GROUPE HOSPITALIER DIACONESSES CROIX SAINT SIMON

centre de référence maladies rares

Centre de Référence des Maladies Lysosomales

DU Maladies systémiques : Maladies Lysosomales

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Centre de Référence Maladies Lysosomales

UMRS 974, UPMC - INSERM

APMF Association des Patients de la Maladie de Fabry

Inserm

VAINCRE LES MALADIES LYSOSOMALES — RARE MAIS PAS SEUL !

CEMI Collège national des Enseignants de Médecine Interne

12 Avril 2019

Disclosure

- Travel grants and speaker honoraria from:
  - Amicus
  - Genzyme/Sanofi
  - Shire

Objectifs pédagogiques

- Connaître les principales maladies lysosomales
- Connaître leur **mode de transmission**
- Connaître leurs principaux **symptômes d'appel**

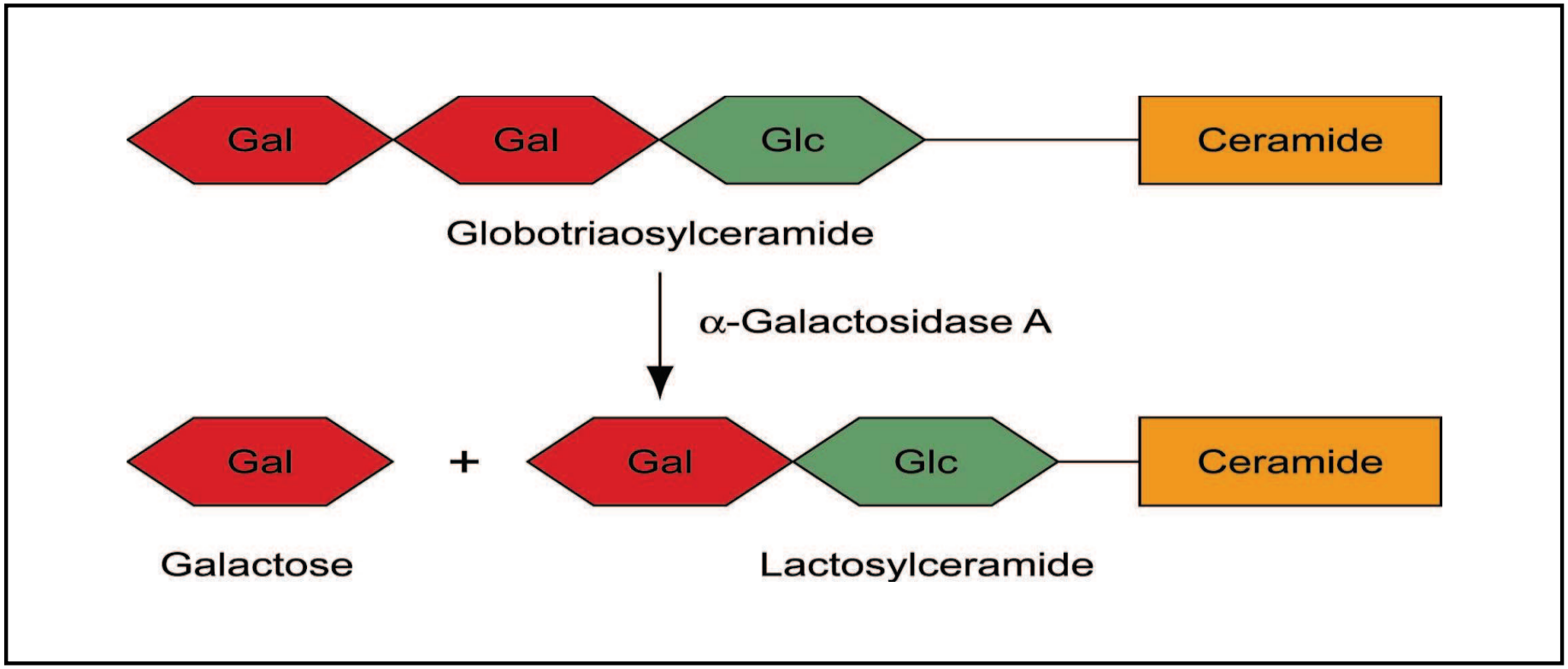
- Connaître la **démarche diagnostique** permettant d'aboutir au diagnostic de ces maladies : dosages biochimiques, analyses génétiques
- Différencier les maladies « macrophagiques » et « endothéliales »
- Reconnaitre les signes d'appel des mucopolysaccharidoses

- Connaître les **traitements** permettant de prendre en charge les patients atteints de maladies de Gaucher et de Fabry

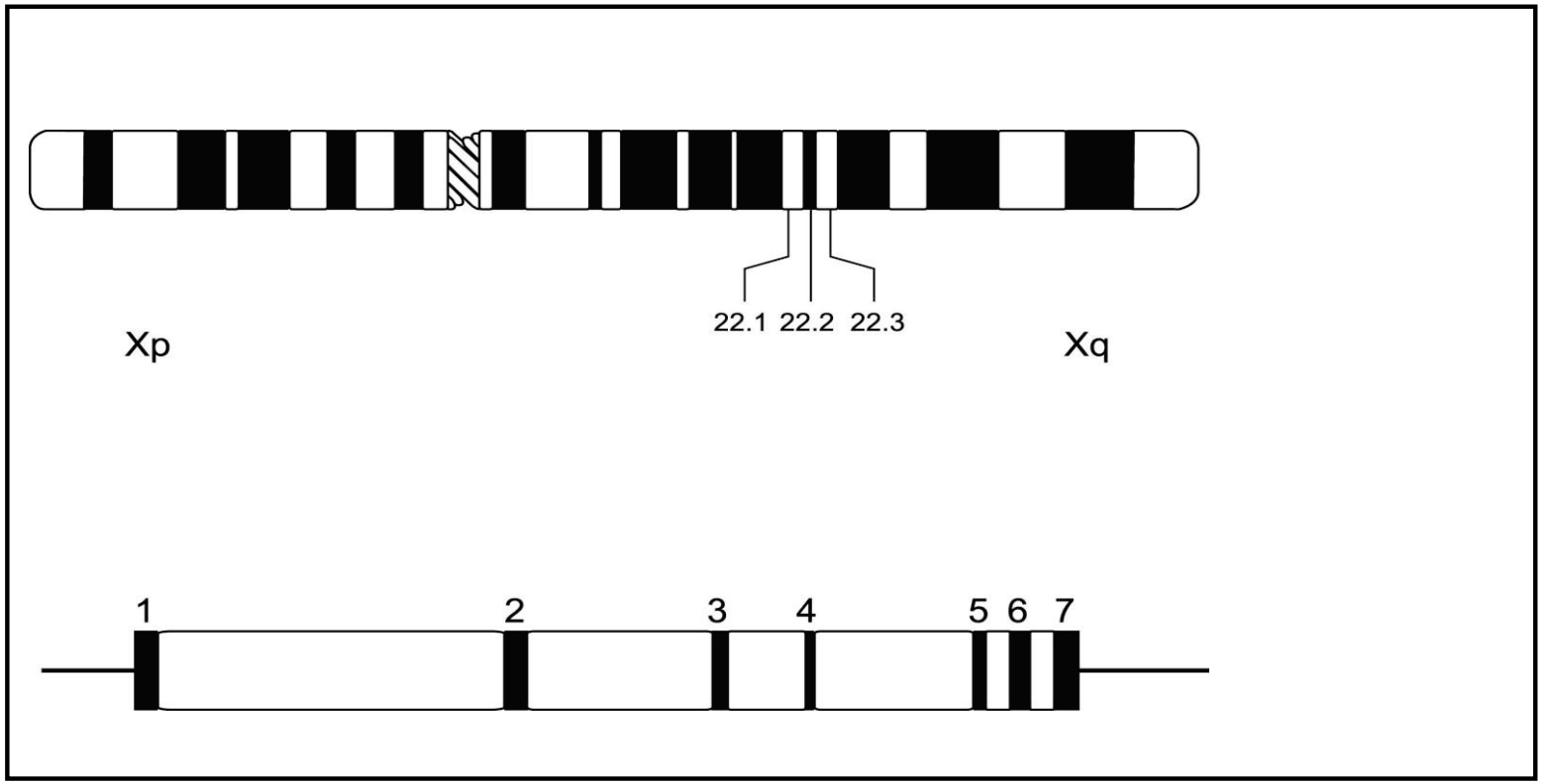
- Maladie génétique : **un patient = une famille**

