Fabry Disease
Are we giving enough attention to Rd?

Alone we are rare , together we are strong.

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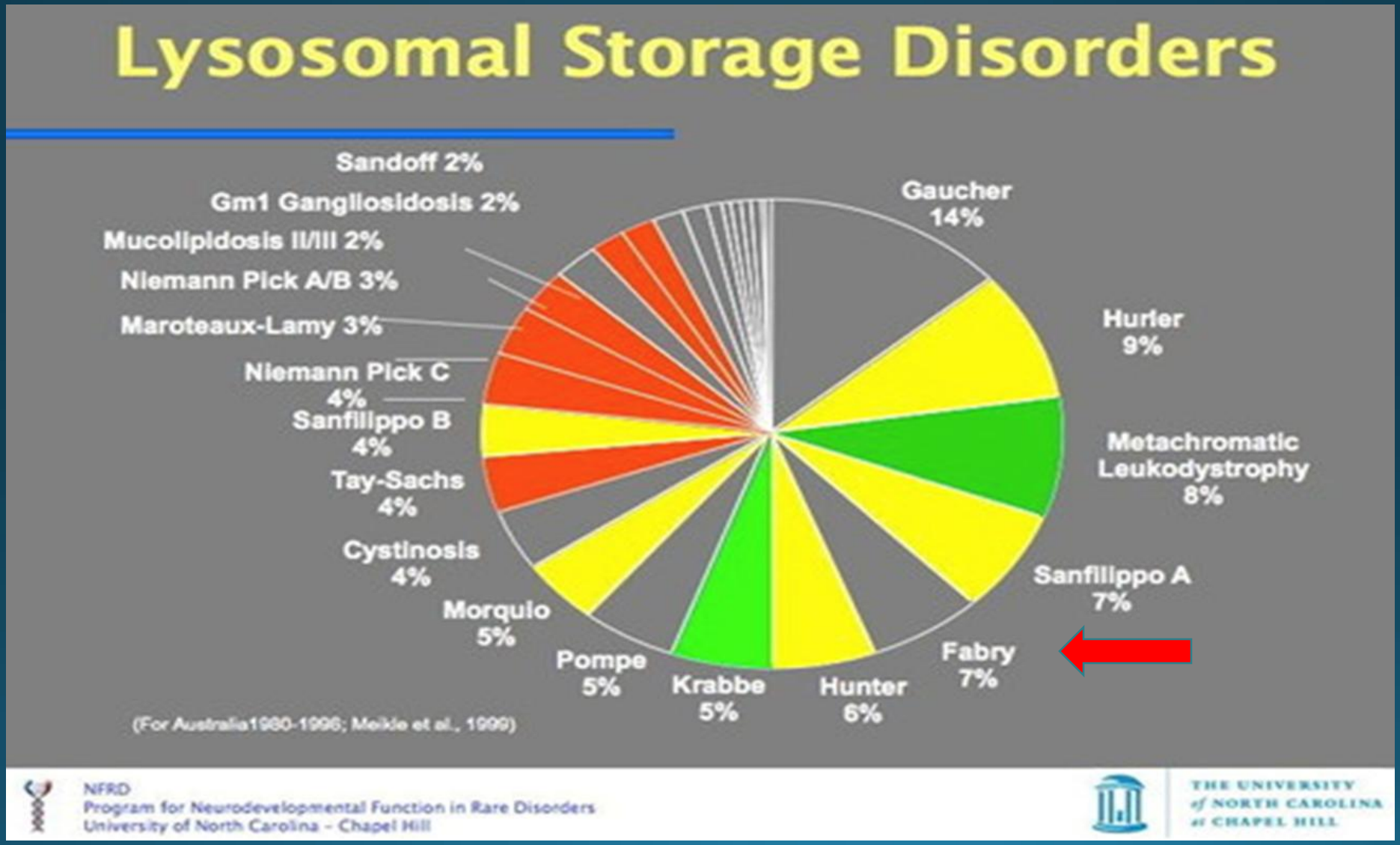
Metabolic Storage Disorders

1- Glycogen Storage Diseases (GSD)
2- Mucopolysaccharidosis (MPS)
3- Lysosomal Storage Diseases (LSD)
4- Peroxisomal Diseases

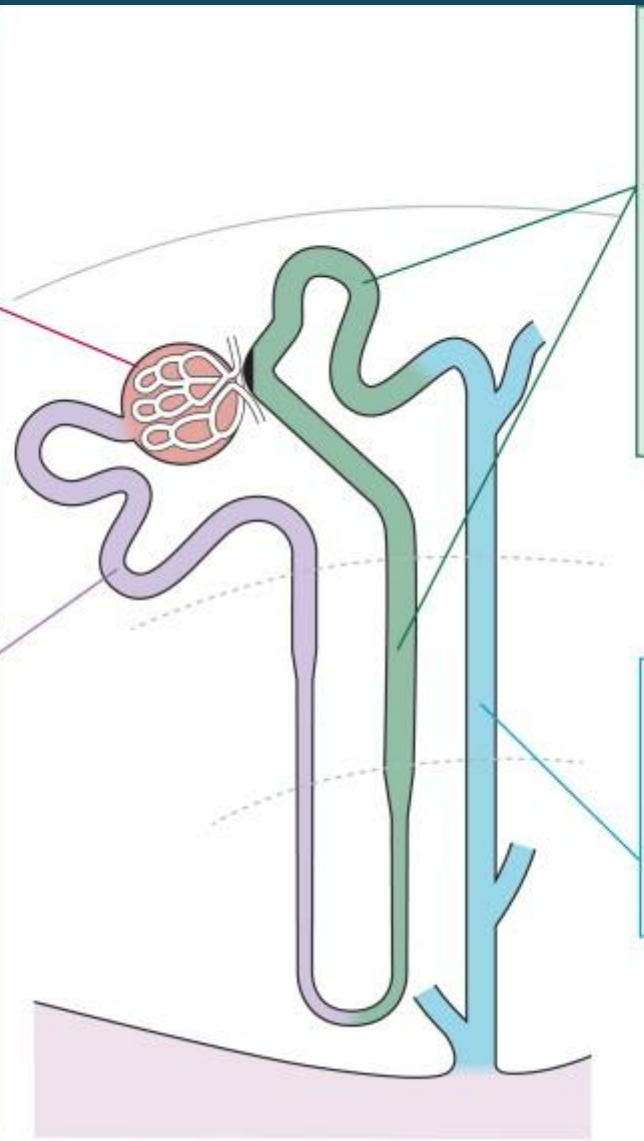
Fabry represents 7 % of LSD



Spectrum of Inherited kidney diseases

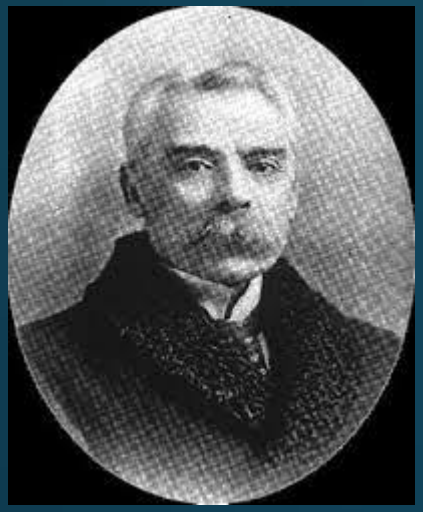
Glomerular diseases
- Congenital steroid-resistant nephrotic syndrome
- Denys-Drash syndrome, Frasier's syndrome
- Wilms' tumour, aniridia, genitourinary abnormalities, and mental retardation (WAGR) syndrome
- Pierson's syndrome
- Nail-patella syndrome
- Schimke immuno-osseous dystrophy
- Mitochondrial disorders with steroid-resistant nephrotic syndrome
- Fabry's disease
- Alport's syndrome
- Benign familial haematuria (thin basement membrane)
- Fechtner syndrome (Alport's syndrome with macrothrombocytopenia)
- Alport's syndrome with leiomyomatosis
- Familial amyloidosis

Thick ascending limb and distal convoluted tubule
- Bartter's syndrome, types 1–4
- Familial hypocalciuric hypercalcaemia
- Neonatal severe hyperparathyroidism
- Autosomal dominant hypocalcaemia
- Gitelman's syndrome
- Pseudohypoaldosteronism type 2 (Gordon's syndrome)
- SeSAME syndrome (EAST syndrome)
- Hypomagnesaemia, types 1–6
- Familial juvenile hyperuricaemic nephropathy



Proximal tubule
- Renal glucosuria
- Dicarboylic aminoaciduria
- Lysinuric protein intolerance
- Proximal renal tubular acidosis
- Hypophosphataemic rickets
- Nephropathic cystinosis
- Primary renal Fanconi's syndrome
- Fanconi-Bickel syndrome (hepatorenal glycogenosis)
- Lowe's syndrome
- Dent's disease, types 1 and 2
- Hereditary renal hypouricaemia
- Cystinuria, types 1–3

Collecting duct
- Liddle's syndrome
- Distal renal tubular acidosis
- Pseudohypoaldosteronism type 1
- Nephrogenic diabetes insipidus, types 1 and 2
- Nephrogenic syndrome of inappropriate antidiuresis



Fabry disease
Anderson –Fabry

first described 1898

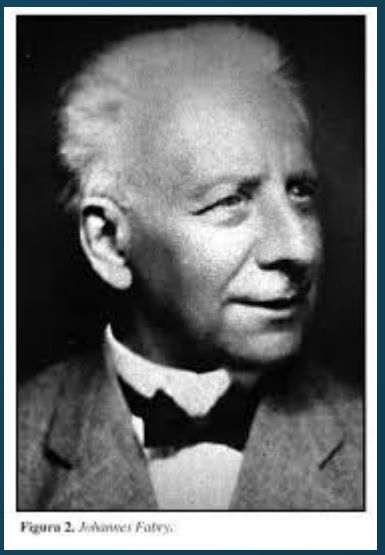


Figura 2. *Johannes Fabry.*

The disease is caused by a deficiency of the lysosomal hydrolase α- galactosidase A (α gal-A), resulting :
in accumulation & storage globo- triaosyl-ceramide (Gb_3) .

Fabry disease

FD is an X-linked multisystem lysosomal storage disorder.

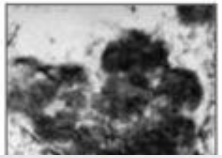
- Estimated birth prevalence of 1:40.000 - 170.000 .

- Late onset forms of the disease are more frequent.

- More than 800 disease caused mutations in the α-galactosidase A (GLA) (> 60% missense)gene have been described.

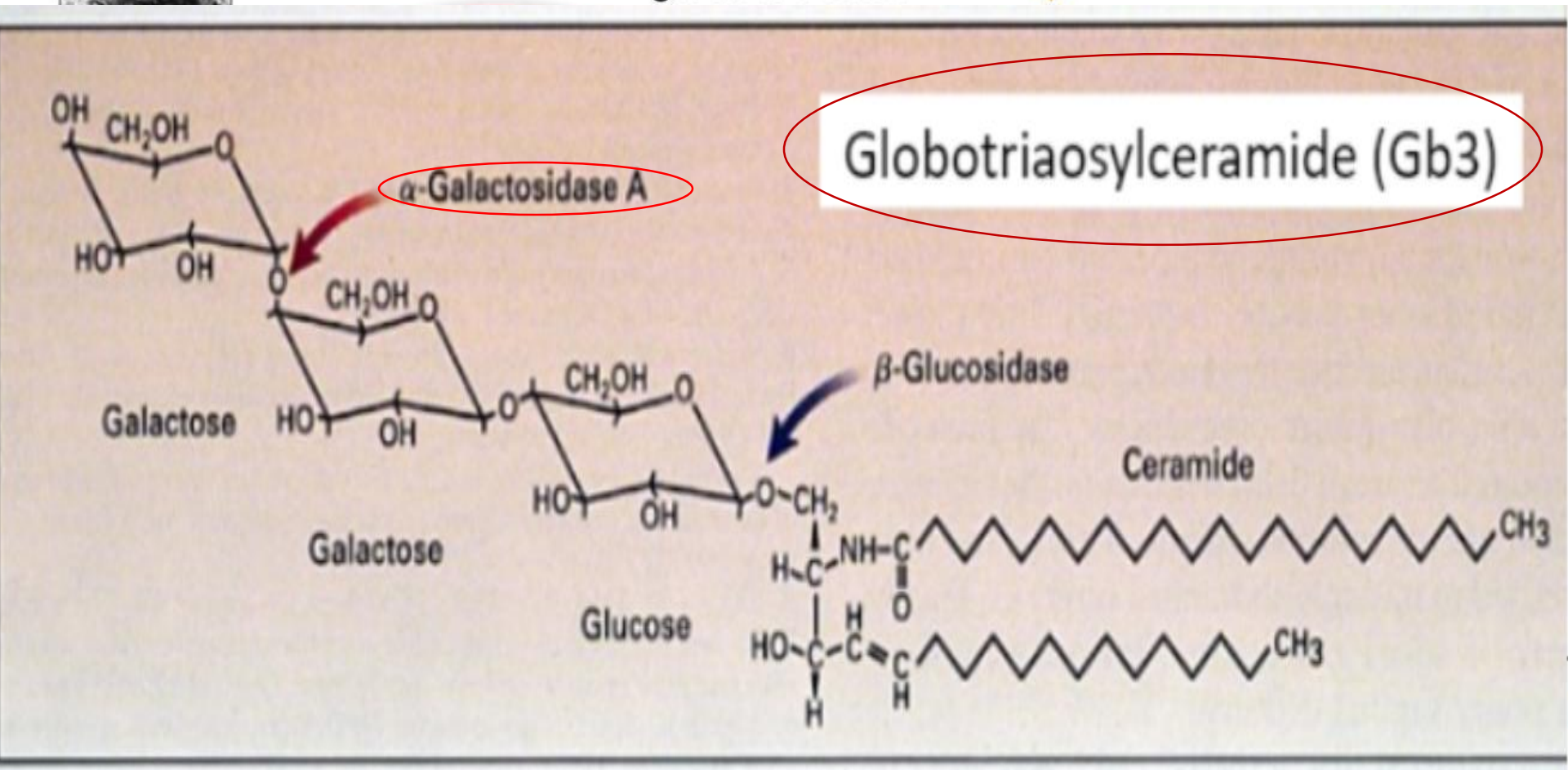
? Type of mutations in Libya

Fabry disease, X-linked genetic, multi-organ disorder



Globotriaosylceramide (Gb-3) → Lactosylceramide + Galactose

α-galactosidase A



Annual Report
The 2016 Fabry Outcome Survey (FOS)

