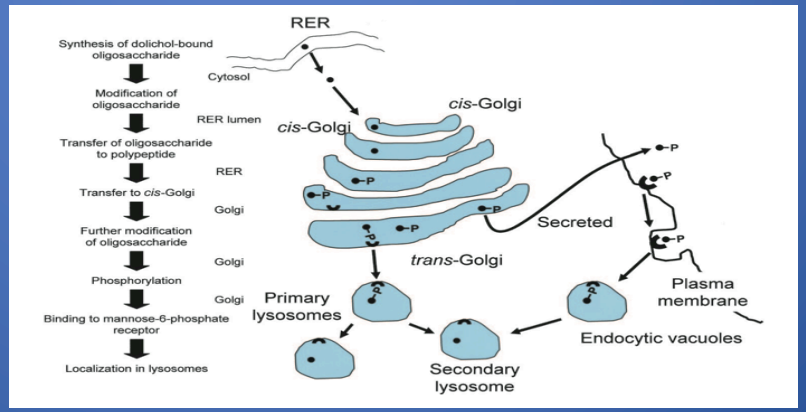
Enzyme Replacement Therapy with rhα-galactosidase A

- infusion every 2 weeks
- taken up via m-6-P receptor, to lysosome
- agalsidase-beta 1.0 mg/kg over 90-500 minutes
- agalsidase-alfa 0.2 mg/kg over 40 minutes
- Issues: iv access, infusion reactions, antidrug antibodies, cost