Fabry

Enzyme = Alpha-galactosidase A

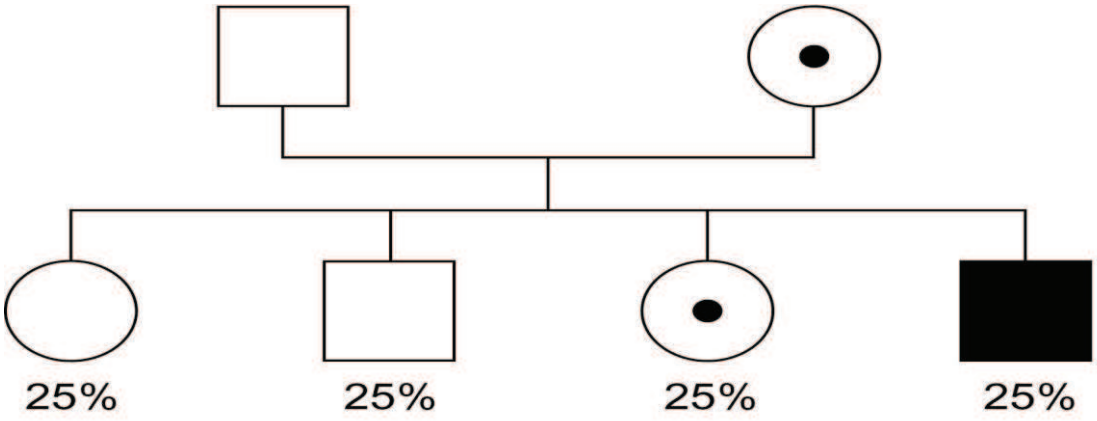


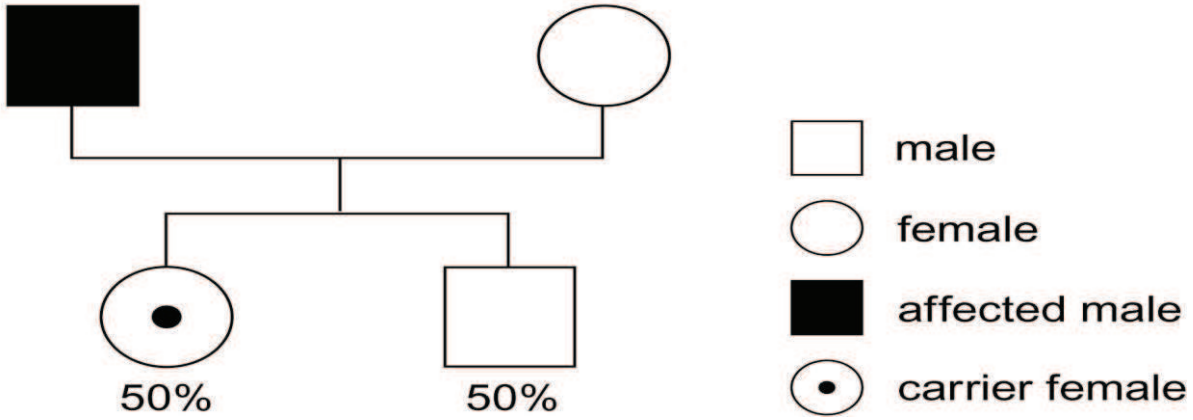
X chromosome



Bishop *et al. Proc Natl Acad Sci USA* 1988; 85: 3903–7.

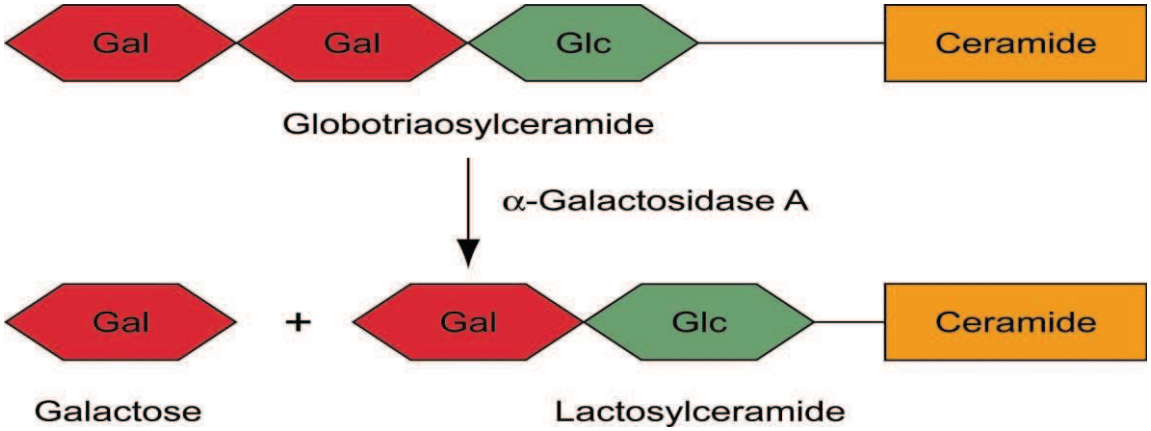
Transmission liée à l'X



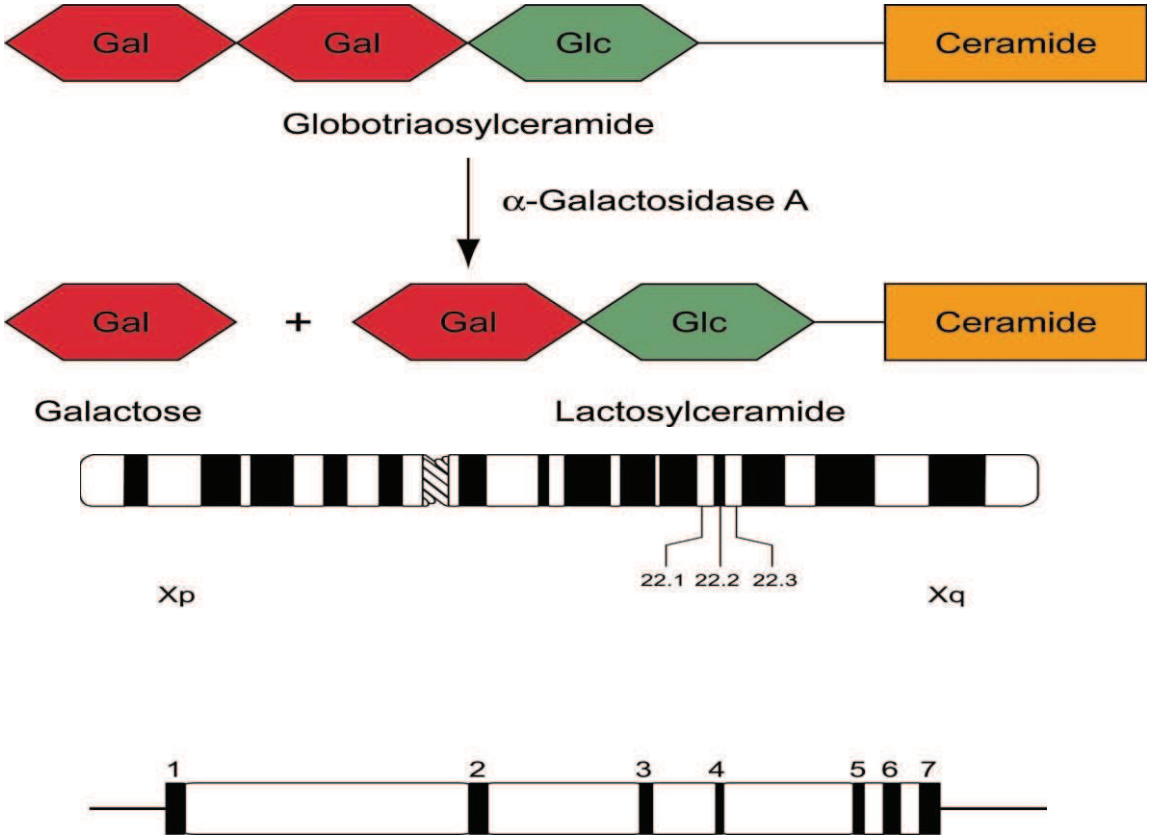


Definition of Fabry disease?

Fabry?


Gal
Gal
Glc
Ceramide
Globotriaosylceramide
α-Galactosidase A
Gal
+
Gal
Glc
Ceramide
Galactose
Lactosylceramide

Fabry?


Gal
Gal
Glc
Ceramide
Globotriaosylceramide
α-Galactosidase A
Gal
+
Gal
Glc
Ceramide
Galactose
Lactosylceramide
22.1 22.2 22.3
Xp
Xq
1
2
3
4
5 6 7

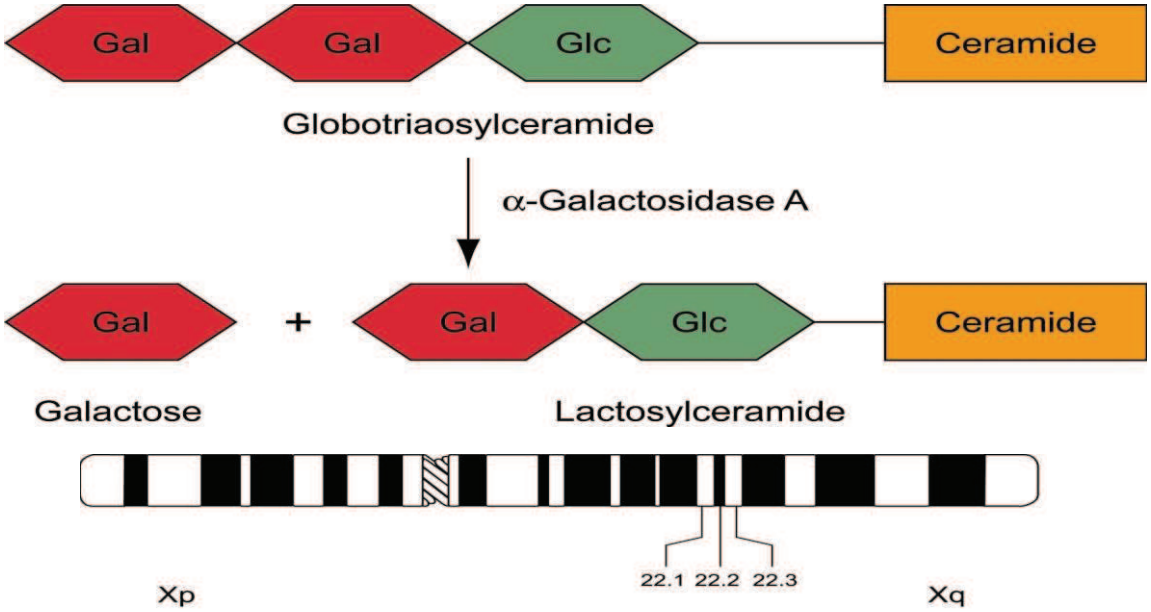
Fabry?