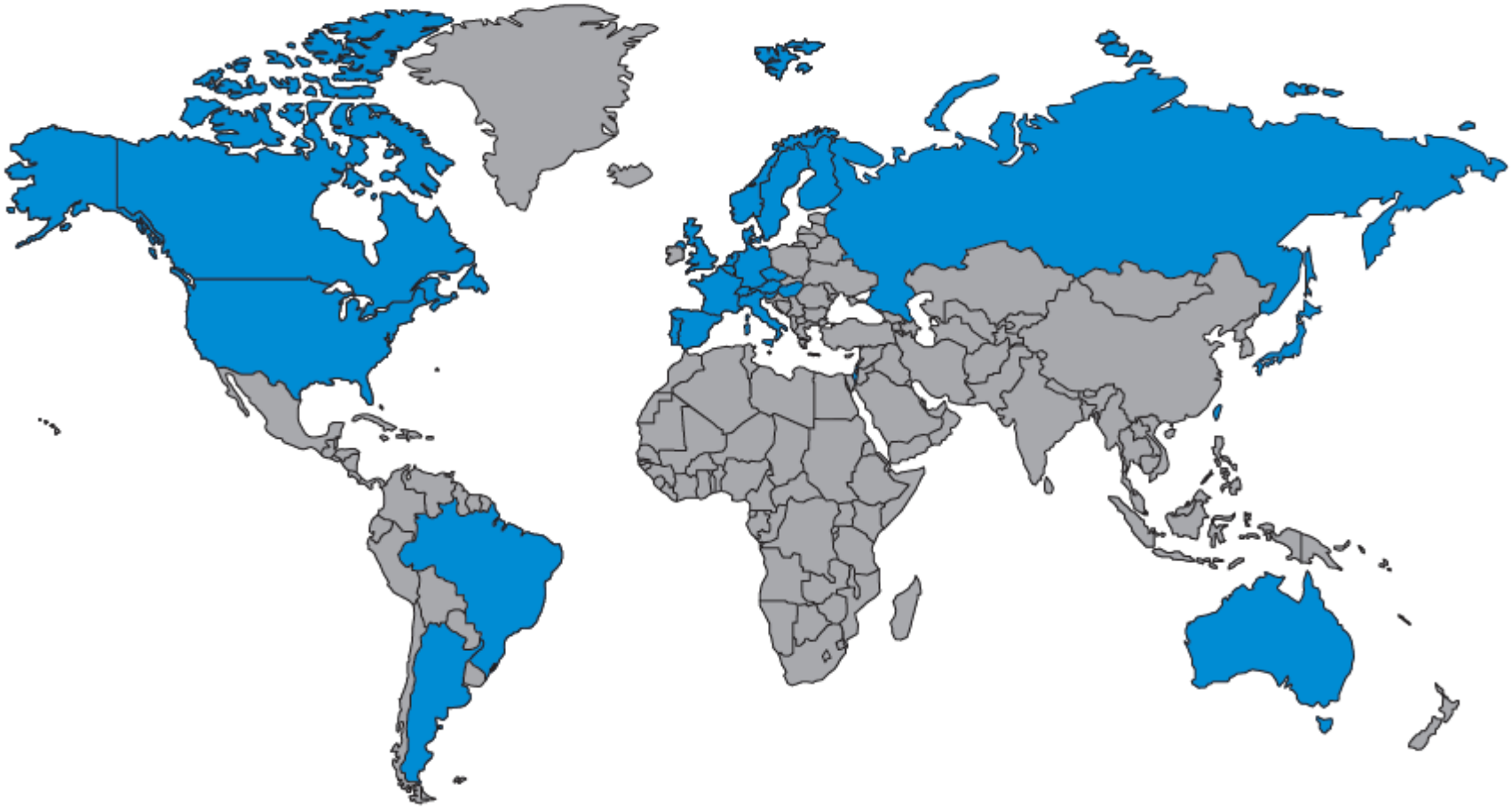


Figure 1. Map highlighting (in blue) the countries in which patients with Fabry disease are enrolled in FOS.

Since the start of FOS in 2001 there has been a continuous increase in the number of patients who are included in the database

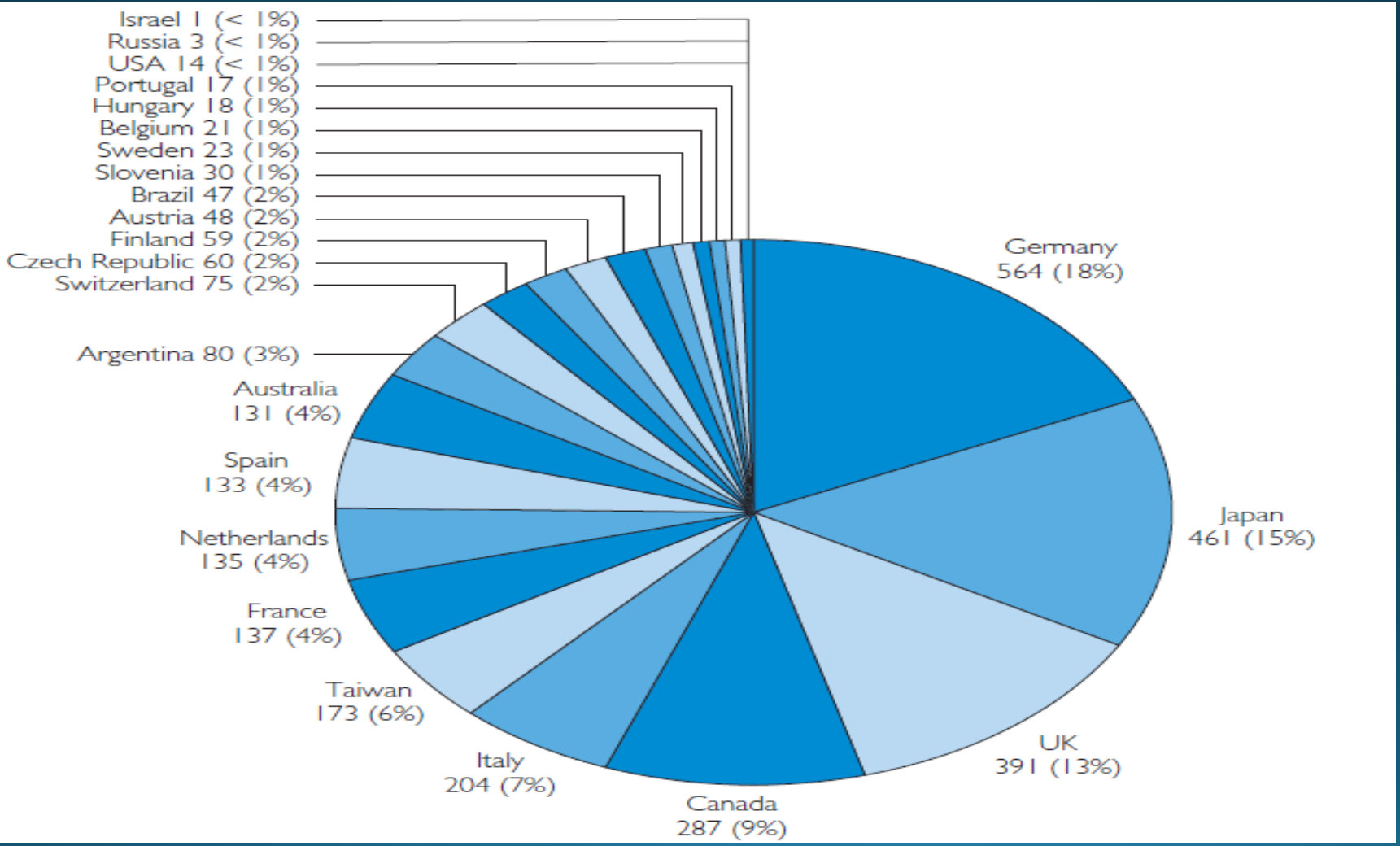
At the end of 2005, data on 815 patients, who were recruited from 87 centers in 13 European countries, had been entered.

So far, the largest groups of patients in Europe come from Germany (22%) and the UK (15%), whereas most other countries each contribute less than 10% of the patient population.

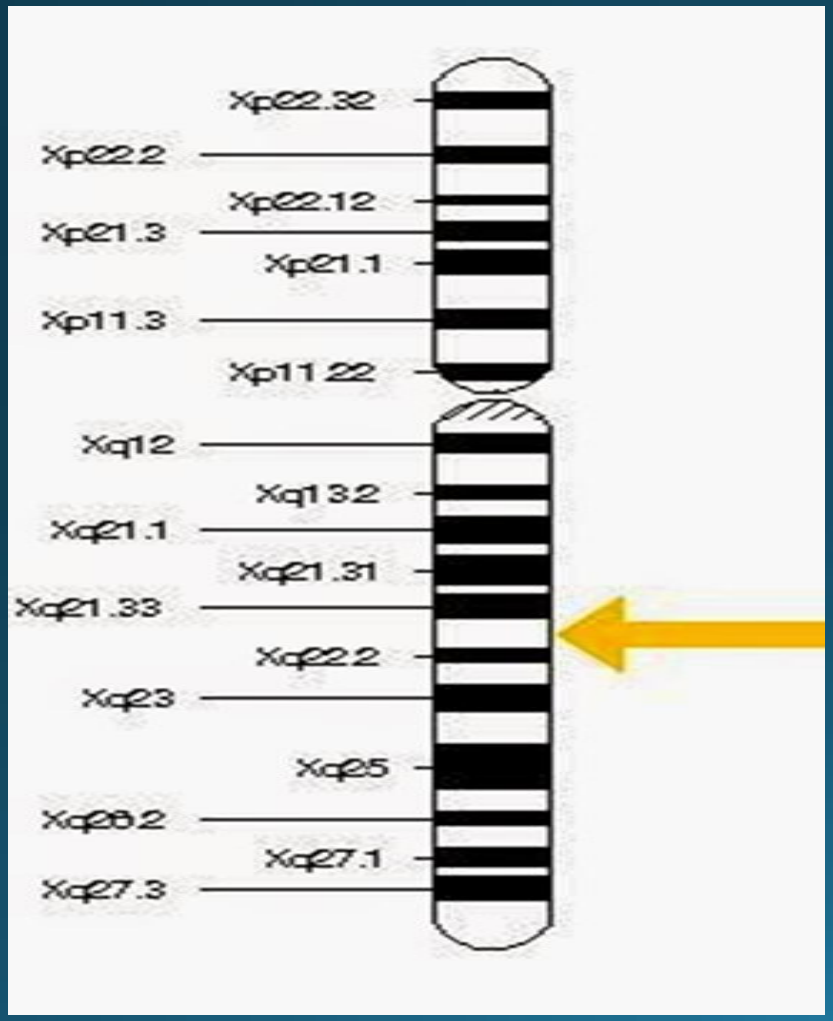

Québec
Ottawa
Toronto
Augusta
St Paul
Cleveland
Virginia Beach
Jacksonville
Tallahassee
San Antonio
Chihuahua
Monterrey
Culiacán
Tucson
Albuquerque
Las Vegas
Carson City
Salt Lake City
Denver
Lincoln
Helena
Portland
Seattle
OR
ID
WY
MT
SD
NE
NV
UT
CO
AZ
NM
TX
MS
GA
TN
MO
NY
VT
UNITED STATES
Gulf Of Mexico

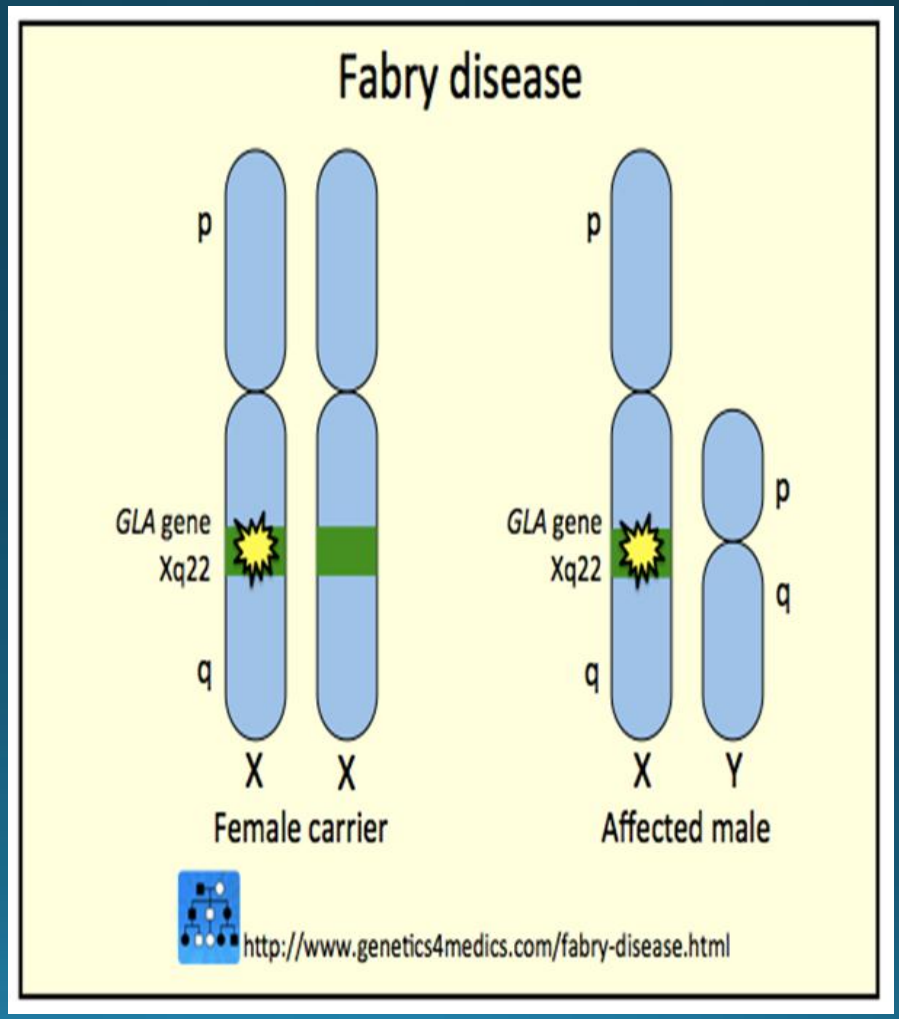
Geographical distribution of patients with Fabry (n = 3112).

proportion (%) of patients enrolled are given for each country.