biweekly infusion agalsidase-β n=58



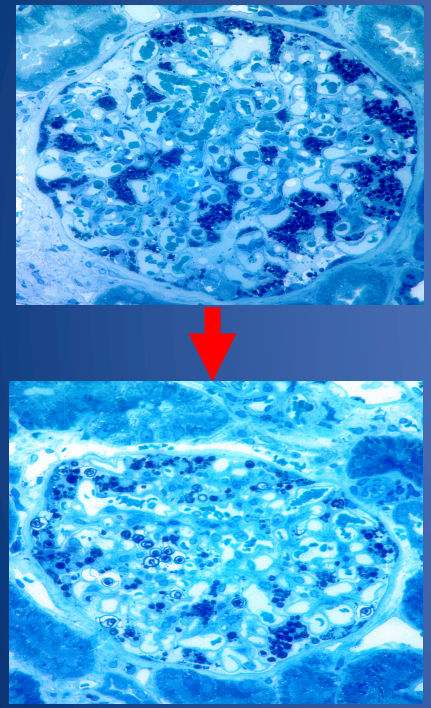
Eng et al NEJM 2001;345:9



Clarke J. Ann Int Med 2007;146:425-433

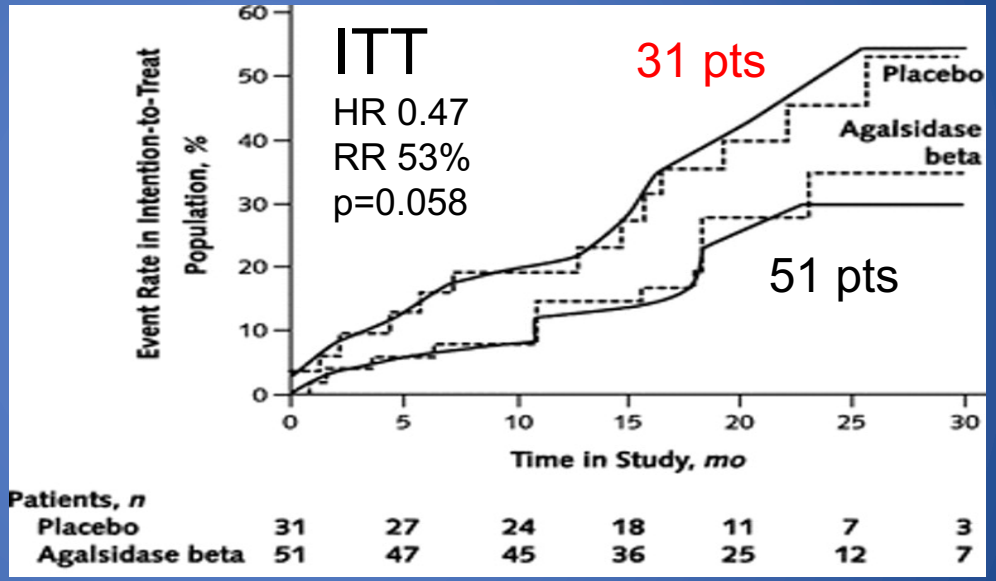
Efficacy of Enzyme Therapy

pre/post agalsidase-α
infusions q 2 weeks x 12



Schiffmann et al JAMA 2001;285: 2743-2749

Phase IV Agalsidase-β Trial: time to first clinical outcome



Proteinuria ratio adjusted Kaplan-Meier predicted probability of an event where baseline proteinuria ratio value = 1.0

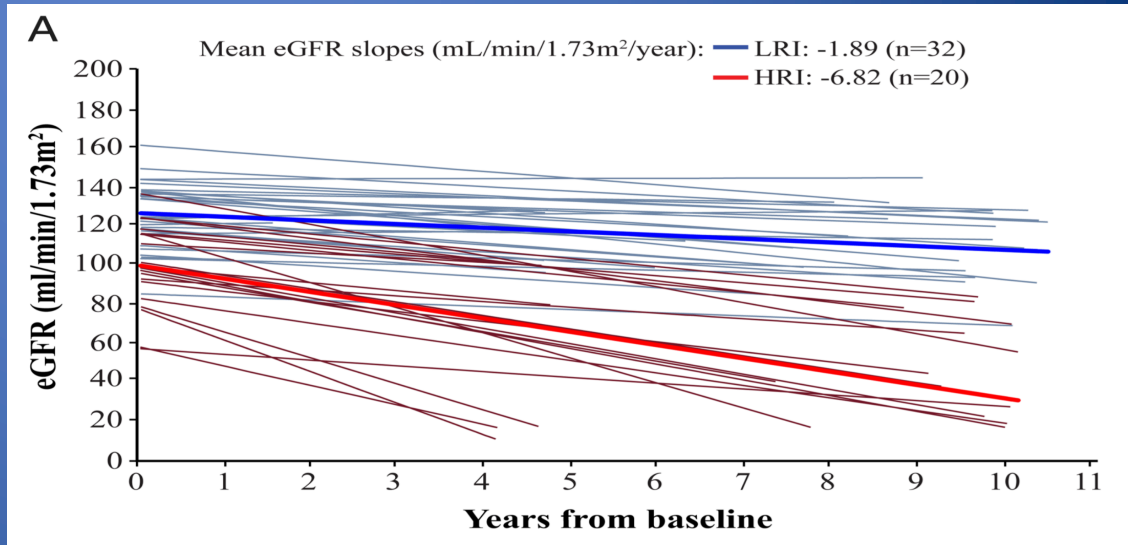
Banikazemi et al Ann Intern Med 2007;146:77-86

Efficacy of ERT

- reduction of GI symptoms diarrhea, gas, bloating,
- reduction of neuropathic pain, stabilization of WML
- return of sweating
- increased well being, exercise tolerance
- return to work, school
- slows decrease in eGFR, increase in LVMI
- May decrease stroke prevalence
- Does not decrease proteinuria

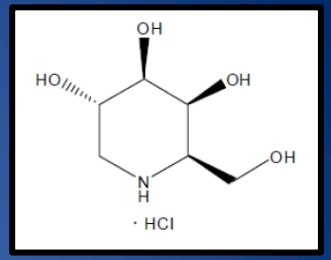
Long Term Renal Outcomes on ERT

- HRI uPCR >0.5 g/g or ≥50% sclerotic glomeruli at BL
- LRI uPCR ≤0.5 g/g & <50% sclerotic glomeruli
- 81%; 42/52) no clinical events
- 94% (49/52) alive at 10 years
- 3 deaths, 2 renal events