- Nephrology
- Adulthood
- Mutation or sequence variant?

- Kidney biopsy with ultrastructural examination can be useful for diagnosis

Van der Tol L, et al. Mol Genet Metab 2015

Fabry?


Gal
Gal
Glc
Ceramide
Globotriaosylceramide
α-Galactosidase A
Gal
+
Gal
Glc
Ceramide
Galactose
Lactosylceramide
22.1 22.2 22.3
Xp
Xq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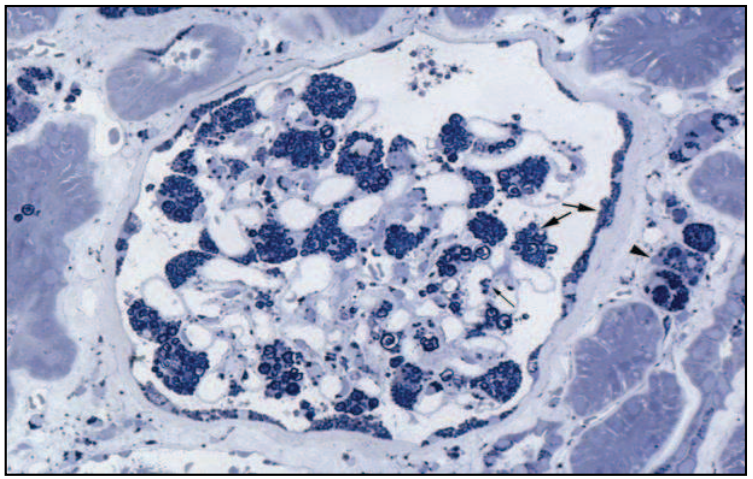
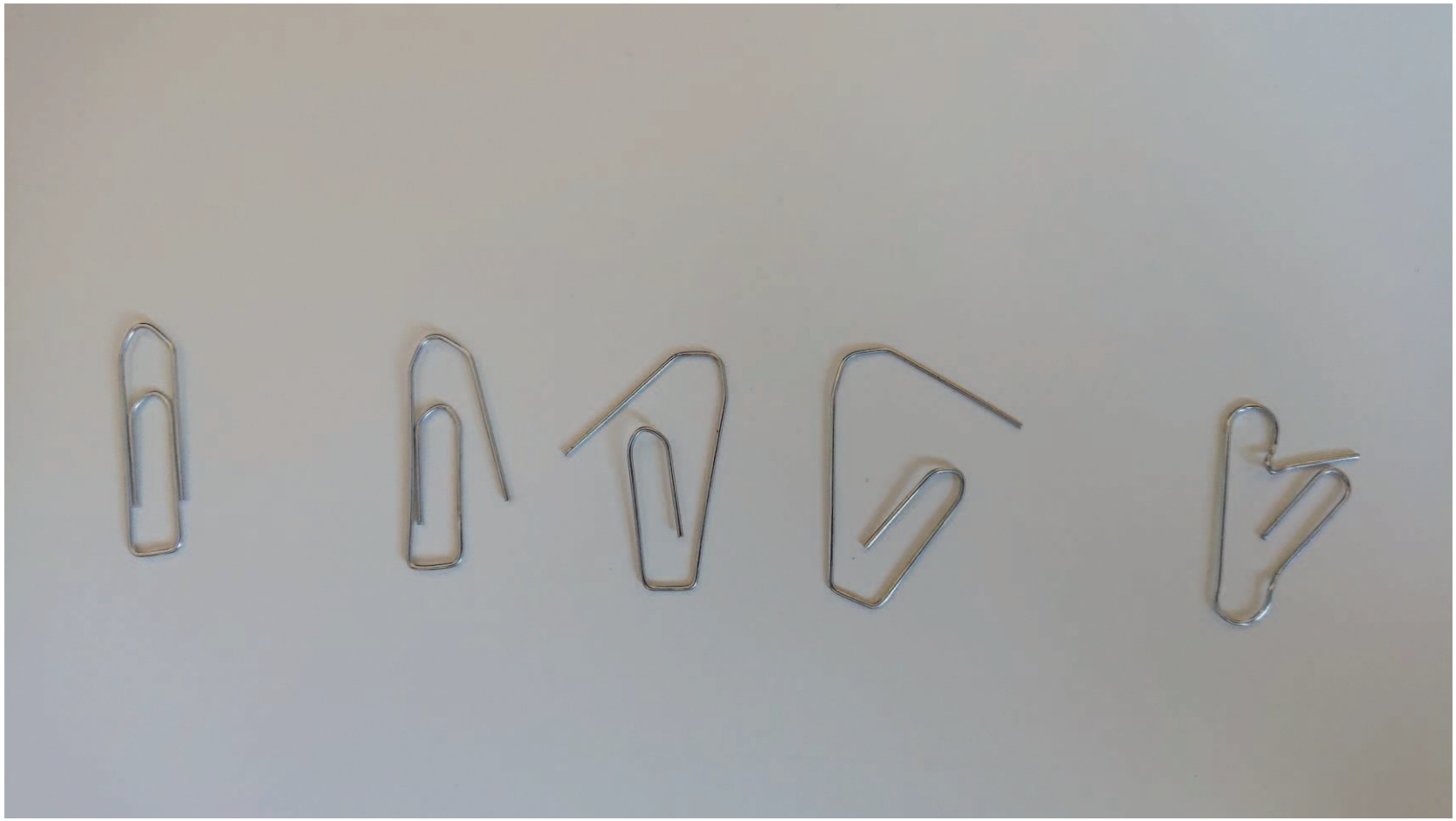
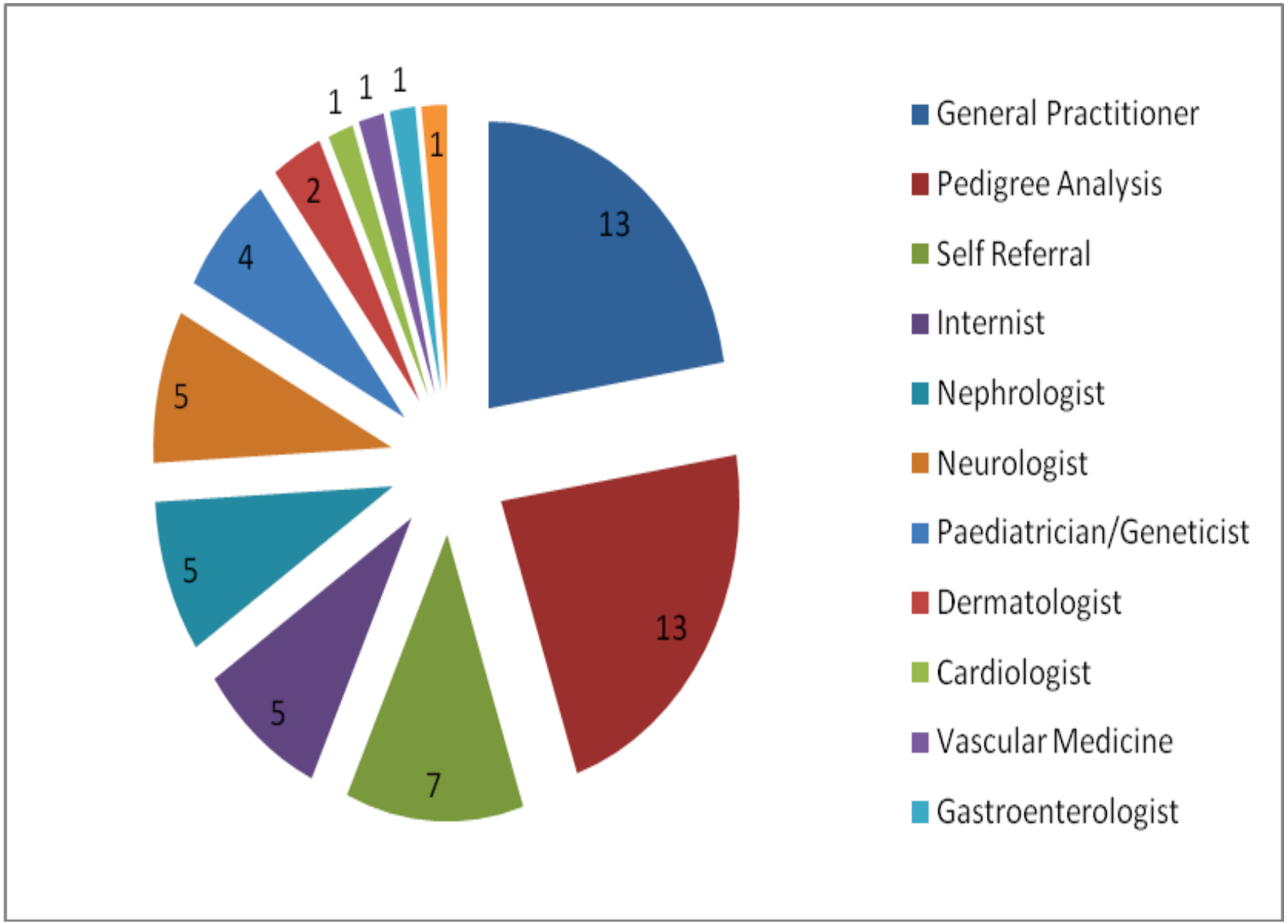