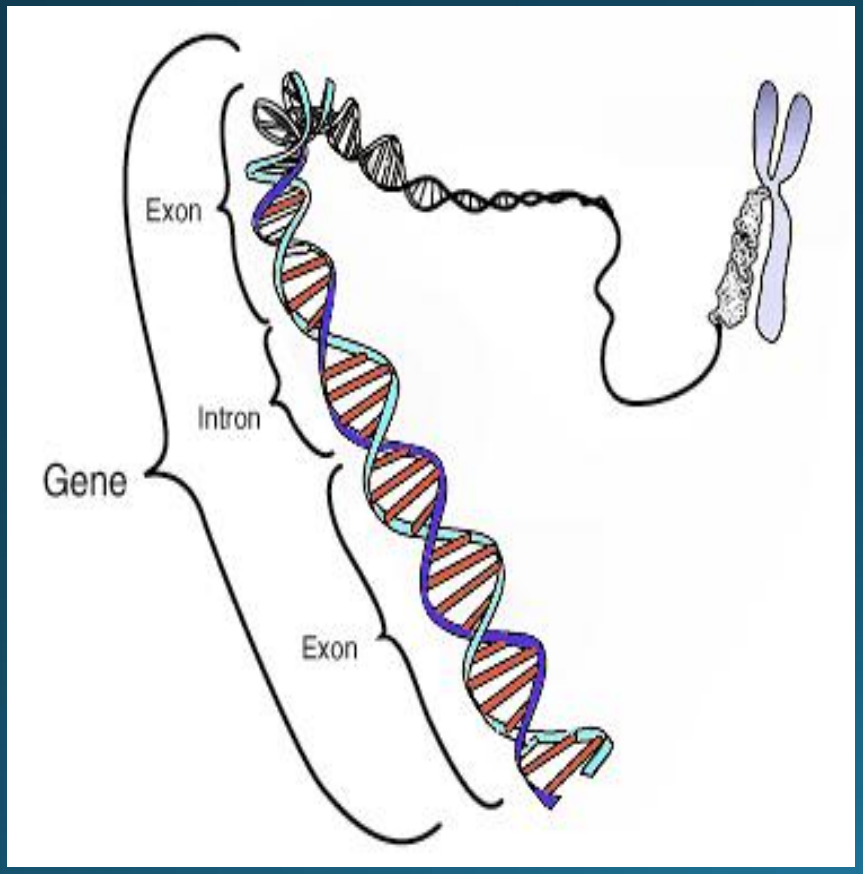
Fabry disease is induced by a mutation in the alpha-galactosidase A gene(GLA gene Xq22 region & exons) causing a deficiency of the enzyme alpha-galactosidase A.

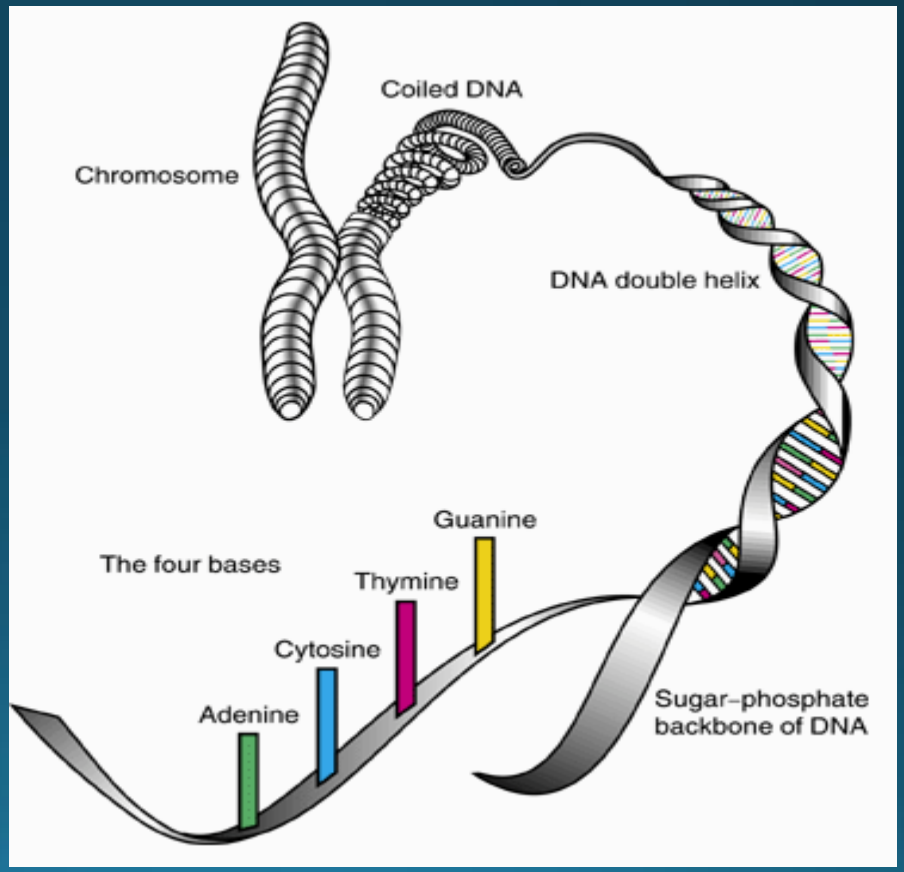




Normal Genome

Human genes are found in the rungs of a DNA double helix. DNA makes up the 23 pairs of chromosomes in the human body.



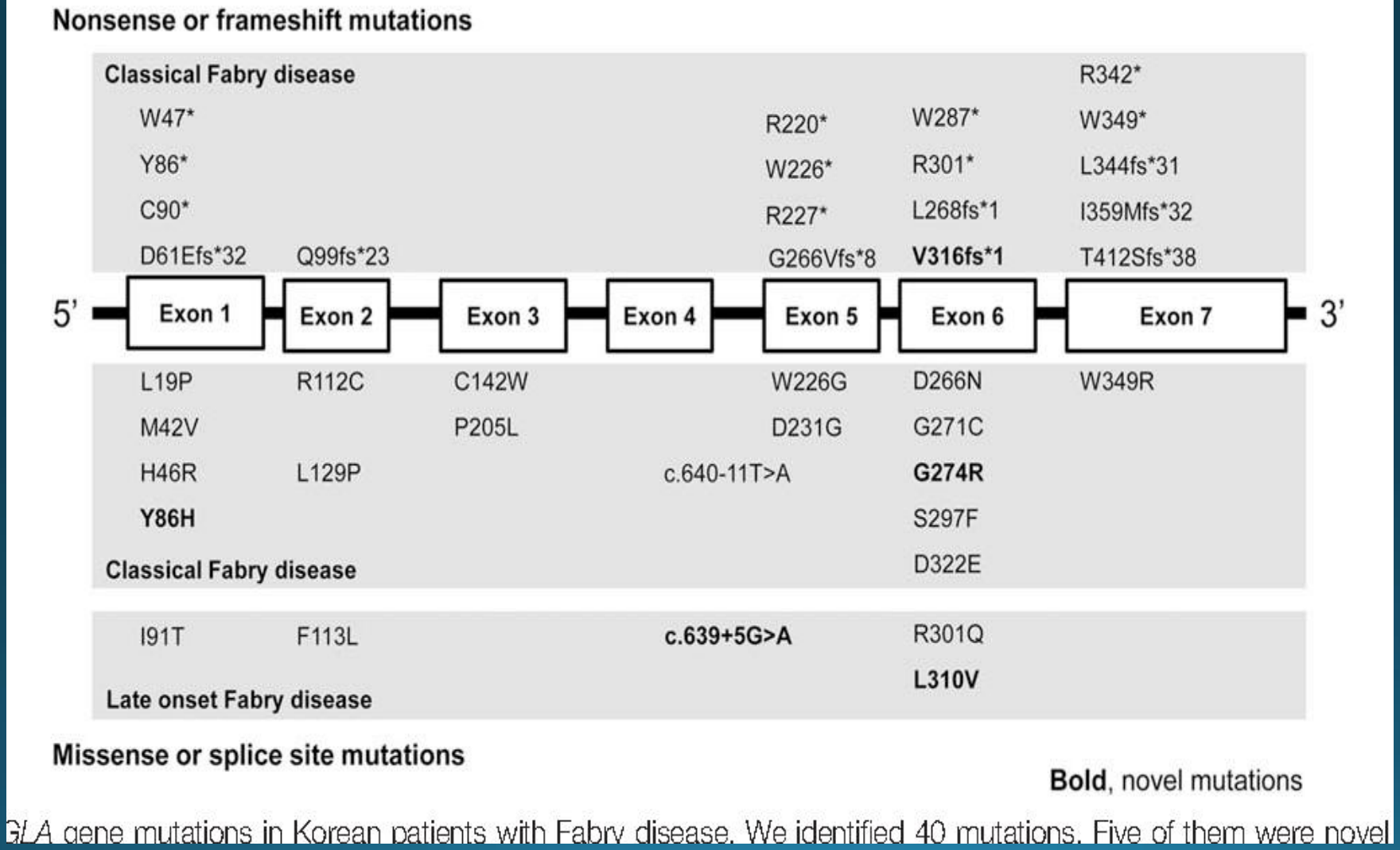


The genetic basis of Fabry disease

The coding region of the α-galactosidase A gene (GLA) consists of 1290 base pairs, is divided into seven exons and defines a polypeptide of 429 amino acids.

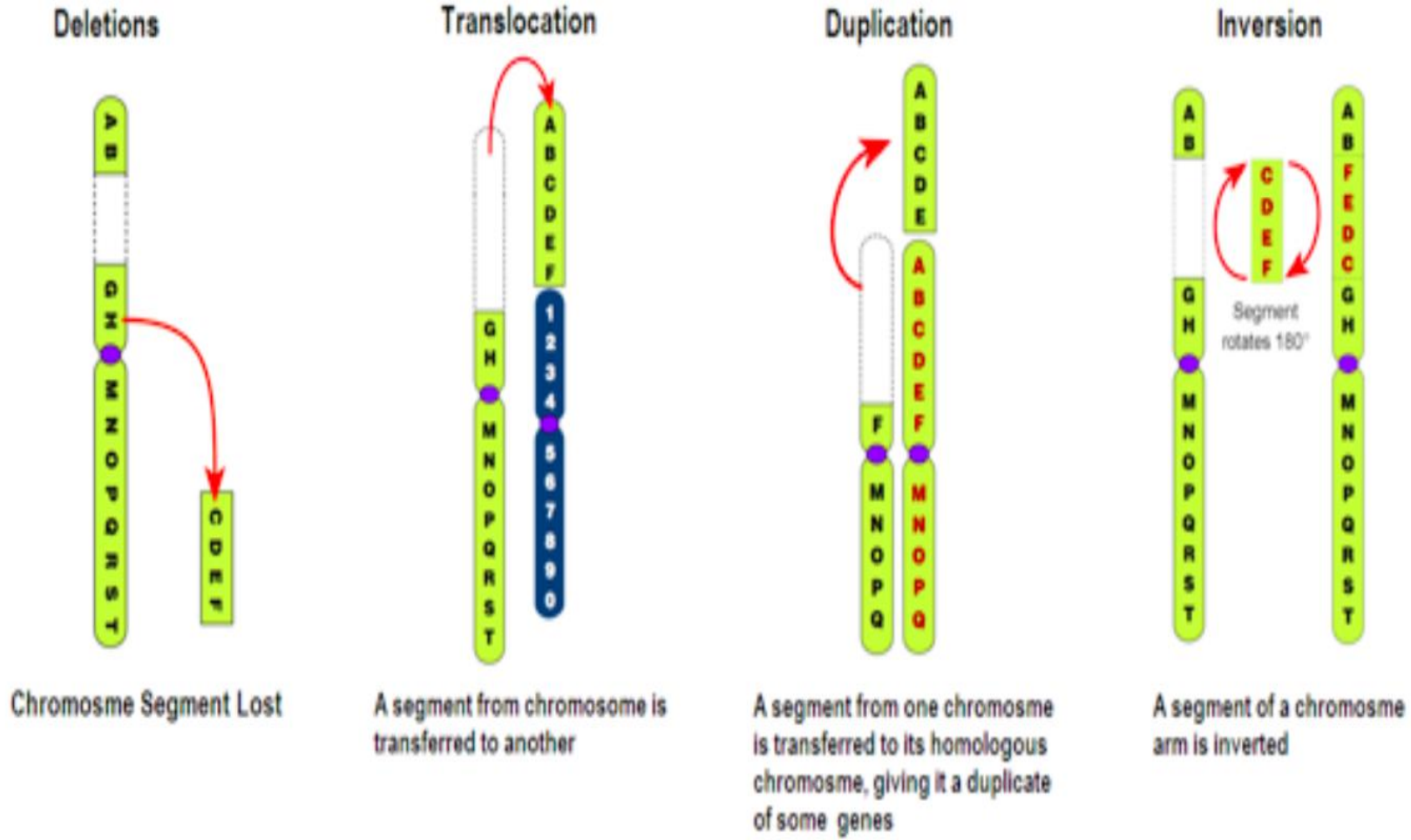
There a list of mutations of the GLA gene from the published literature, including 306 point mutations (missense, nonsense and those affecting splice sites).