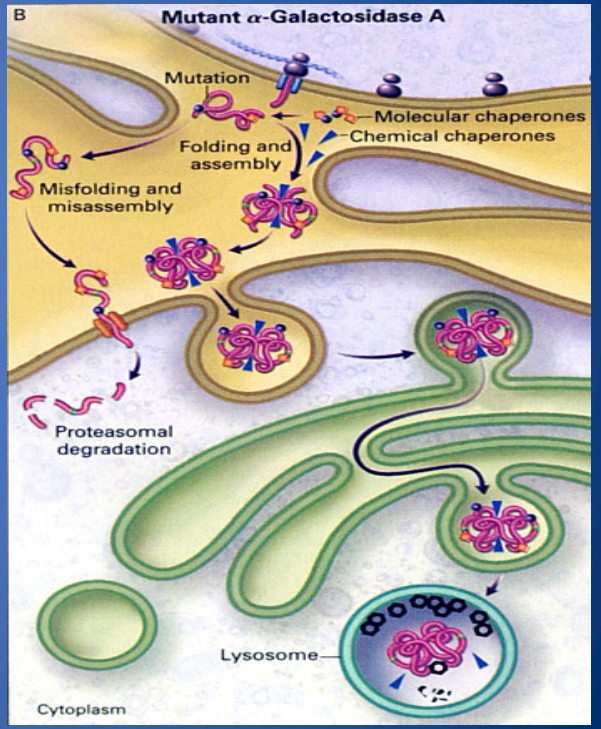


Germain et al J Med Genet 2015;52:353-358.

Pharmacologic Chaperone-Migalastat



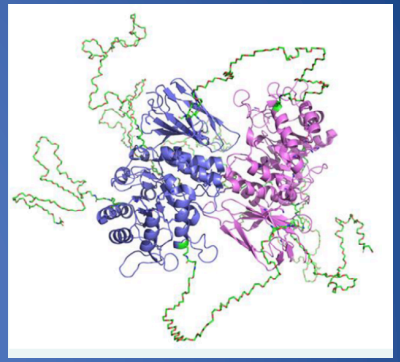
- oral EOD, nontoxic, reversible, competitive inhibitor of a-gal A
- promotes enzyme folding, dimerization, processing in ER
- prevents proteasomal degradation of misfolded mutant enzyme
- increases residual a-gal activity
- useful for only certain α-gal A mutations -25% FD pts in Canada
- No infusion reactions, antibodies



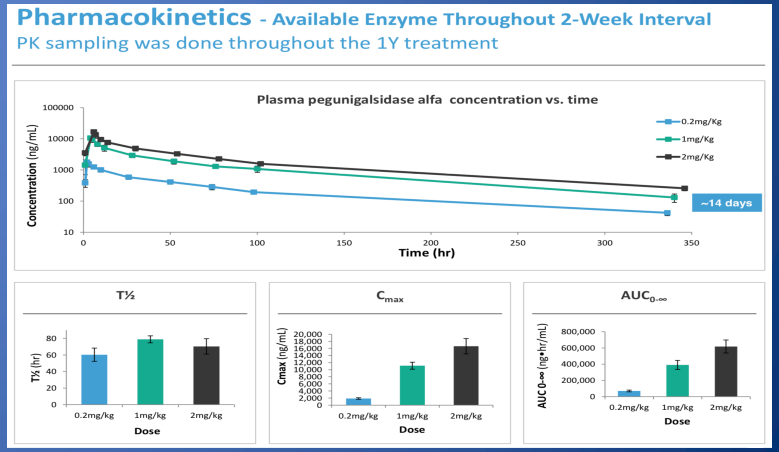
Frustaci et al NEJM 2001;345:25-32

Modified ERT-Pegunigalsidase

- human α-galactosidase enzyme made in tobacco plant cells *in vitro*
- more stable, safe, effective, well tolerated
- may cause less antidrug antibodies,
- different structure: 5 PEG molecules on surface
- phase III studies in adults
- lasts 25x longer with higher levels in blood than current ERT
- 1 mg/kg iv q 2 weeks