GVUS

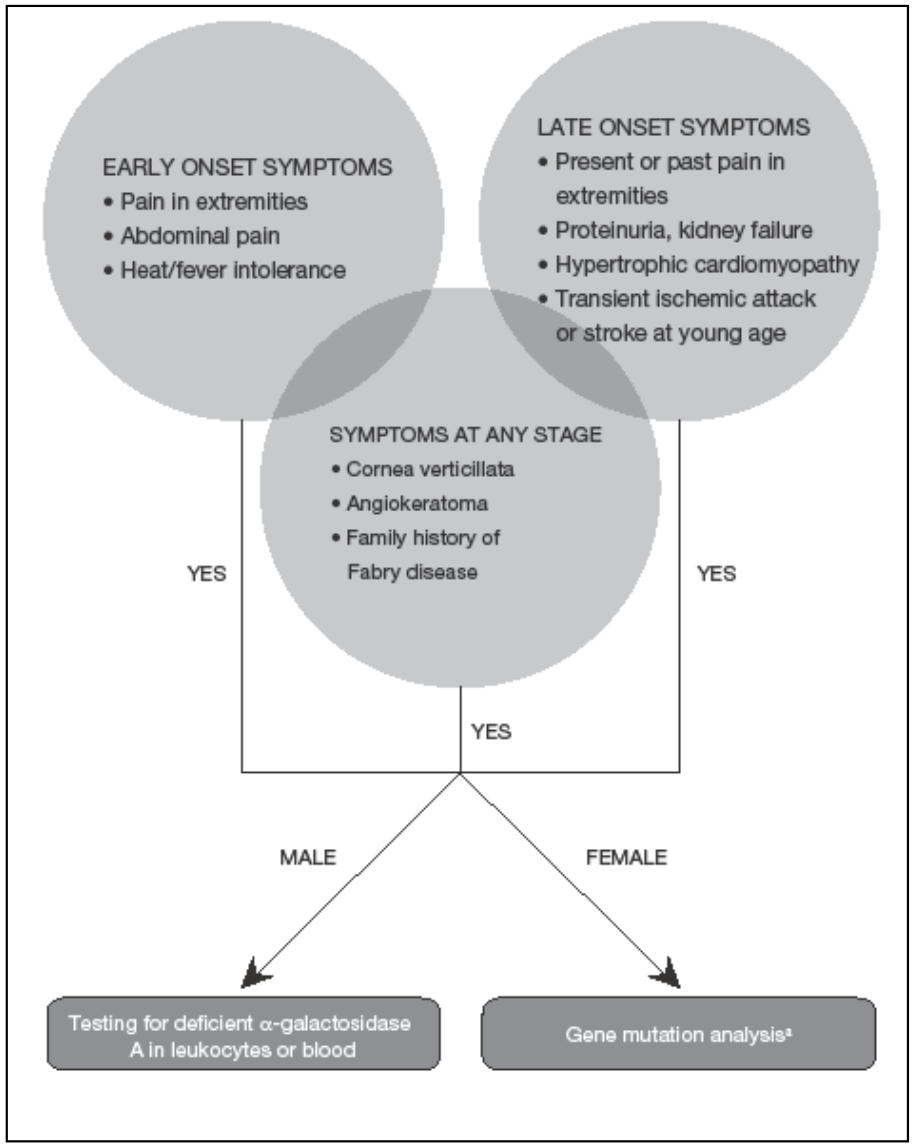


Origine des patients (N=58)



Lidove O, et al. Clin Genet 2012

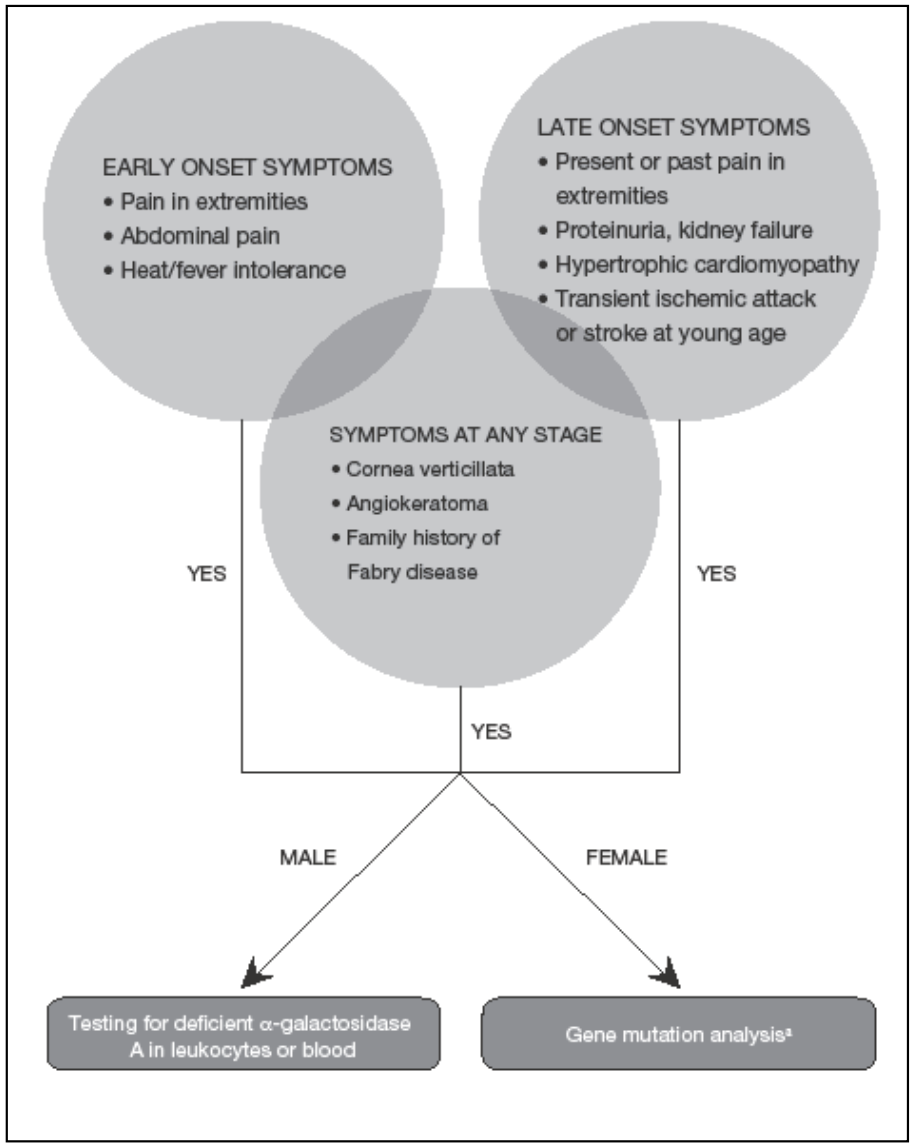
Fabry disease: the « new great imposter »



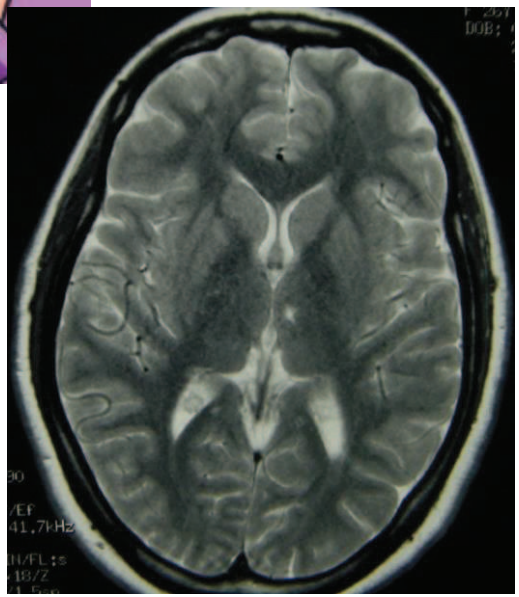
Early Onset

Lidove O, et al. Clin Genet 2012.