Abnormal gene location:

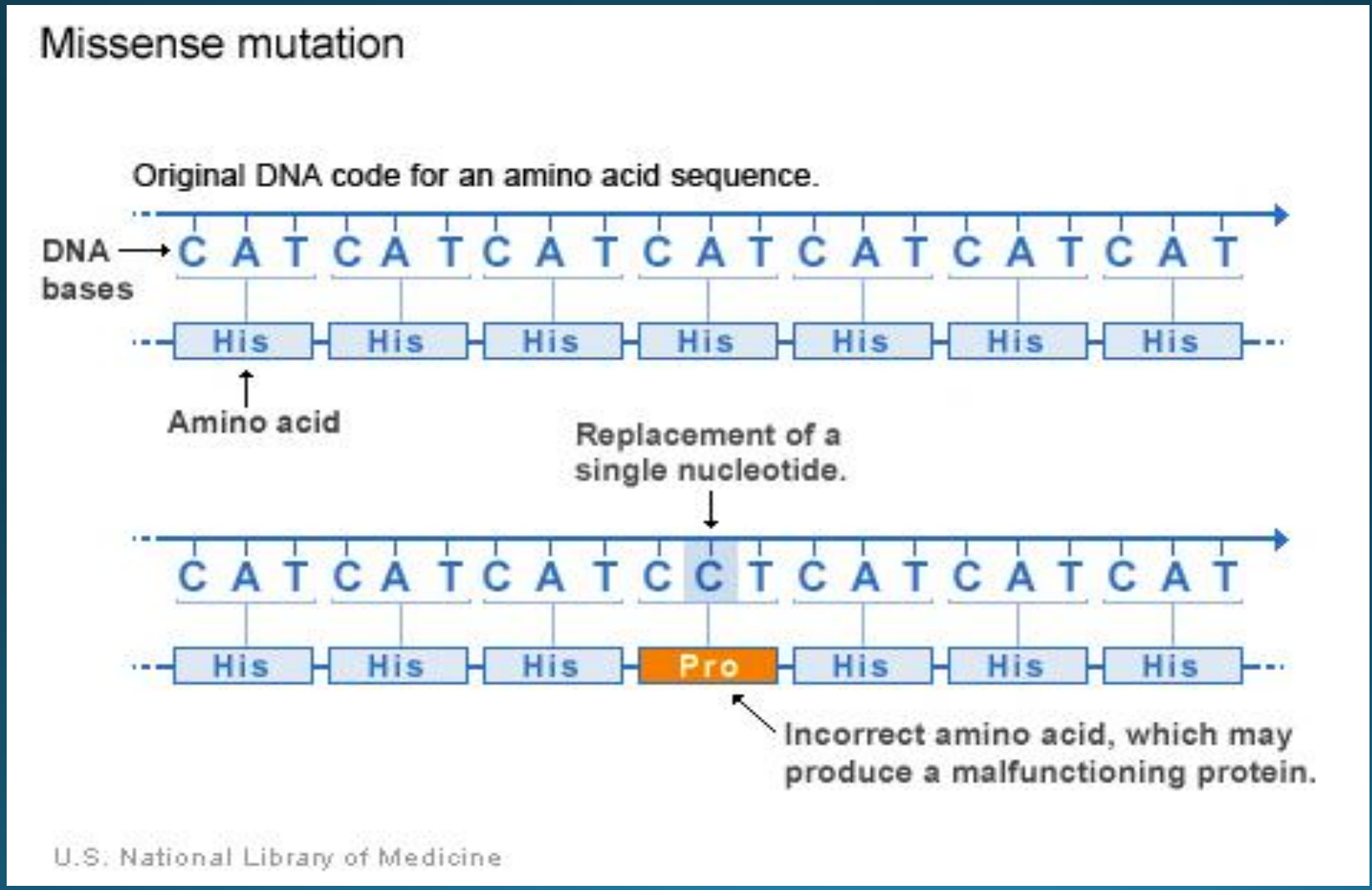


GLA gene mutations in Korean patients with Fabry disease. We identified 40 mutations. Five of them were novel

Types of mutations

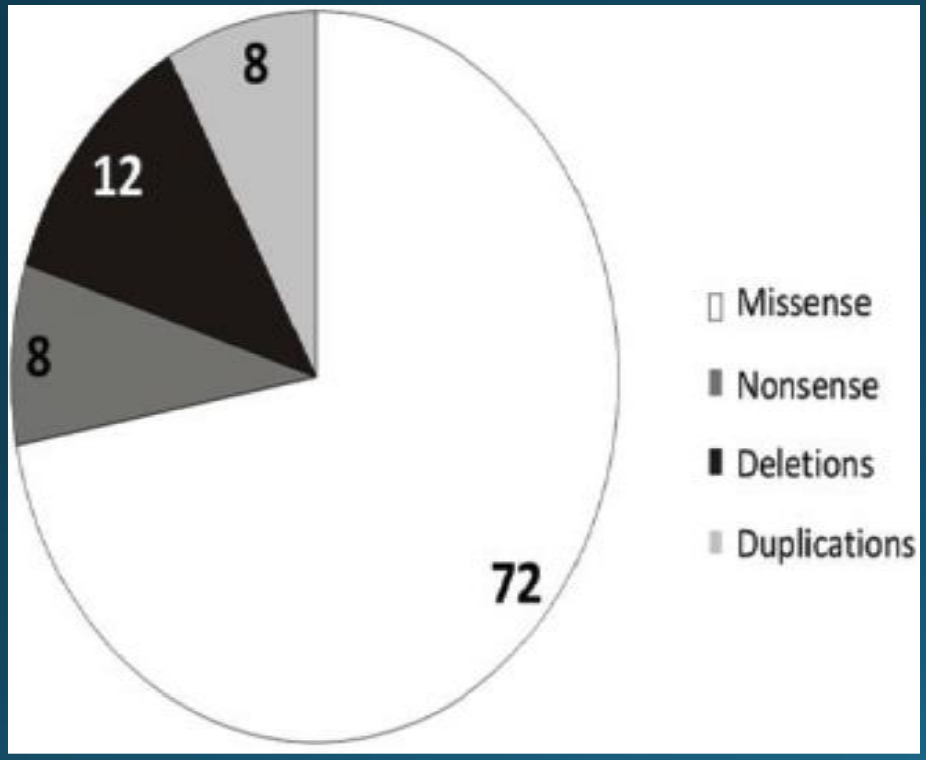


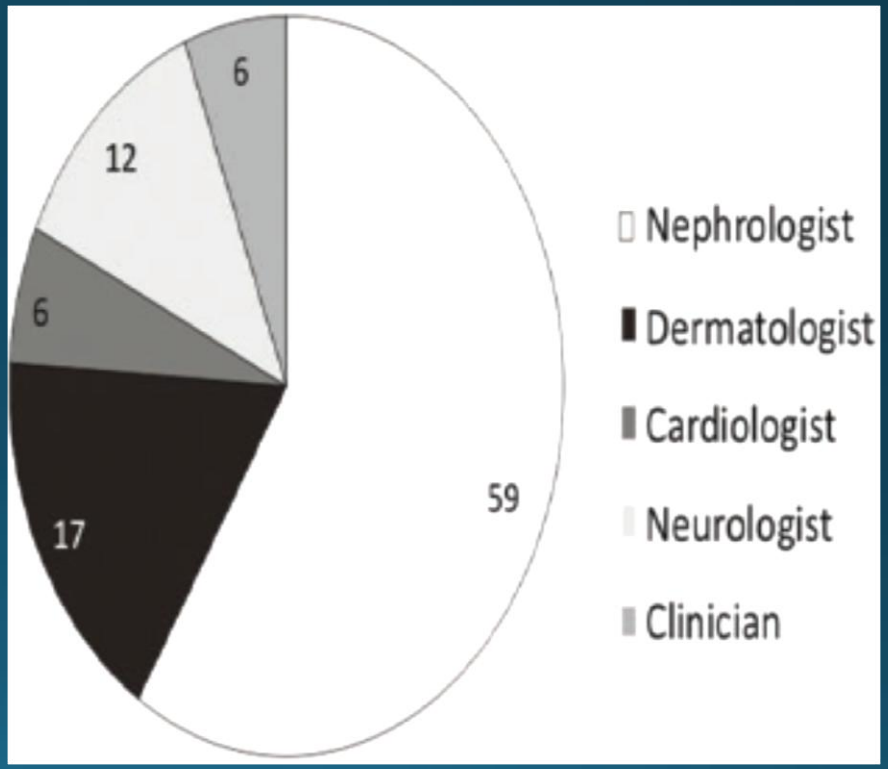
In genetics, a missense mutation is a point mutation in which a single nucleotide change results in a codon that codes for a different amino acid.



Study : Fabry disease in Argentina:

Genotype, and New Learnings ..... October 2015





Missense mutations majority

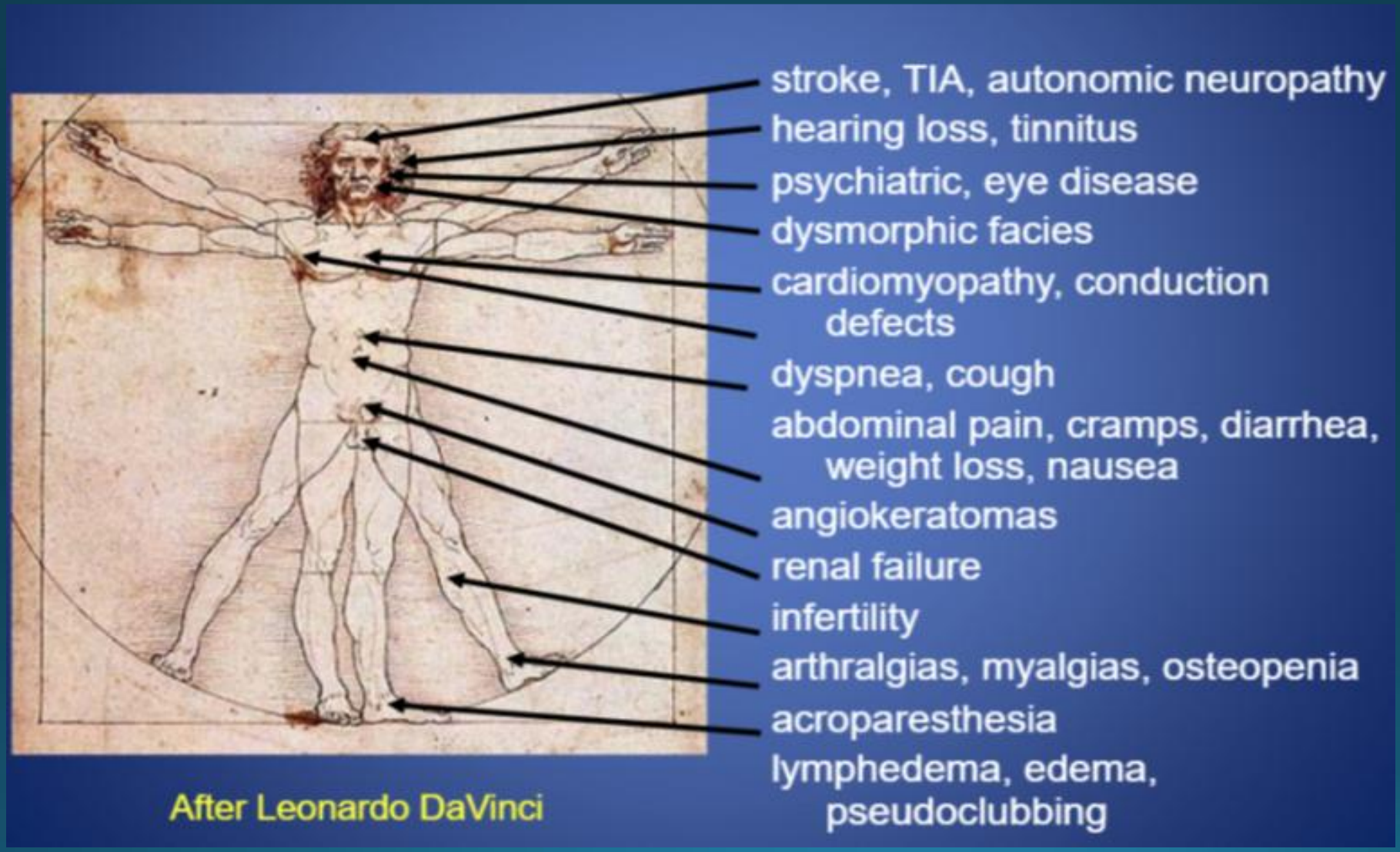
Table 1. List of Mutations From 25 Families of Argentinean patients with Fabry disease.[a]

Family	cDNA	Exon	Protein	Type of Mutation	Reference	De novo	Specialist	Phenotype	Age at Diagnosis	Relatives Studied	Number of Positive Relatives
1	c.679C>T	5	p.Arg227X	Nonsense	11		Nephrologist	Classic	24	253	8
2	c.728T>G	5	p.Leu243Trp	Missense	12		Nephrologist	Classic	39	54	5
3	c.463G>C	3	p.Asp155His	Missense	13		Dermatologist	Classic	23	319	73
4	c.1244T>C	7	p.Leu415Pro	Missense	14		Dermatologist	Classic	32	67	18
5	c.281G>A	2	p.Cys94Tyr	Missense	3		Nephrologist	Classic	46	13	8
6	c.572T>C	4	p.Leu191Pro	Missense	Cooper, 1998		Patient	Classic	25	5	2
7	c.1088G>A	7	p.Arg363His	Missense	Cooper, 1998		Screening hemodialysis	Variant (Cerebrovascular)	62	9	5
8	c.286-287dupA	2	Truncated	Frameshift			Nephrologist	Classic	46	3	2
9	c.581C>T	4	p.Thr194Ile	Missense	15		Patient	Classic	44	59	29
10	c.874G>A	6	p.Ala292Thr	Missense	16		Clinician	Classic	27	8	8
11	c.1145G>A	7	p.Cys382Tyr	Missense	17	De novo	Nephrologist	Classic	30	3	1
12	c.520 T>G	3	p.Cys174Gly	Missense			Cardiologist	Variant (Cardiac)	56	279	51
13	c.680G>A	5	p.Arg227Gln	Missense	18		Dermatologist	Classic	26	15	8
14	c.790G>T	5	p.Asp264Tyr	Missense	19		Neurologist	Classic	62	3	2
15	c.1122_1125delAGGA	7	Truncated	Frameshift			Nephrologist	Classic	31	5	2
16	c.160C>U	1	p.Leu54Phe	Missense			Nephrologist	Variant (renal)	50	6	3
17	c.644A>G	5	p.Asn215Ser	Missense	11		Nephrologist/pathologist	Variant (renal)	61	75	15
18	c.647A>G	5	p.Tyr216Cys	Missense	20		Neurologist	Classic	26	11	6
19	c.448delG	3	Truncated	Frameshift		De novo	Nephrologist	Classic	30	4	1
20	c.772G>T	5	p.Gly258Stop	Nonsense		De novo	Nephrologist	Classic	45	13	2
21	c.782-783dupG	5	Truncated	Frameshift		De novo	Nephrologist	Classic	46	5	1
22	c.718_719delAA	5	Truncated	Frameshift		De novo	Patient	Classic	15	3	1
23	c.335G>A	2	p.Arg112His	Missense	21		Screening hemodialysis	Variant (renal)	72	24	15
24	c.902G>A	6	p.Arg301Gln	Missense	22		Cardiologist	Classic	48	35	17
25	c.100A>G	1	p.Asn34Asp	Missense			Nephrologist	Classic	16	3	3

Abbreviation: cDNA, complementary DNA.

[a]Also shown is the phenotype of the index patient, the specialist who made the clinical suspicion, the reference if the mutation has been reported, the age at diagnosis of the index case, and the number of members of each family that were studied and the number of positive ones.

Fabry disease – Clinical features



Fabry : renal involvement

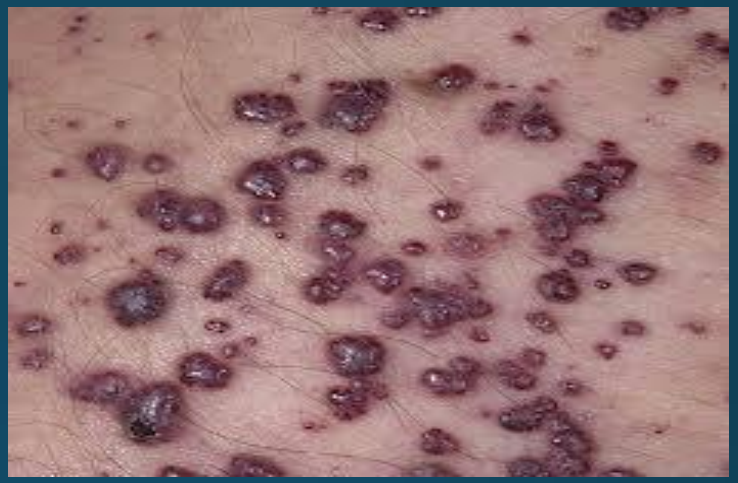
- Overall, 91% of patients had Fabry disease involvement in ≥2 organ systems, indicating significant disease burden.
- In Study 011, all patients had clinical manifestations, and 90% of patients had renal involvement, 52% had cardiac involvement, and 54% had CNS involvement.
- In Study 012, all patients had clinical disease manifestations, and 75% of patients had renal involvement, 72% had cardiac involvement, and 53% had CNS involvement.