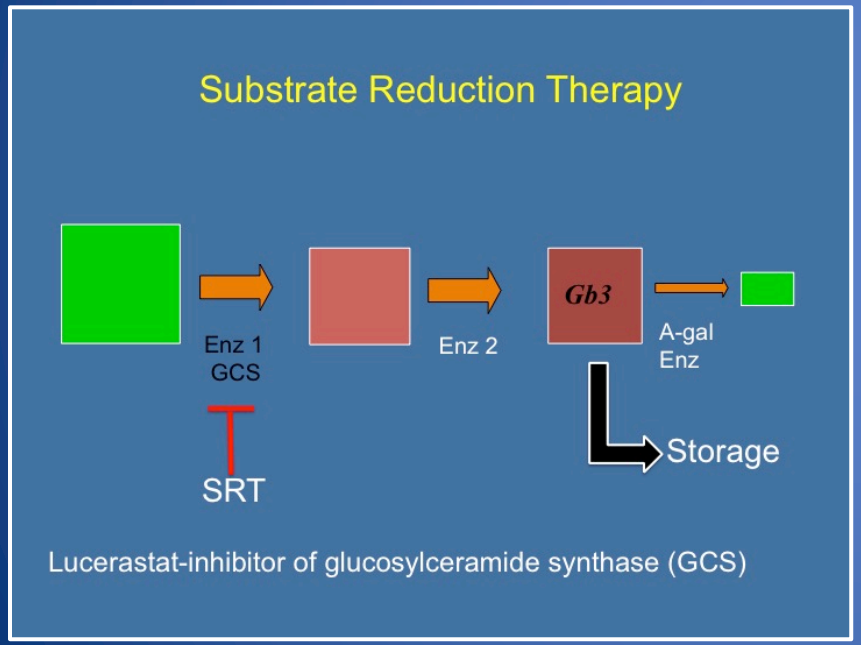


Ruderfer Bioconjugate Chem 2018;29:1630

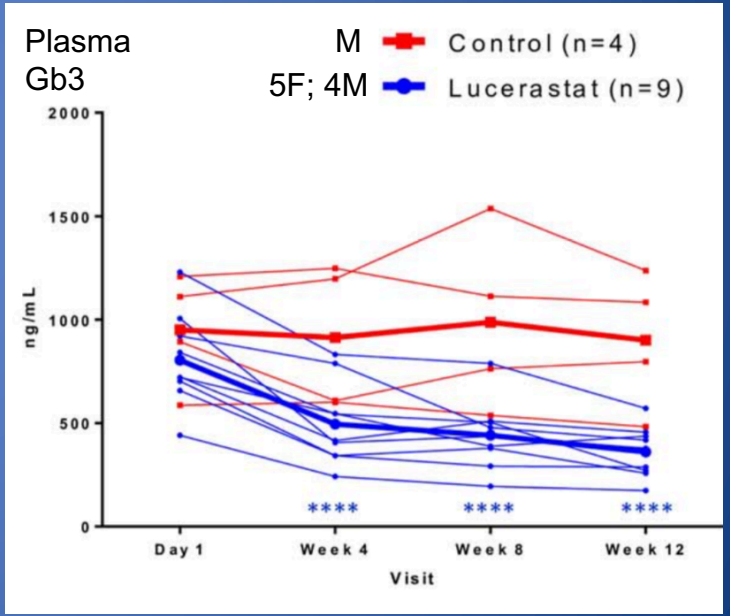


Schiffmann New Horizons in Fabry Disease 2017 Prague

Substrate Reduction Therapy Lucerastat



ERT agalsidase alfa 0.2-1.0 mg/kg EOW vs. Agalsidase beta 1.0 mg/kg EOW 4; alfa 0.2 mg/kg EOW 6 + SRT