Fabry disease: the « new great imposter »

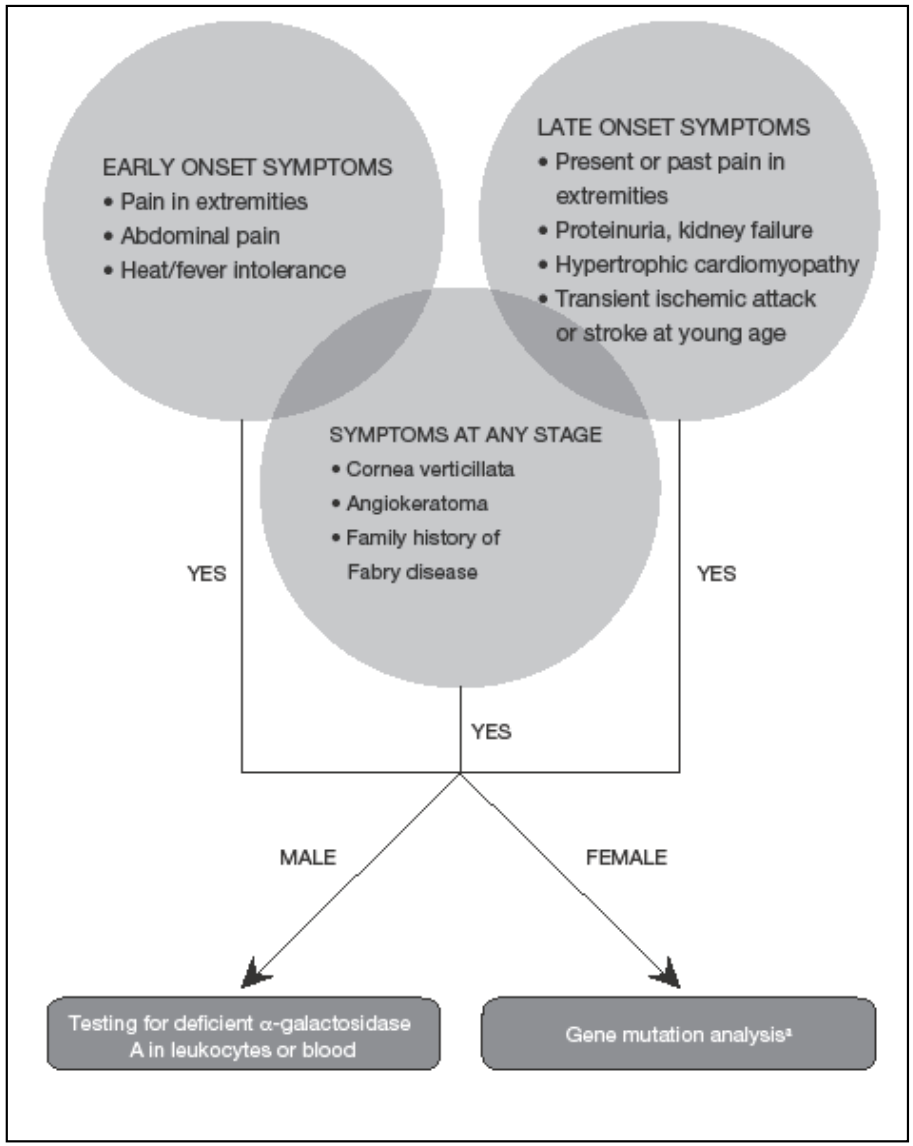


Late Onset

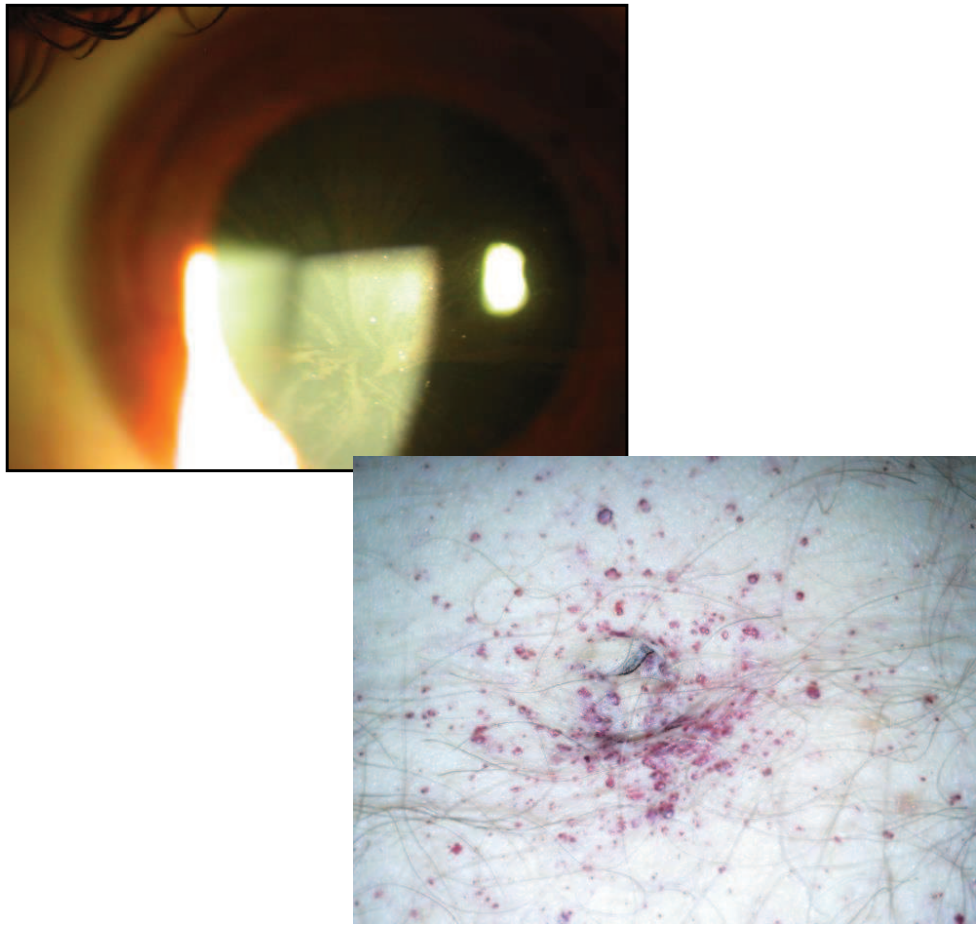


Lidove O, et al. Clin Genet 2012.

Fabry disease: the « new great imposter »

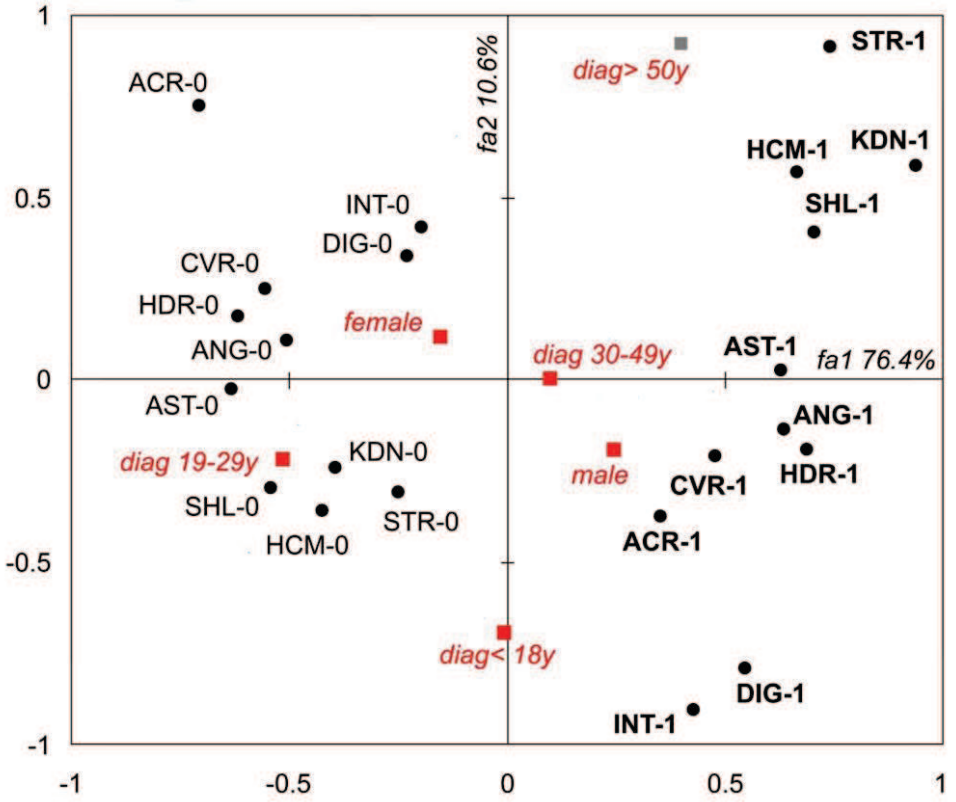


Any Stage



Lidove O, et al. Clin Genet 2012.

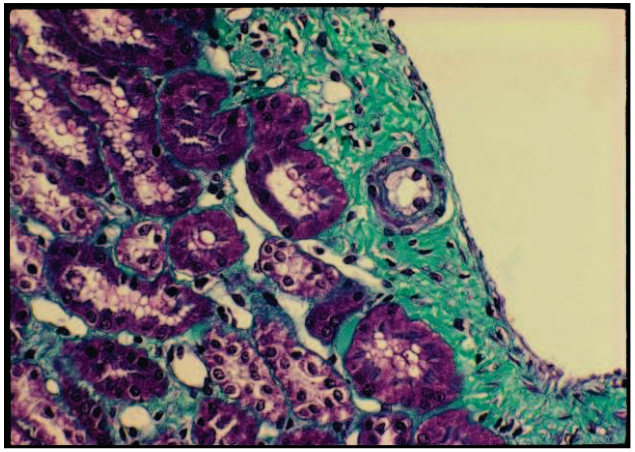
FD: a vascular phenotype

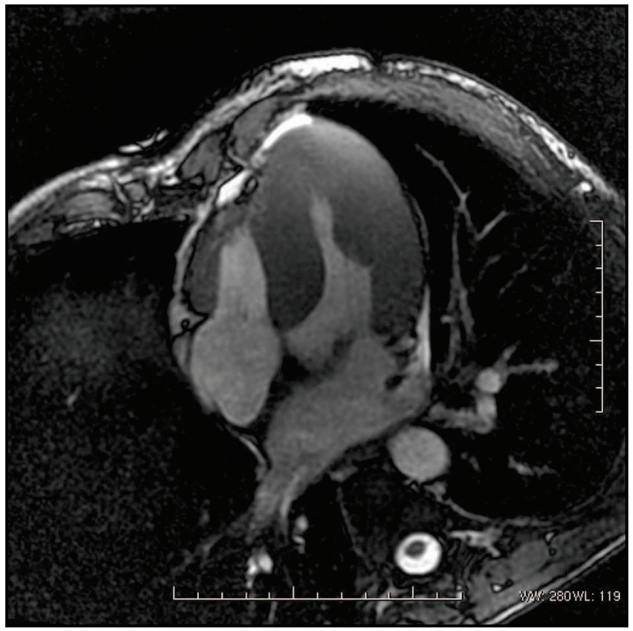


Multiple analysis of correspondence (n = 108)

Kaminsky P, et al. Int J Clin Pract 2013.