Phenotype of Fabry Disease in Patients with Mutations Amenable to Migalastat

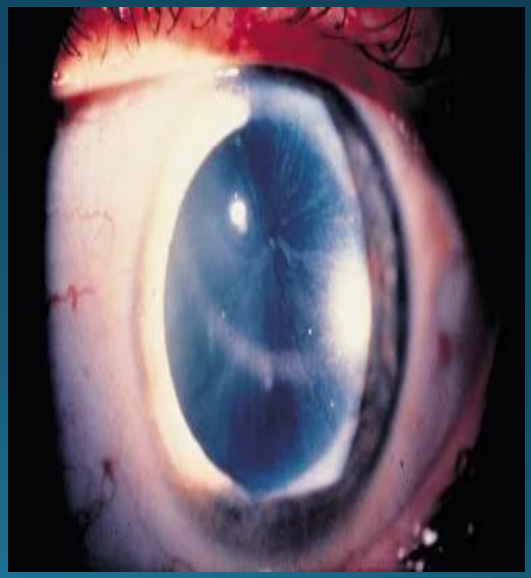
Hughes, D[1], Bichet, DG[2], Germain DP[3], Giugliani R[4], Schiffmann R[5], Wilcox W[6], Castelli J[7], Benjamin E[7], Skuban N[7], and Barth J[7]

Clinical features

Skin :
Angiokeratomas, acroparaesthesia, abnormal sweating (hypohidrosis and hyperhidrosis) and lymphoedema



Eye :
- Conjunctival vascular abnormalities,
Corneal opacities (cornea verticillata),
- Lens opacities.

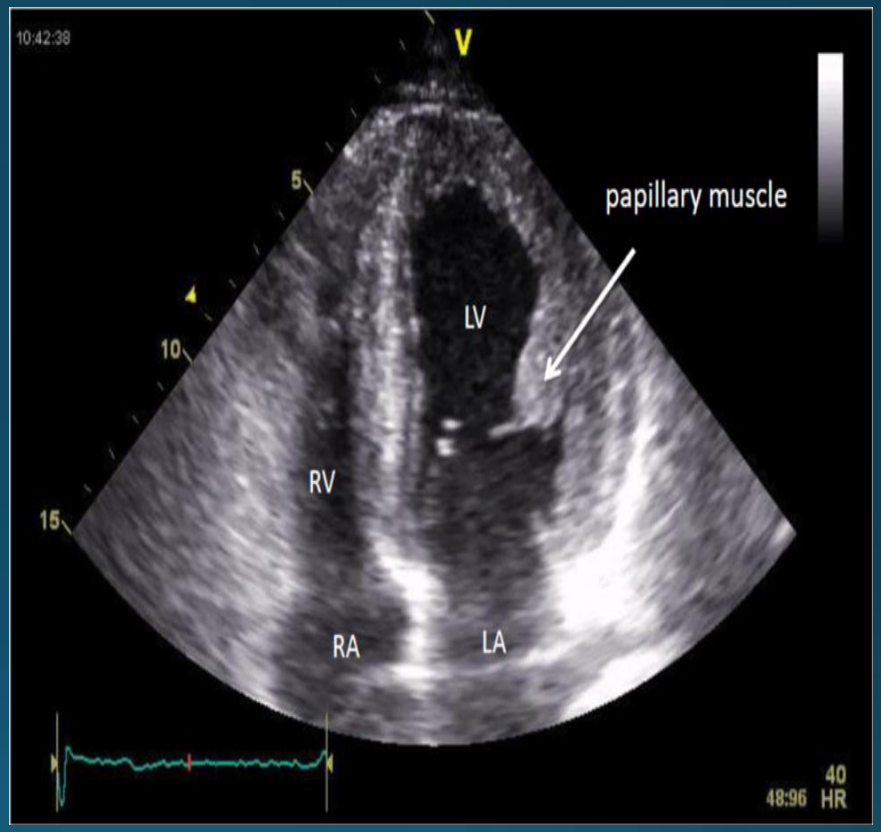


Fabry cardiac disease

Cardiac involvement is common and presents as concentric left ventricular hypertrophy.

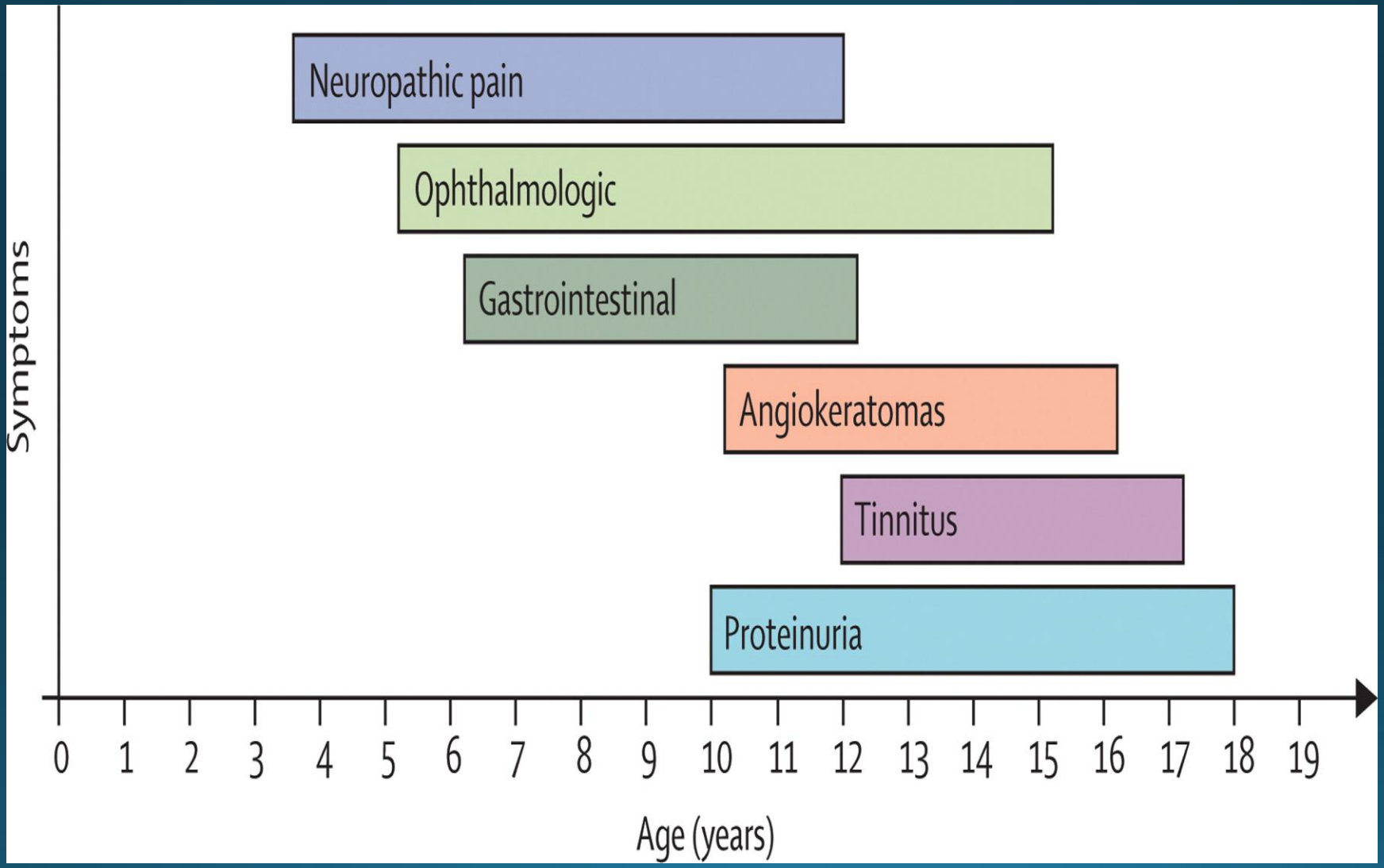
Myocardial fibrosis is a typical feature of more advanced stages of Fabry cardiomyopathy.

If therapy started early, before myocardial fibrosis has developed, a long-term improvement of myocardial morphology, and function can be achieved.



This apical four-chamber view is showing a prominent papillary muscle as well as a thickened interventricular septum and lateral wall of left ventricle.

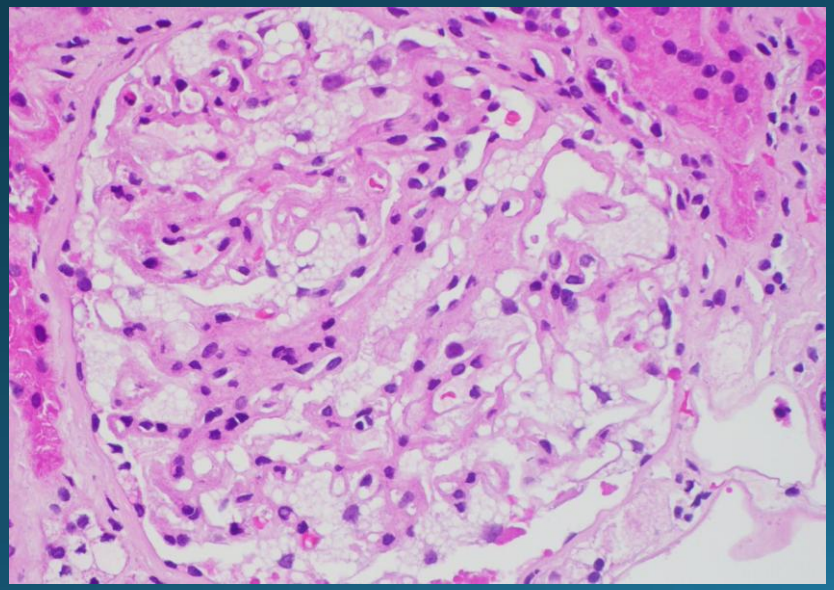
Proteinuria ….. after 10 years



Kidney biopsy in Fabry

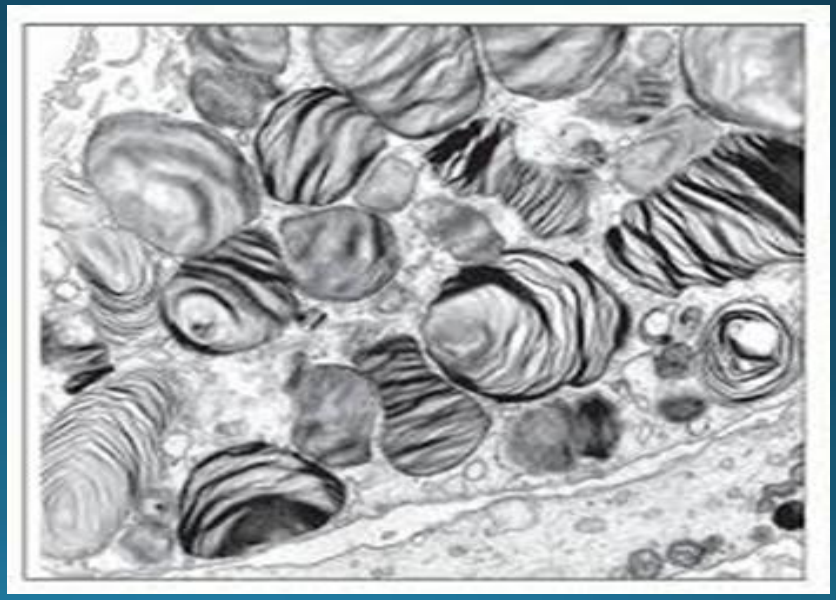
Glomerulus showing vacuolated podocytes

(hematoxylin and eosin).

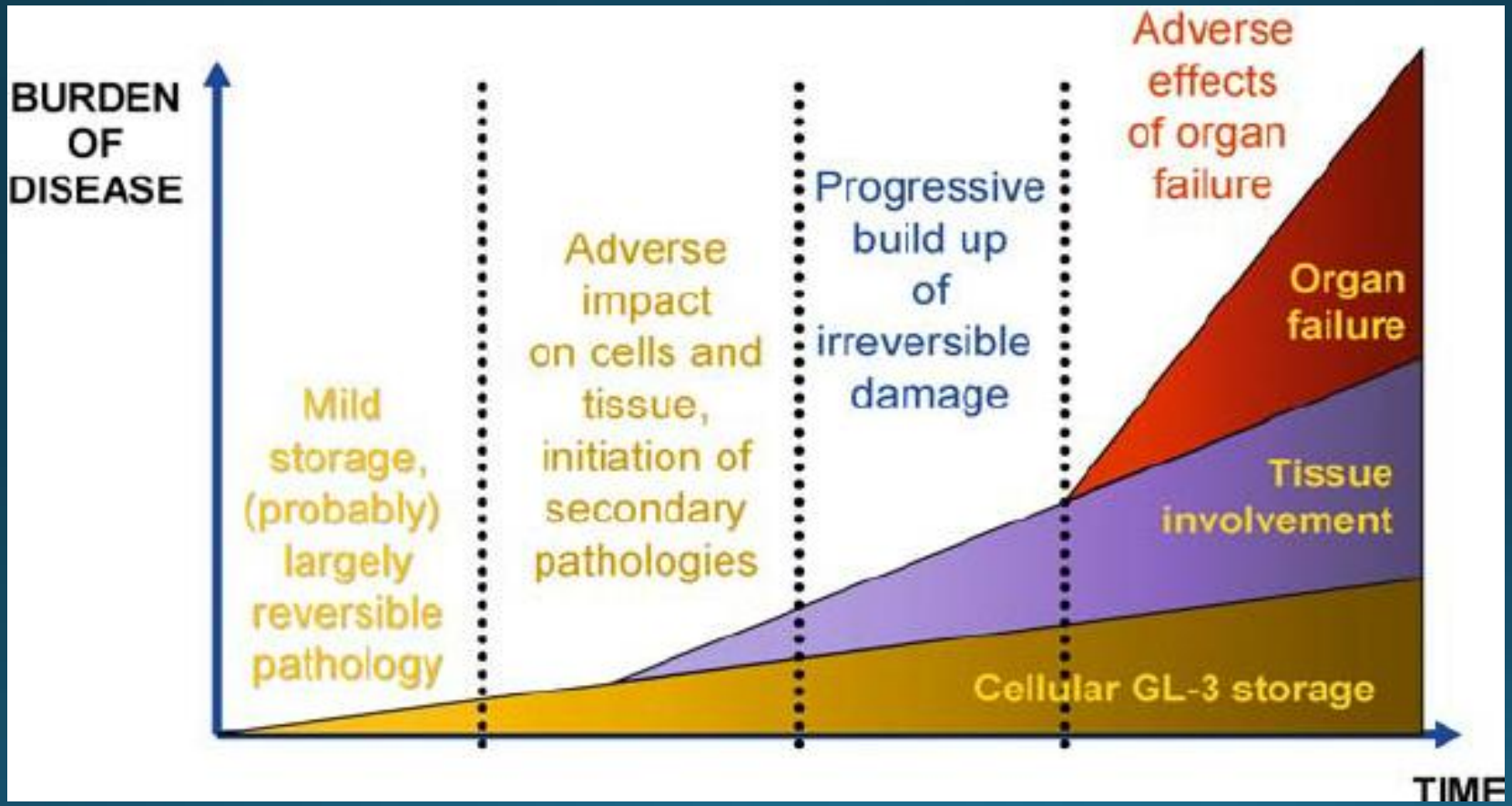


Electron-dense laminated myelin figures in glomerular epithelial cells.