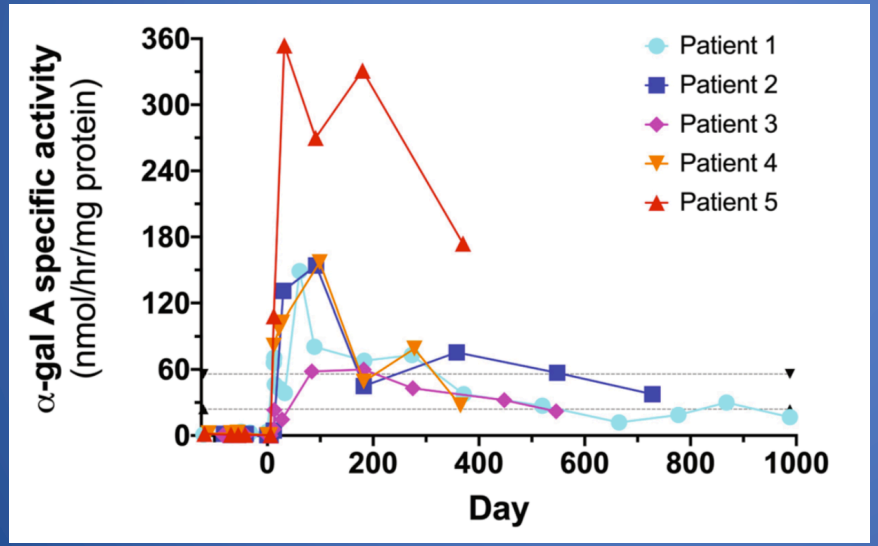


Guerard et al Clin Pharmacol Therap 2018:103:703

Lentivirus-mediated gene therapy for Fabry disease

Aneal Khan[1], Dwayne L. Barber[2,3], Ju Huang[2], C. Anthony Rupar[4,5,6], Jack W. Rip[4], Christiane Auray-Blais[7], Michel Boutin[7], Pamela O'Hoski[8], Kristy Gargulak[9], William M. McKillop[9], Graeme Fraser[10], Syed Wasim[11], Kaye LeMoine[12], Shelly Jelinski[13,14], Ahsan Chaudhry[15], Nicole Prokopishyn[16], Chantal F. Morel[17], Stephen Couban[18,24], Peter R. Duggan[19], Daniel H. Fowler[20], Armand Keating[2,21], Michael L. West[22], Ronan Foley[8] & Jeffrey A. Medin[2,9,23]✉

Permission was obtained to use patient image

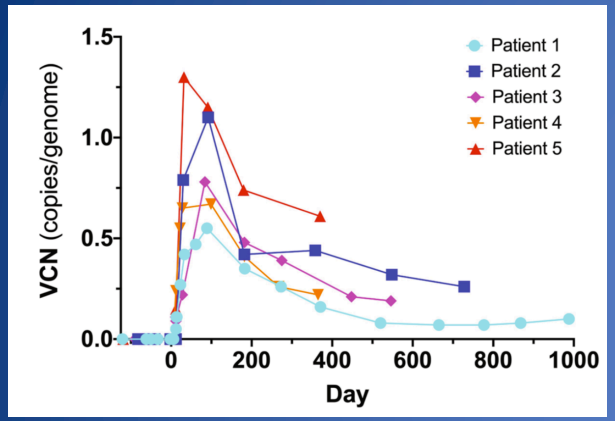


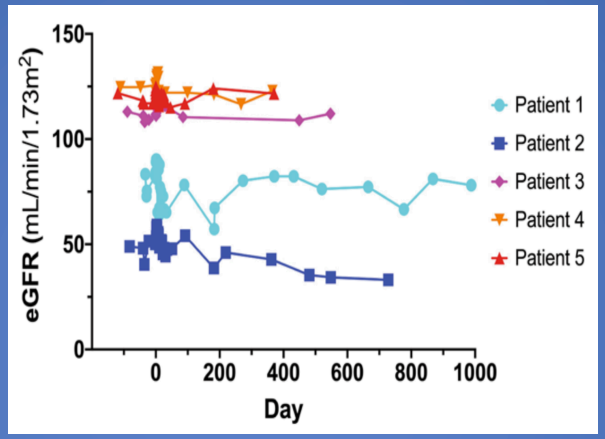
Nov. 2018: patient 4 during infusion of transduced cells in Halifax

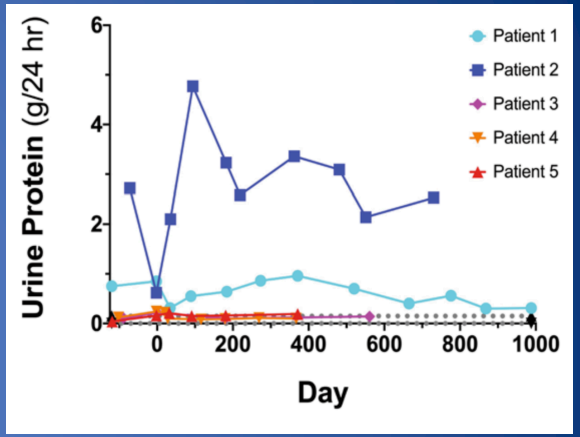
Khan et al Nature Communications 2021;12:1178