Ischemia / Fibrosis





Women are not only carriers

Comparison of frequency of symptoms:

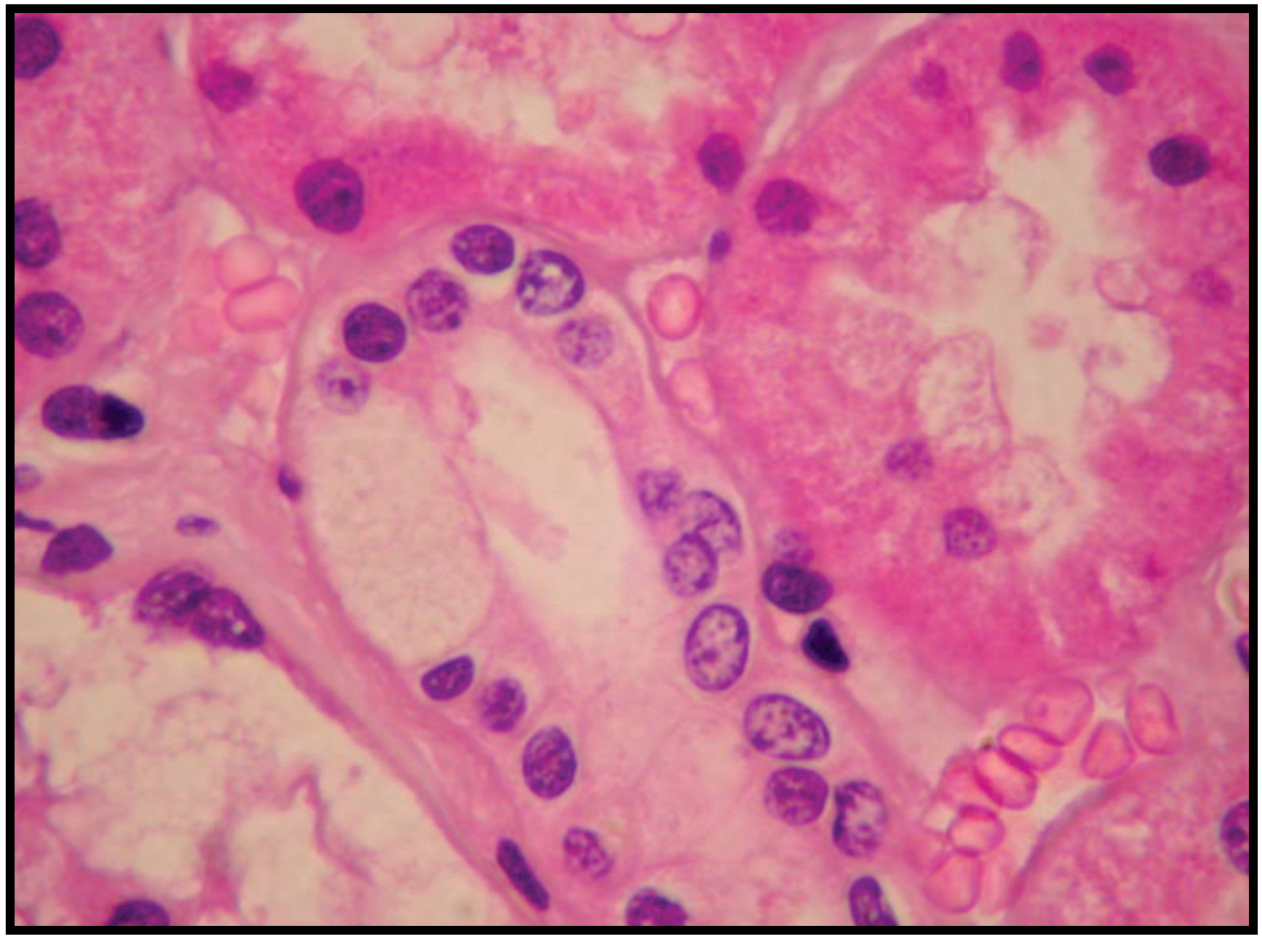
- Male versus female (%)

- Cornea verticillata: 75% each
- Dialysis: 12% of Fabry patients are female patients (USA and EU)

Tsakiris D, Nephrol Dial Transplant 1996

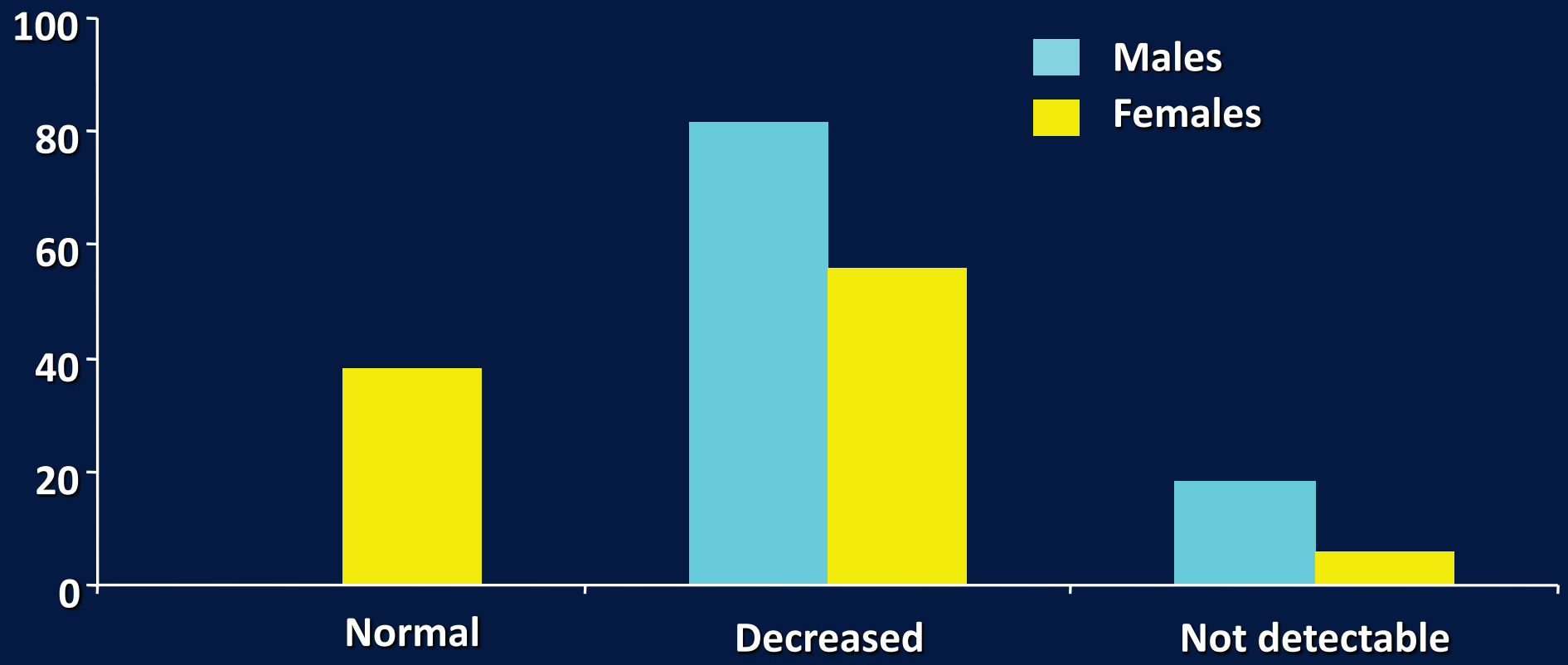
Thadhani R, Kidney Int 2002

Lyonisation



With Courtesy F Barbey, Lausanne.