(Electron micrograph).

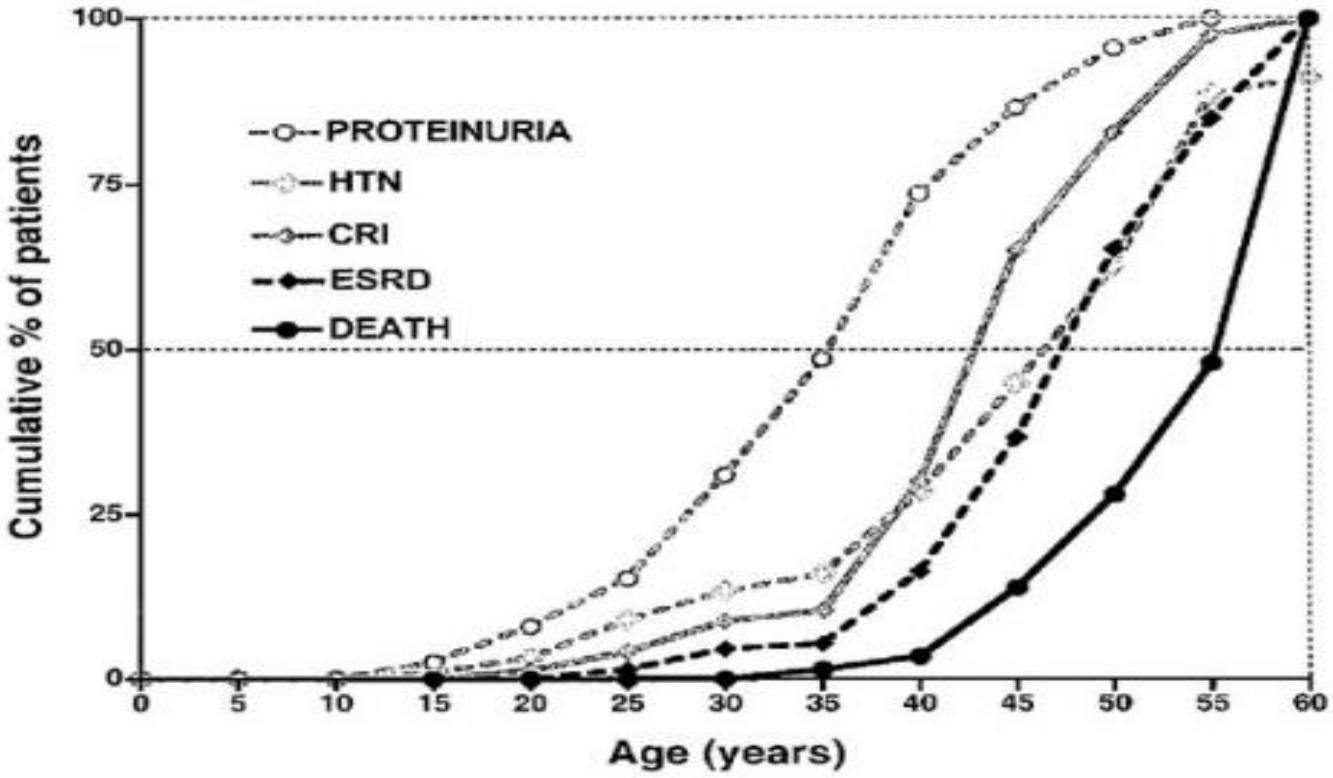


Fabry kidney disease model



Progression Fabry renal disease

Microalbuminuria, isolated proteinuria , hematuria
106 males pts. FD in a retrospective study (over 30 y) before ERT
Renal insufficiency at 30's , ESRD at 40's and death at 55-60's



Branton et al., Medicine, 2002

Why screening Fabry?

Rational for early detection of Fabry :

- Earlier therapy will protect organs and gives best results
- Genetic counseling , informed reproductive advice is very beneficial.
- Screening may identify undiagnosed relative having the disease.

Think of Fabry disease when:

- Un explained CKD
- LVH, Arrthymia
- Chest pain with negative cardiac cath.
- Stroke / TIA under 55
- Un explained Myalgia , arthralgia
- Sensory peripheral neuropathy
- Angiokeratomas

KDIGO Recommendation: screening

Screening for Fabry in renal units /dialysis is feasible ,testing accurate ,and affordable.

Important to accurately identify undiagnosed patients to provide earlier therapy ,genetic counseling better outcome.

kidney international 2016

How to screen for Fabry disease

- Dried blood spot Whole blood
- Galactosidaes activity , plasma WBC.
- Females can have normal a-gal levels
- Biomarkers Gb3 urine/plasma
- GLA mutational analysis

Diagnosis

- Family HX ; but there is new mutation by 5%
- Males : a-gal Enzyme activity : < 5%normal
- Females mosaics; a-gal low / normal ,DNA analysis
- Biopsy kidney .
- Increase in Gb3 plasma ,urine enzyme substrate

Fabry disease therapy

How to treat?

- Missing enzyme: **replace** the enzyme

  Enzyme **replacement** therapy: ERT
  Agalsidase alfa 0.2 mg/kg/EOW or Agalsidase beta 1.0 mg/kg/EOW iv enzyme

- Target organ injury: tissue **protective** therapy

  e.g. renin angiotensin system (RAS) blockade

Fabry disease therapy

General

- Control CV risk factors (dyslipidemia ,smoking ,HBP)
- Stroke prophylaxis (ASA , clopidogrel)
- Limit proteinuria -RAS inhibition
- ERT early before irreversible organ scarring
- Transplant kidney vs. dialysis
- Control neuropathic pain avoid narcotics
- Multidisciplinary team , regular follow up

Enzyme replacement therapy with α-galactosidase A

- Recombinant human enzyme given as infusion q2 wks.
- Replace missing enzyme
- Uptake into lysosome via mannose -6-phosphate receptor
- Cost : around $229.000-$289,000 per pt. per year

ERT for Fabry disease

Enzyme replacement therapy (ERT) may halt or attenuate disease progression.

Since administration is burdensome and expensive, appropriate use is mandatory.

The European consensus recommendations for the initiation and cessation of ERT in patients with FD simplified treatment protocol.

1-Fabrazyme

Agalsidase beta

(Fabrazyme®, Genzyme-Sanofi, Cambridge, MA, USA), purified from genetically engineered Chinese hamster ovary (CHO) cells

Agalsidase beta 1.0 mg/kg over 100 minutes.

FAACET trial

(Fabrazyme and ARBs/ ACE Inhibitor Treatment): ACEI/ARB+ERT

- 24 FD patients,9 F / 15 M , Age 43.1 yrs.
- ERT agalsidase beta 1.0 mg/kg iv Every other week
- ARB/ACEI tittered to decrease proteinuria
- 21 months follow up
- 18/24 (75%) achieved target UPCR< .5 g/d

Group	N	Age yrs	eGFR BL ml/min/1.73m^2	GFR slope per year
Met uPCR goal < 0.5	6	40.6	88	-0.1
	12	46.6	62	-4.2
uPCR >0.5	6	41.5	61	-7.0

Warmock et al J Med Genet 2015

2- Replagal

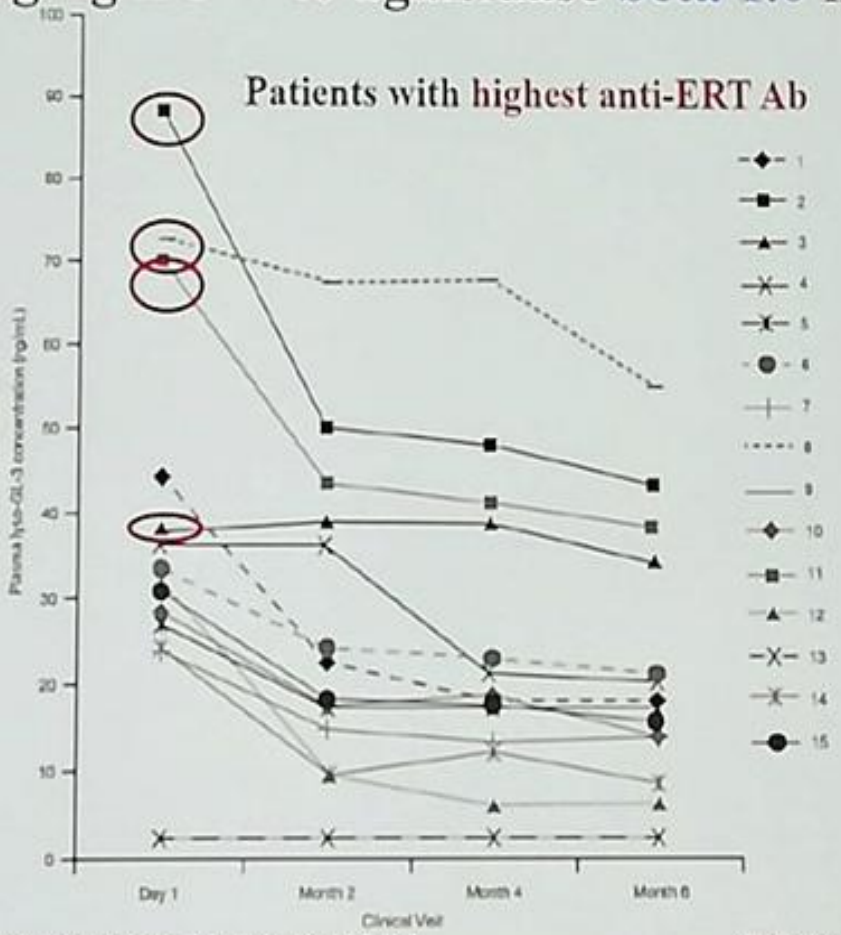
Agalsidase alfa

(Replagal®, Shire, Lexington, MA, USA) , from a genetically engineered human fibroblast cell line.

Agalsidase-alpha 0.2 mg/kg over 20 minutes.

The dose of replacing enzyme matters

Plasma lyso-Gb3 decreased when ERT switched from agalsidase alfa 0.2 mg/kg/EOW to agalsidase beta 1.0 mg/kg/EOW



Efficacy and safety of Fabrazyme (agalsidase beta) in patients aged 0-7 years has not been established.
Per approved leaflet in Brazil, Fabrazyme (agalsidase beta 1mg/kg/every two weeks) is indicated in adults and adolescents aged 16

Goker-Alpan, et al. Reduction of Plasma Globotriaosylsphingosine Leve
After Switching from Agalsidase Alfa to Agalsidase Beta as Enzym

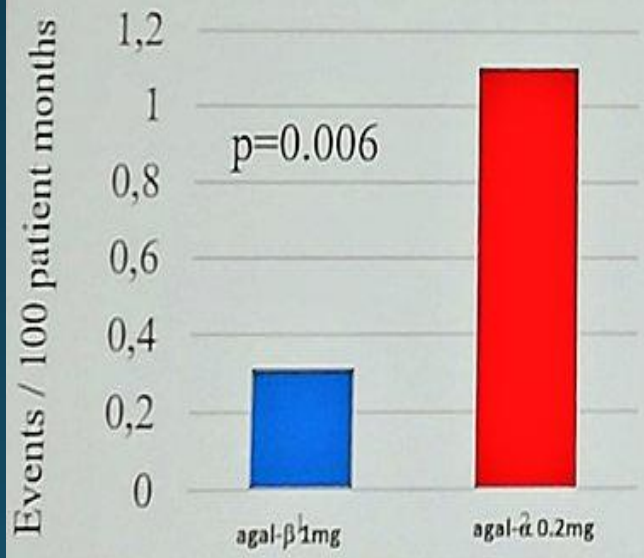
CFDI : ERT 10 years outcome

CFDI: The Canadian Fabry Disease Initiative

10 year outcomes of an RCT of enzyme replacement therapy (ERT)

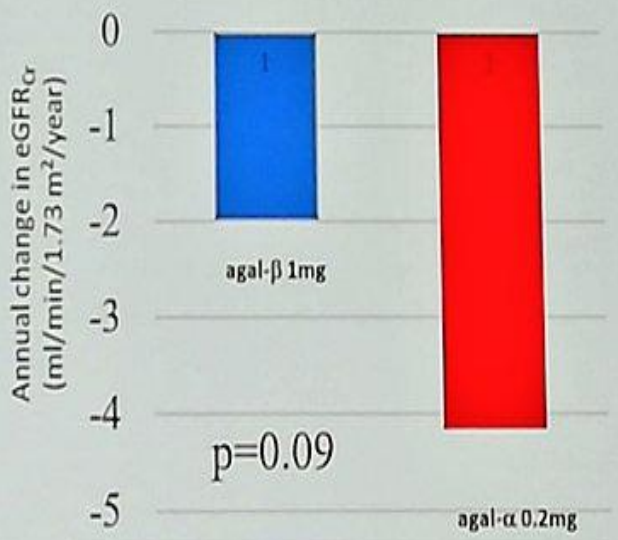
SSIEM 2018 abstract - Differential effects of agalsidase alfa and agalsidase beta in Fabry outcomes: 10 year outcomes form the Canadian Fabry Disease Initiative.
Sirs SM, Bichet DG, Iwanochko RM, Khan A, Doucette S, Lemoine K, West ML

Events: (renal replacement therapy, doubling of serum creatinine, proteinuria>3.5 g/day)



More renal events in males receiving AGALα than males receiving AGALβ (1.1 versus 0.31 events/100 patient months IRR 0.24 p=0.006)

Loss of eGFR



Faster rate of decline of eGFR lower in male patients on AGALα than those on AGALβ (-1.98 vs. -4.15 ml/min/1.73m2/year; p=0.09).