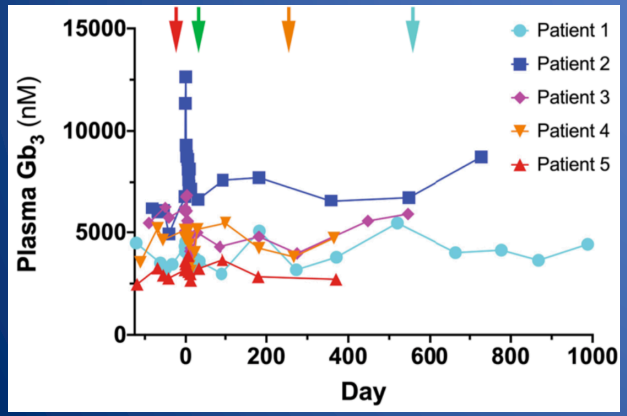
LV mediated gene therapy

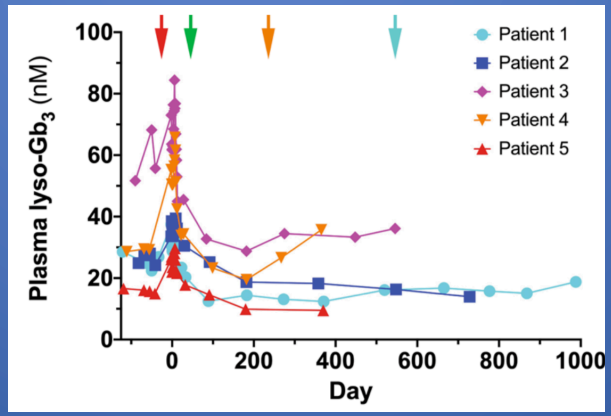
Khan et al Nature Communications 2021;12:1178

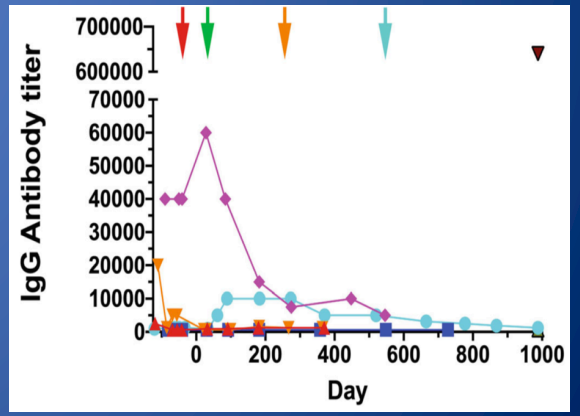












Conclusions

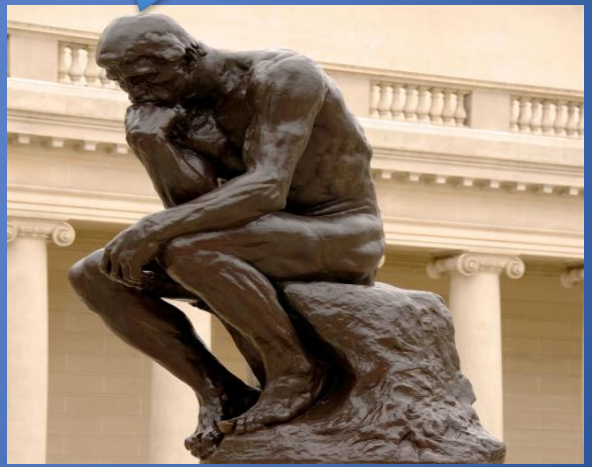
- Fabry disease not so rare; RF predominates in men
- Hard to recognize due to marked variability in phenotype, common clinical features: CKD, early strokes, cardiomyopathy with dysrhythmias
- Screening for FD recommended to improve outcomes as a treatable cause of CKD; need novel strategies
- Control proteinuria, blood pressure, vascular risk factors
- Treat early: ERT, chaperone therapy
- Future therapies: gene transfer therapy

Questions?