Patients Fabry : α-galactosidase A



Sémiologie « tardive »

- Atteintes cérébrales
- Néphropathie glomérulaire << ischémique
- Atteintes cardiaques

- Espérance de vie en l'absence de traitement : 58 ans (hommes), 74 ans (femmes)

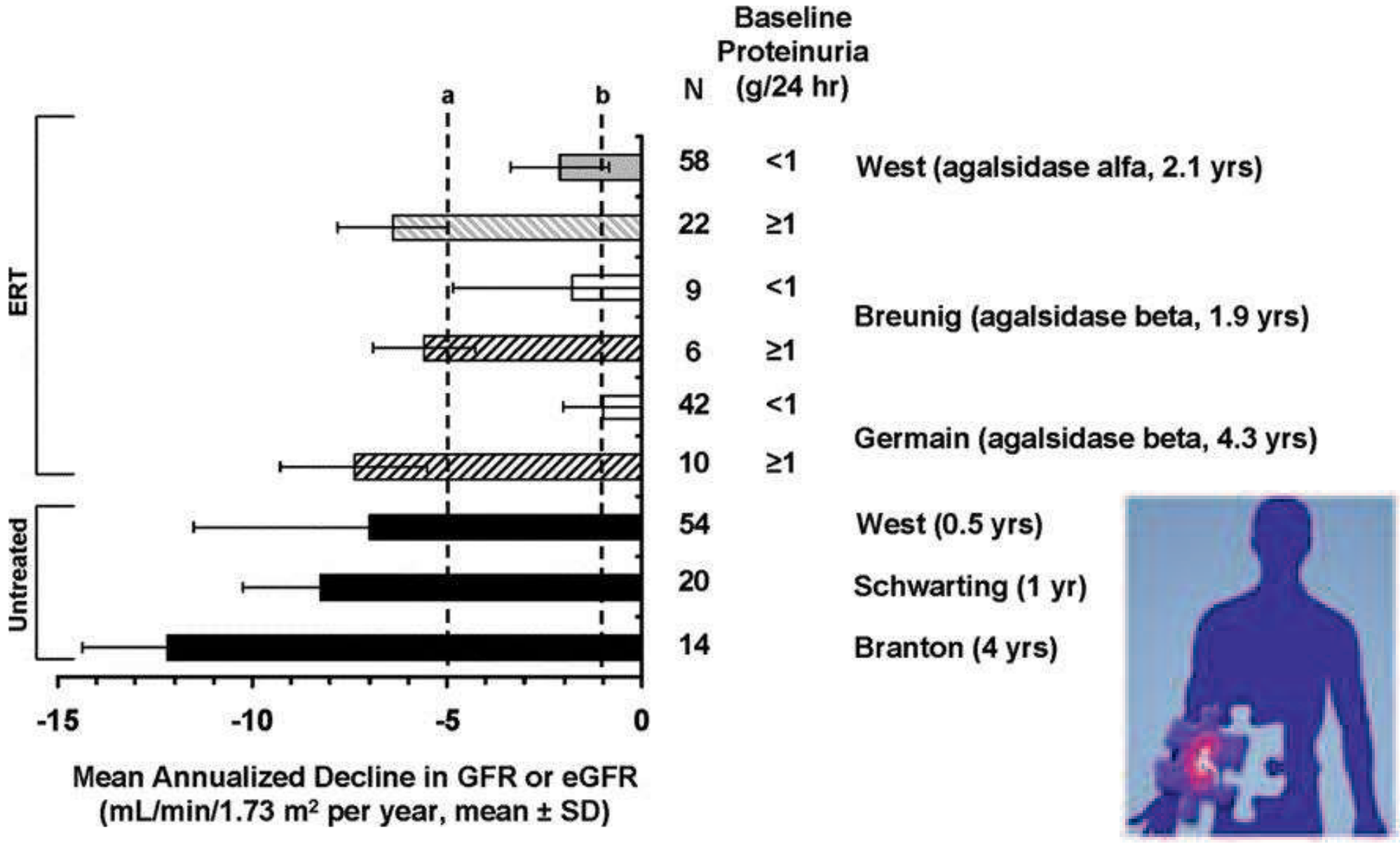
Waldek S, et al. Genet Med 2009.

Traitement (1)

- **Traitements symptomatiques toujours à l'ordre du jour : TABAC STOP**
  - **Acroparesthésies**
  - **Angiokératomes**
  - **IEC, aspirine, AVK (rarement), statines**
  - **Dialyse, transplantation rénale**
  - **Soutien psychologique**
- **Assistante sociale, 100% …**

Traitements (2)

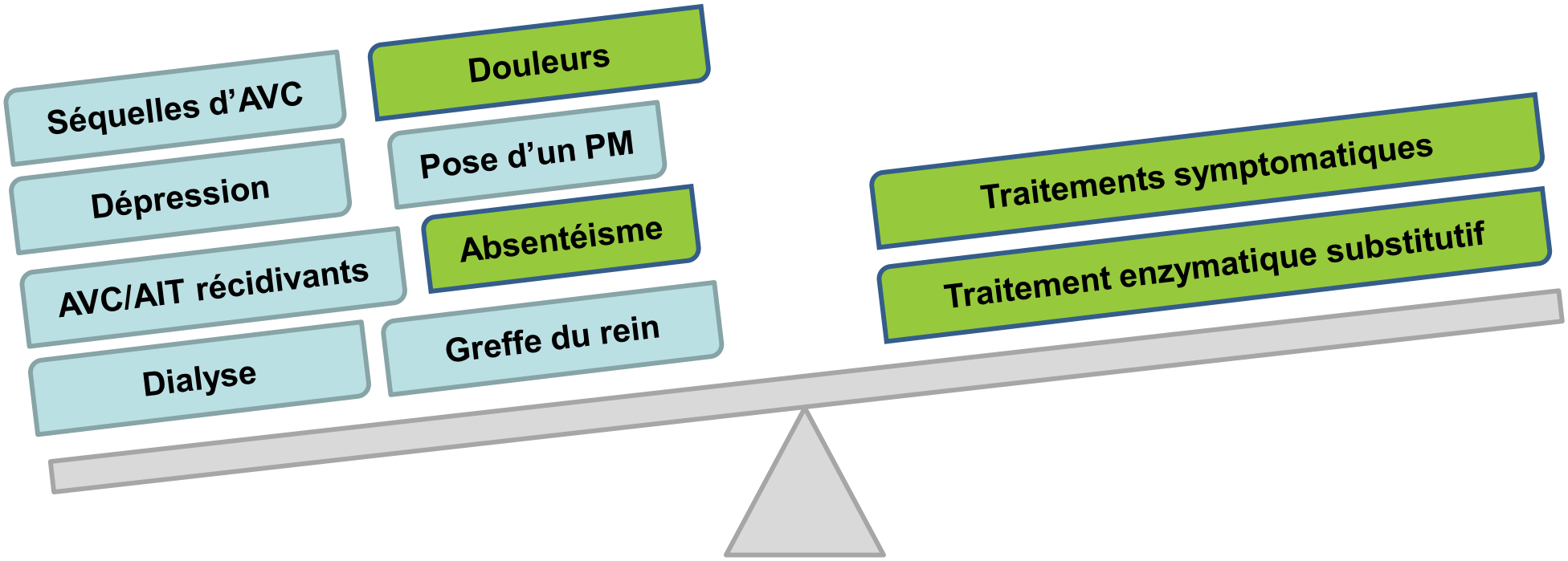
- **Efficacité thérapeutique des enzymes (TES) très dépendante de l'âge auquel on commence :**
- **Agalsidase bêta et agalsidase alpha**
  - **Rein : point de non-retour**
  - **Cœur : fibrose irréversible**
  - **SNC : les TES ne passent pas la barrière hémato-encéphalique**



(Adapted from Journal of the American Society of Nephrology, Volume 20, West M et al., pages 1132-1139, 2009, with permission from the American Society of Nephrology).

Lidove et al. Genet Med 2010.

Tøndel C, et al.
J Am Soc Nephrol 2013



Age précoce au diagnostic +++

Chaperone molecule

Fabry disease: a disorder of protein conformation

GLA: Approximately 60% missense mutations

↓

Impaired trafficking of α-galactosidase A

↓

Premature clearance of the unstable enzyme

--

Unstable
Catalytically competent

↓

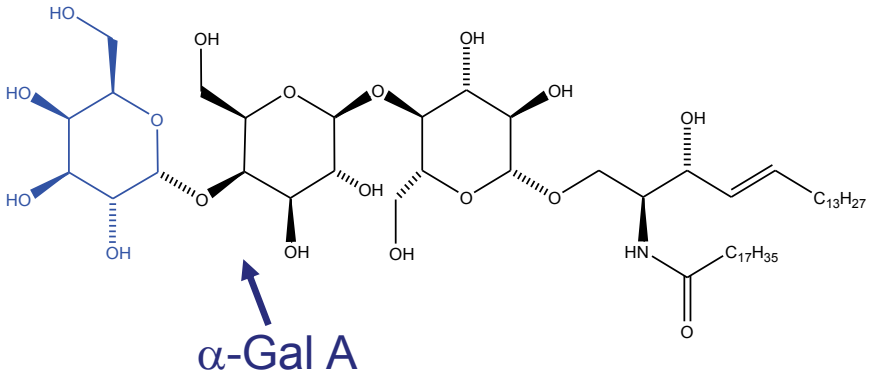
Pharmacological chaperones may play a role

↓

Restored α-Gal trafficking to the lysosomes

1-deoxygalactonojirimycin (DGJ) = migalastat : a pharmacological chaperone for certain mutant forms of a-Gal A associated with Fabry disease