N = 132 patients
N = 56 agalsidase-β 1mg/kg/eow
N = 76 agalsidase-α
Median duration follow-up 99 mos (range 5-123)

The rates of cardiac or neurological events or death did not differ between the two treatment groups.

32

- In Registry data, agalsidase-β 1.0 mg/kg/2 weeks was associated with a roughly 50% lower incidence rate of severe events from 6 months to 5 years than during the first 6 months of ERT, even in patients with advanced disease

- This observation is in line with results from the phase IV placebo-controlled, agalsidase-β trial with primary endpoint severe events

- CFDI head-to-head RCT further supports the efficacy of agalsidase-β to prevent kidney events in males

- However, older age at start of ERT was associated with a higher incidence of severe events: start early within the recommendations of prescribing information

Efficacy and safety of Fabrazyme (agalsidase beta) in patients aged 0-7 years has not been established.
Per approved leaflet in Brazil, Fabrazyme (agalsidase beta 1mg/kg/every two weeks) is indicated in adults and adolescents aged 16 years and older.

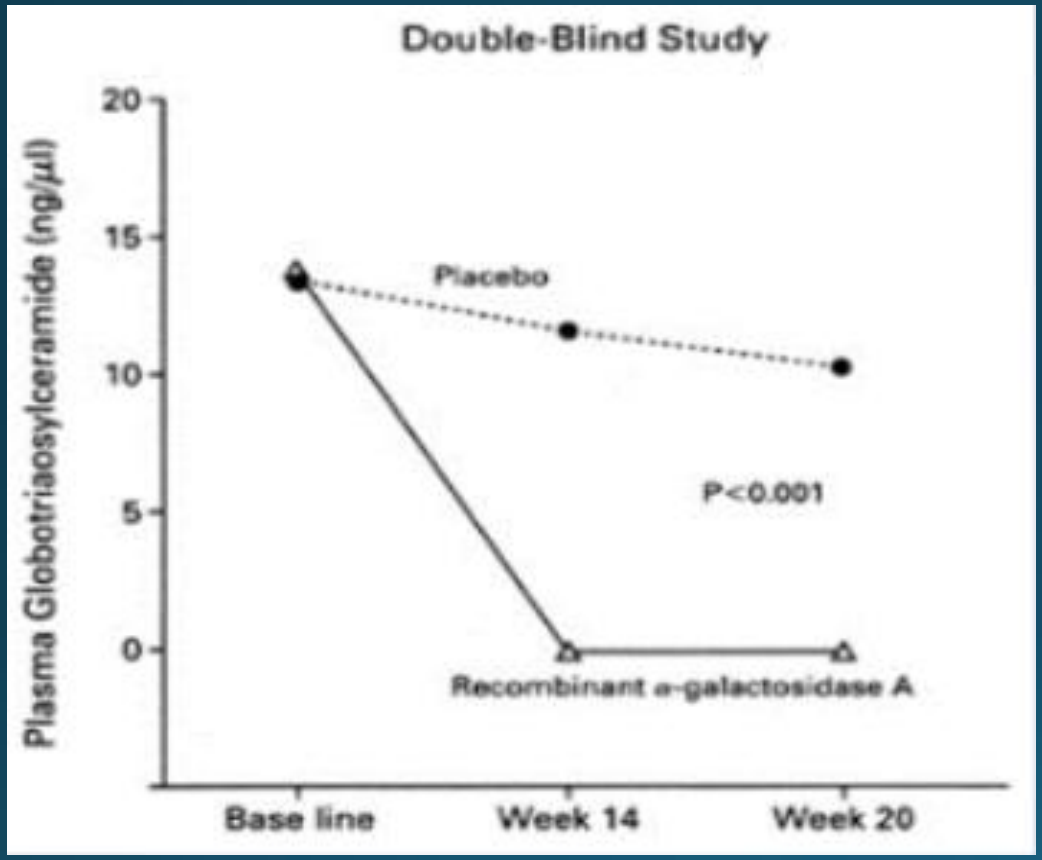
3- Migalastat

Oral Medication Receives FDA Approval for Treatment of Fabry Disease (AUGUST 13, 2018)

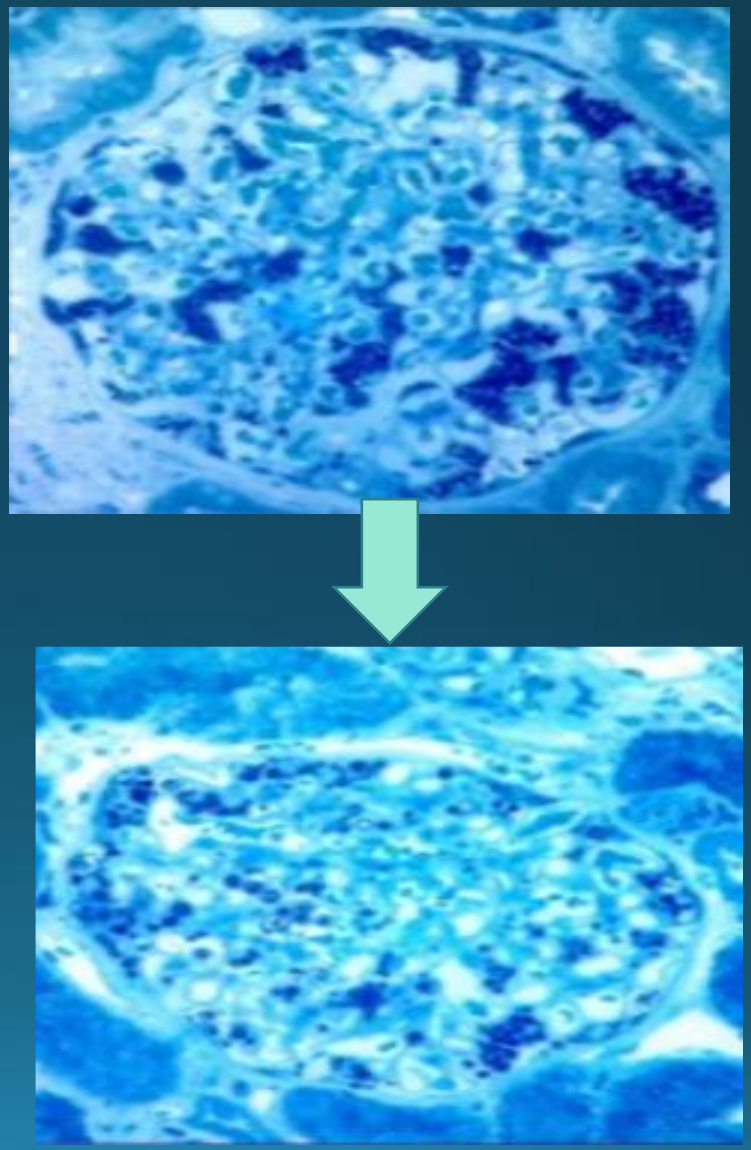
Officials with the FDA have approved migalastat (Galafold, Amicus Therapeutics), the first oral medication for the treatment of adults with Fabry disease.

Amenable mutations !!!

Efficacy of enzyme therapy
biochemical & histological response



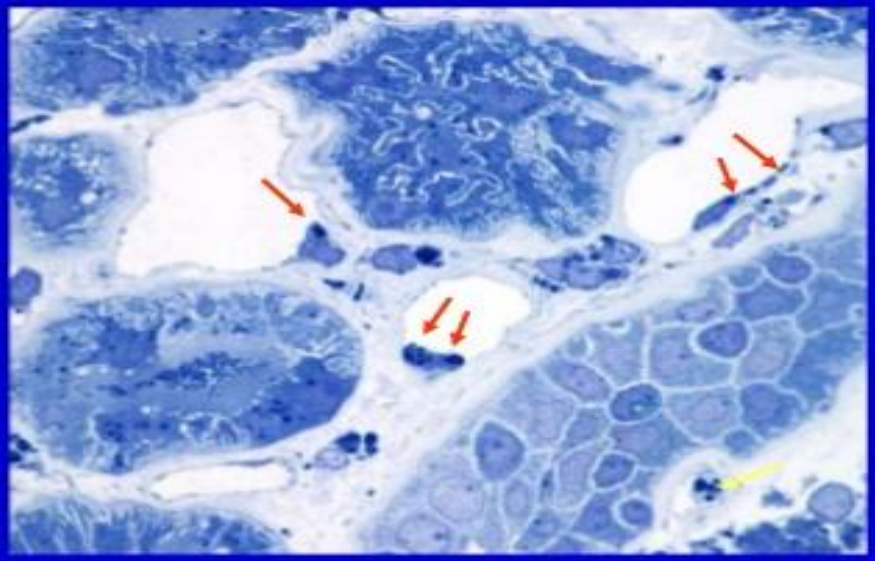
Significant reduction of Gb3 after 14 weeks



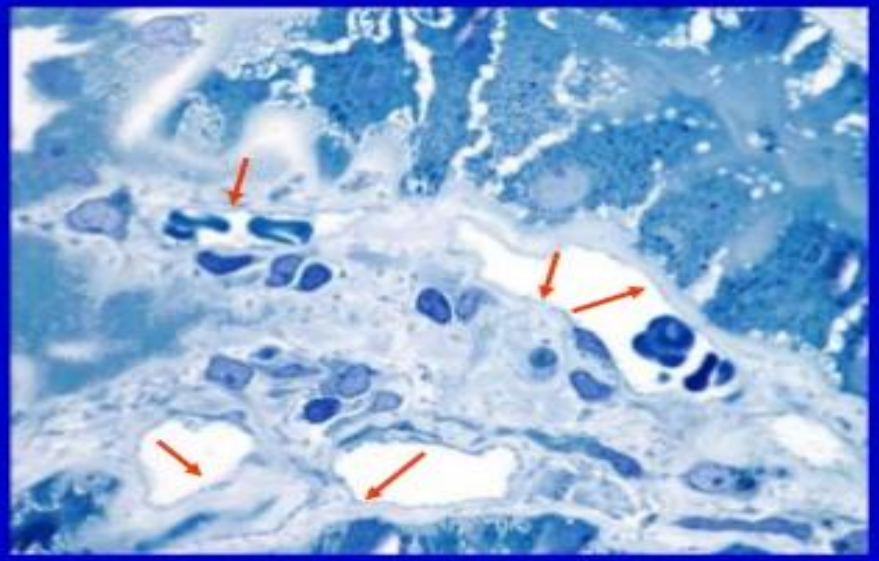
Eng et al NEJM 2001;345:9
Schiffman et al JAMA ;285:2743

Efficacy of enzyme therapy

Primary Endpoint
GL-3 Is Cleared From Peritubular Capillary Endothelium



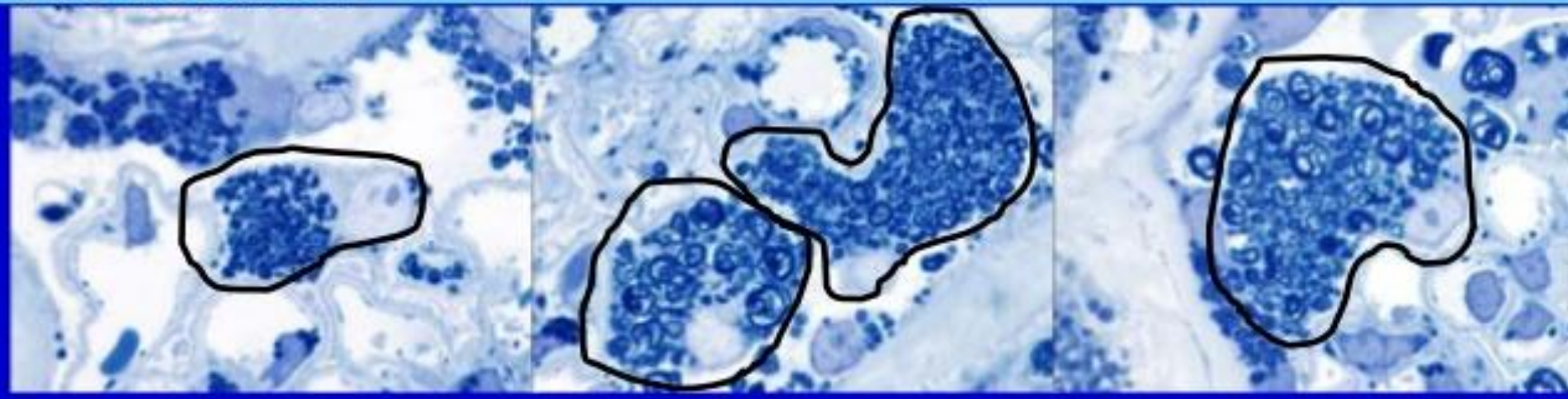
Pre-treatment



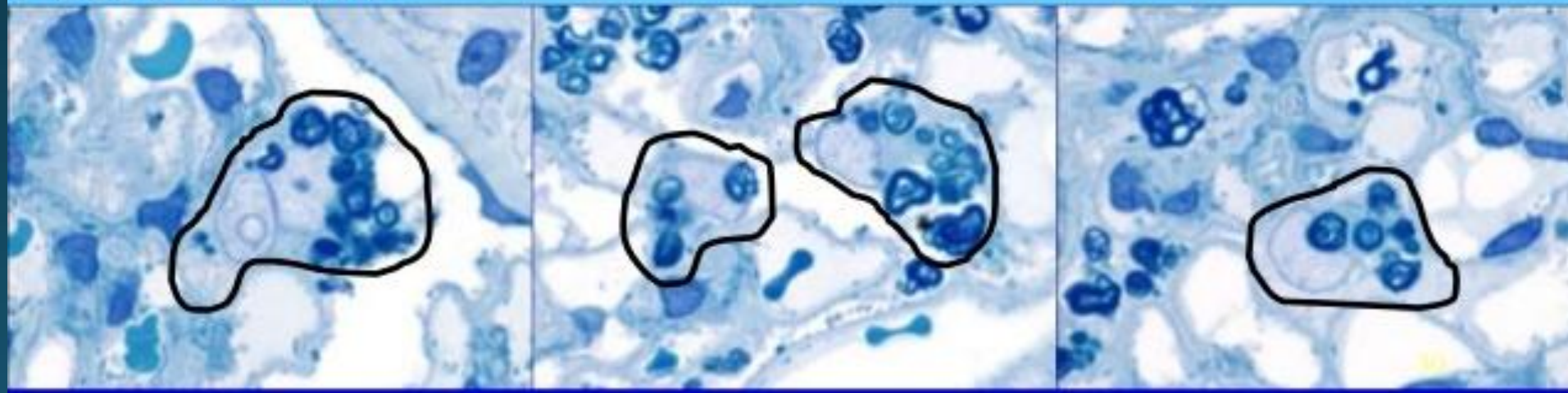
Post-treatment

GL-3 Levels Are Reduced in Podocytes

Pre-treatment



Post-treatment



The European Consensus Recommendations for: the Initiation of ERT in patients with FD

ERT is recommended as soon as there are early clinical signs of kidney, heart or brain involvement, but may be considered in patients of ≥16 years in the absence of clinical signs or symptoms of organ involvement.