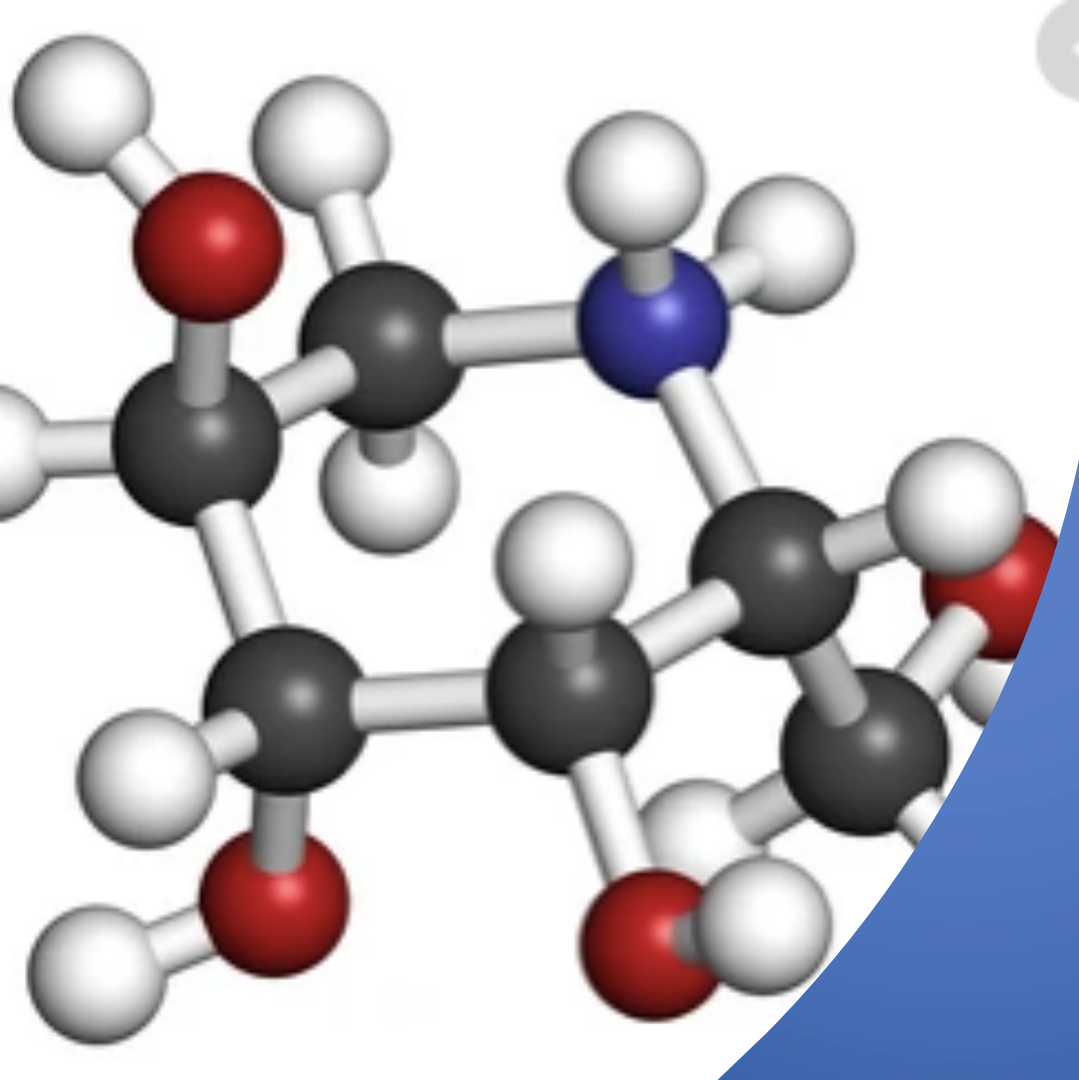
Classical Phenotype?

Venus de Milo, Alexandros of Antioch; https://www.louvre.fr/sites/default/files/medias/medias_images/images/louvre-

Could it be Fabry disease?



The Thinker, Auguste Rodin; https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.tripimprover.com%2Fblog%2Fthe-thinker-by-auguste-rodin&psig=AOvVaw1w5E_HvQByHdvd5a2r3Cbv&ust=1611364064785000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCPCCooetru4CFQAAAAAdAAAAABAD



QUESTIONS & ANSWERS

- Evaluation survey will be sent to you within 48 hours after this webinar. Please complete the evaluation so to get your CME credits

- CSN members will receive 1 hr Section 1 Group Learning credits by e-mail

THANK YOU