Treatment should not be withheld from patients with severe renal insufficiency (GFR < 45 ml/min/1.73 m2) and from those on dialysis, but carefully considered on an individual basis.

Biegstraaten et al. Orphanet Journal of Rare Diseases (2015) 10:36

Treatment with A galsidase Alfa during Pregnancy

There are very few data on the safety of ERT during pregnancy.

Case report: The patient, a 22-year-old woman, was diagnosed with FD three years prior to pregnancy.

She started treatment with agalsidase alfa (0.2 mg/kg every 2 weeks) with a substantial amelioration of the disease over time.

Conclusion :. ERT with agalsidase alfa during pregnancy seems to be well tolerated, without negative effects on the mother or child.

Journal of Genetic Disorders & Genetic Reports Citation: Pisani A, Bifulco G, Sardo ADS, Riccio E (2016) Treatment with Agalsidase Alfa during Pregnancy in a Heterozygous Female with Fabry Disease. J Genet Disor Genet Rep 5:4. doi: 10.4172/2327-5790.1000143

When cessation of ERT should be considered ?

-In patients with end stage FD or other co-morbidities, leading to a life expectancy of <1 year.

-In those with cognitive decline of any cause, or lack of response for 1 year when the sole indication for ERT is neuropathic pain.

-In patients with end stage renal disease, without an option for renal transplantation, in combination with advanced heart failure (NYHA class IV).

-In patients who are non-compliant or fail to attend regularly at visits should be stopped.

Issues with ERT

Do we have Fabry disease in Libya?

Screening program for Fabry in 50 dialysis units that failed to find a single case .

Credit to Dr. Medhat Bialy Dr Moatez AL Ashri (Genzyme)

First diagnosis : Libya

Universitätsklinikum Hamburg-Eppendorf

metabolic laboratory
Hamburg University Medical Center
Department of Pediatrics and Institute of
Clinical Chemistry - Building N23
House N23, Martinistr. 52, 20246 Hamburg
Tel.: +49-40-42803 5026
Fax: +49-40-42803 5984

metabolic laboratory, UKE, Department of Pediatrics and Institute (N23)
Martinistr. 52, 20246 Hamburg, Germany

Genzyme Middle East
P.O. Box 911821

11191 Amman
Jordanien

Patient No 51,

Born:	01.01.1984
Lab.number:	29511849
Sample taken:	22.02.2008,
Received:	04.03.2008, 13:22
Reporting date:	28.04.2008, 17:44
External requestnumber:	

Final report

Submitter code: 7266

Dear colleague,

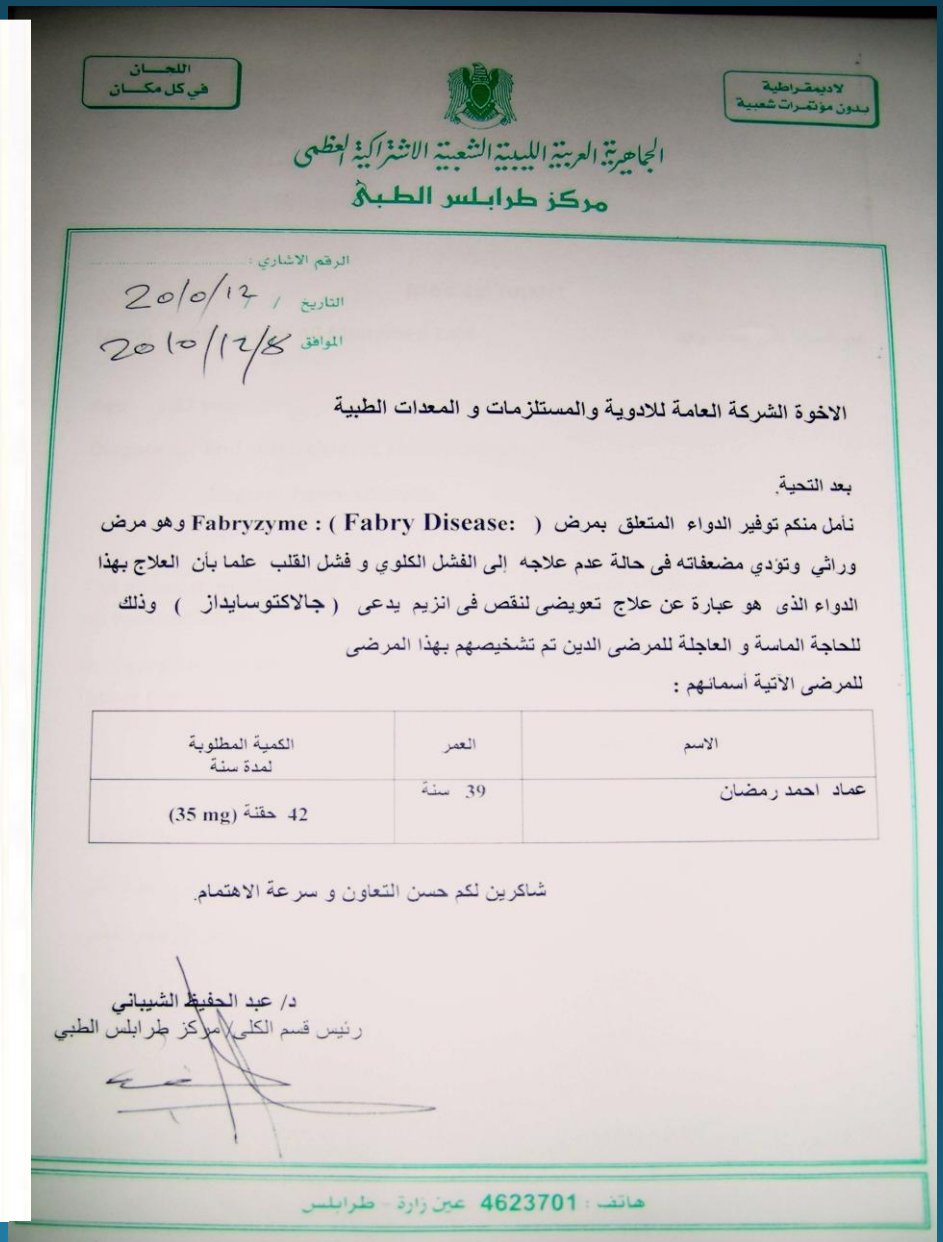
the analysis of the sample which has been sent to our laboratory yielded the following results:

Parameter	Result	Reference range	
Lysosomal Enzymes from Dried Blood			
alpha-galactosidase	0	- 0,15 - 1,0	nmol/spot*45h
alpha-galactosidase with inhibition	0	- 0,10 - 1	nmol/spot*45h
beta-glucuronidase	0.89	- 0,9 - 1,8	nmol/spot*21h
beta-galactosidase	0.60	0,5 - 3,2	nmol/spot*21h

Evaluation
Dear colleague,
the activity of alpha-galactosidase is below its reference range and with specific inhibition the activity is not detectable. This is indicative of classical Fabry disease. We recommend to verify the diagnosis in fibroblasts and to do molecular genetic testing, especially when enzyme replacement therapy is under consideration.
If you have any questions feel free to contact us anytime.

Dr. rer. nat. Z. Lukacs
Laboratory director

Prof. Dr. med. R. Santer
Medical director



Pedigree Libyan family chart

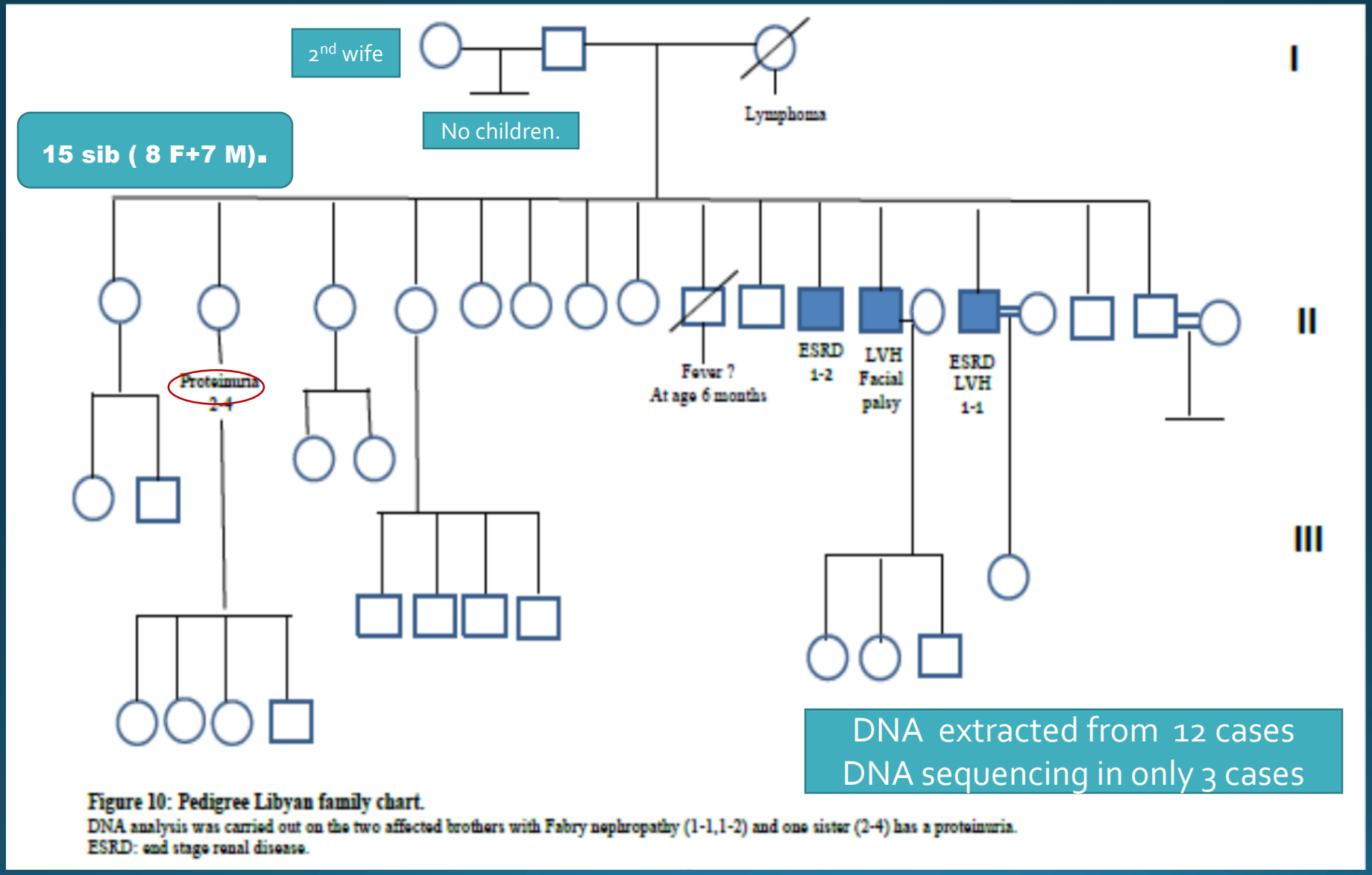


Figure 10: Pedigree Libyan family chart.
DNA analysis was carried out on the two affected brothers with Fabry nephropathy (1-1,1-2) and one sister (2-4) has a proteinuria.
ESRD: end stage renal disease.

Possibility of new mutations in Libyan family with Fabry

Case-series: two brothers with classic Fabry disease predominantly with nephropathy both on hemodialysis, they previously diagnosed in 2001 with Fabry's disease, unfortunately, without receiving enzyme replacement therapy and one sister with proteinuria in a Libyan family were studied clinically and genetically, only patient 1-1 has renal and cardiac involvement.

We aimed to identify a mutation of alpha-galactosidase A gene in this family. Three whole blood samples were obtained to extract purified deoxyribonucleic acid by nucleoSpin kit, consequently weighted in agarose gel, the genomic concentration was measured by nanodrop spectrophotometer.

Mutations were identified in exon 5 (missense mutation) of alpha-galactosidase A .
C **782**G >A present in 3 members (2 classic plus one female carrier)

How we did it ?

1-Blood sampling : 3 members of the family
2-DNA extraction
3-Electrophoresis : confirm the concentration of DNA
4-Spectrophotometer : measurement of DNA concentration
5-Primer designing
6-PCR : Amplificat
7-Electrophoresis :
8-DNA sequencing
9-Using the compu
give the results of

Fabry mutants list

id	locus	mtype	gtype	ptype	structure	str with wild	mut_str_feature	race
611	Exon 7	nonsense mutation	p.E338X	classic				
612	Exon 7	deletion	Del 11b (#1017-1027)	classic				German
613	Exon 7	others	Ins 24b (#1017) + Del 4b					
614	Exon 7	missense mutation	p.W340R	hetero	W340R	W340R	mutation of a buried residue	German
615	Exon 7	nonsense mutation	p.W340X	classic				African-America
616	Exon 7	missense mutation	p.W340S	Classical	W340S	W340S		Japanese
617	Exon 7	missense mutation	p.E341D	classic	E341D	E341D	mutation of a buried residue	
618	Exon 7	missense mutation	p.E341K		E341K	E341K	mutation of a buried residue large structural change	
619	Exon 7	deletion	Del 1b (#1019)	classic				German
620	Exon 7	deletion	Del 1d (#1025)					
621	Exon 7	missense mutation	p.R342Q	classic	R342Q	R342Q	mutation of a buried residue	Dutch
622	Exon 7	nonsense mutation	p.R342X	classic				Greek/English
623	Exon 7	missense mutation	p.R342L	症状なし／分類なし	R342L	R342L		
624	Exon 7	missense mutation	p.R342P	症状なし／分類なし	R342P	R342P		
625	Exon 7	missense mutation	p.P343L		P343L	P343L		
626	Exon 7	missense mutation	p.L344P		L344P	L344P		
627	Exon 7	deletion	Del 2b (#1030-1031)	classic				
628	Exon 7	missense mutation	p.S345P		S345P	S345P		
629	Exon 7	nonsense mutation	p.S345X					
630	Exon 7	deletion	Del 2b (#1033-1034)	classic				
631	Exon 7	deletion	Del 1b (#1036)	classic				Spanish
632	Exon 7	insertion	Ins T (#1038)	classic				Dutch

Conclusions

- Fabry disease is a serious LSD
- Results in premature deaths from kidney ,Heart disease and stoke if not treated early .
- Specific treatment is available with enzyme replacement therapy .
- RAS inhibition essential to limit proteinuria and GFR decline
- We need further studies to confirm our genetic studies and complete the rest of the family to find out the type and site of mutations .

Tripoli Libya