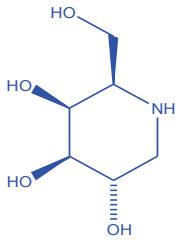
Natural Substrate



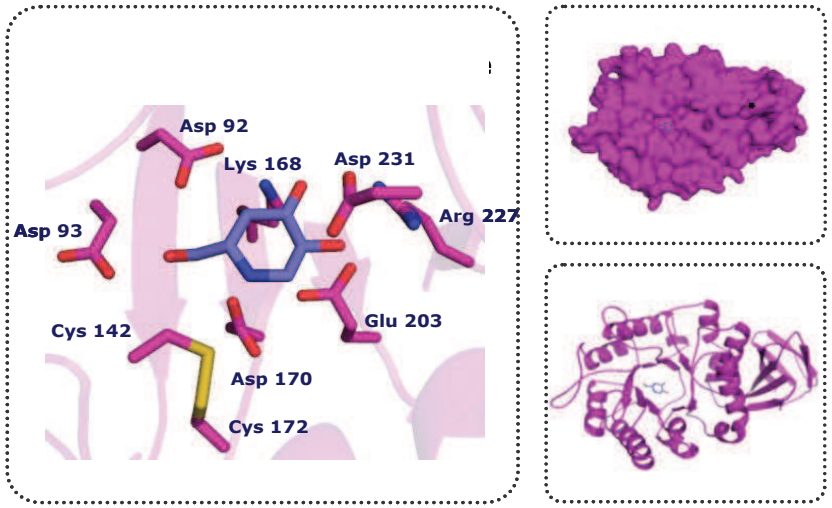
α-Gal A

Globotriaosylceramide (Gb3)
Lyso-Gb3

Pharmacological Chaperone

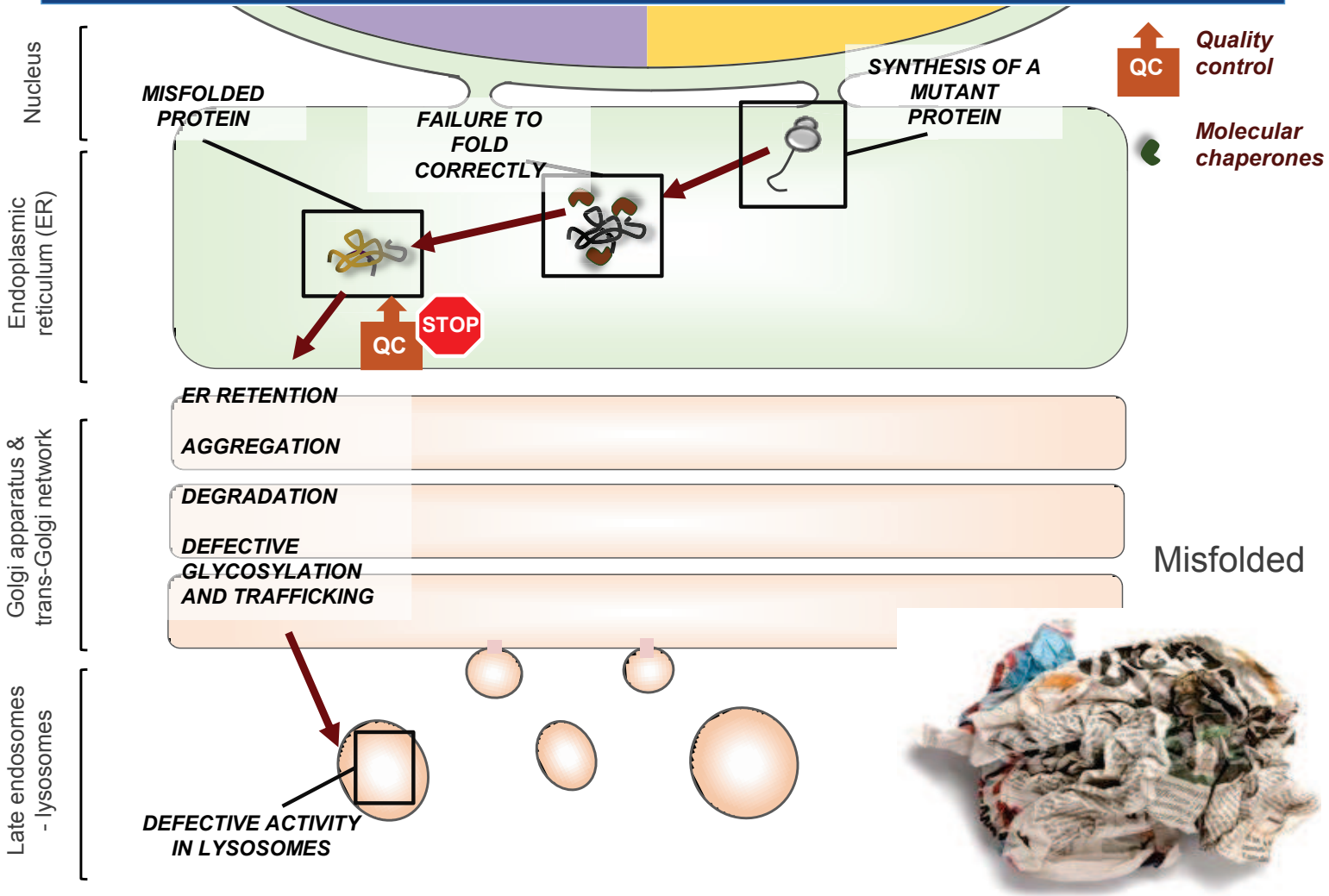


1-deoxygalactonojirimycin (DGJ) = Migalastat HCl
(referred to as 'AT1001' in preclinical studies)



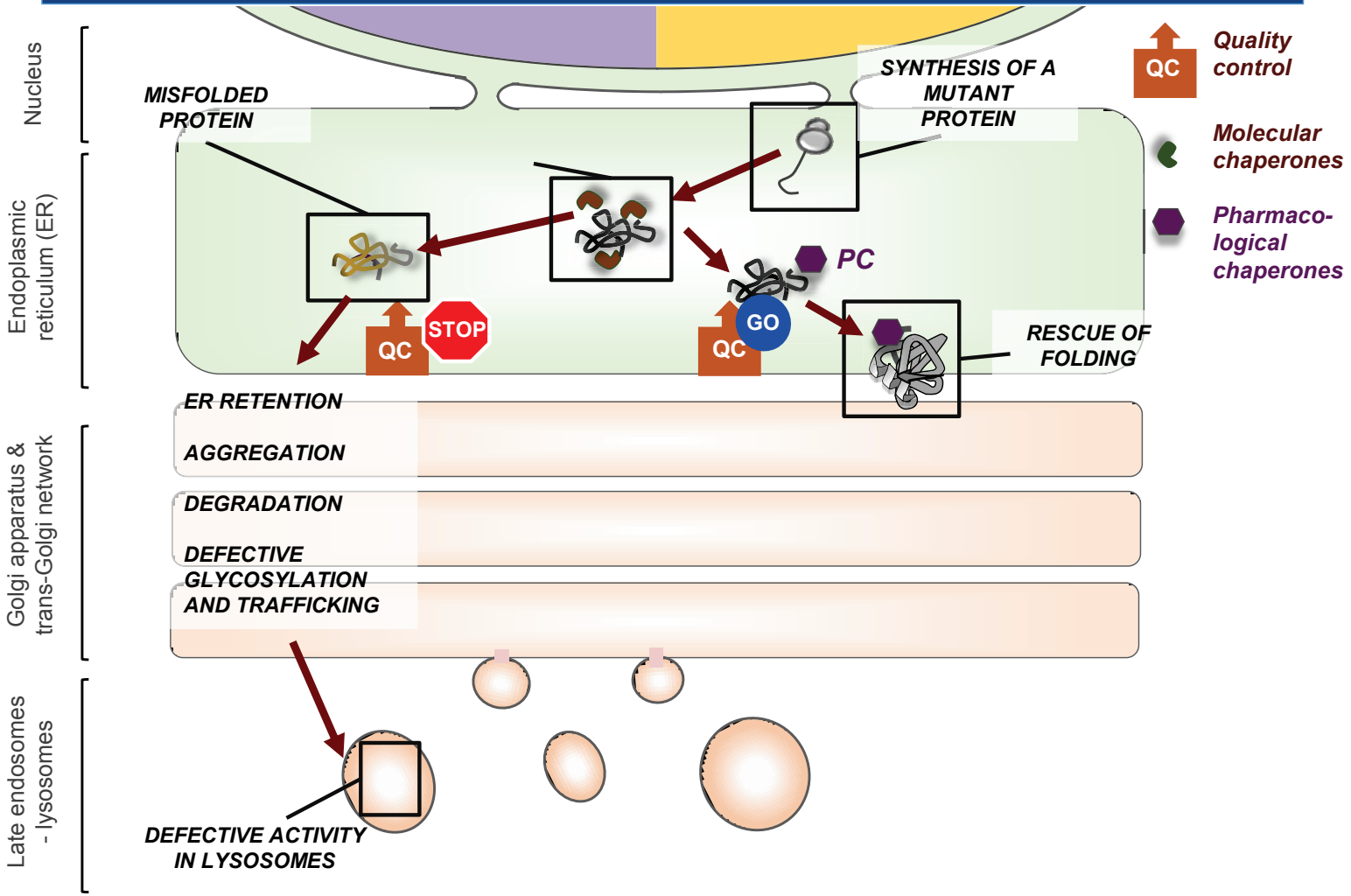
Migalastat **reversibly binds** certain mutant forms of a-Gal A associated with **at the active site** of α-galactosidase

Mechanism of action of chaperones



Adapted from: Parenti G, Andria G, Valenzano K, *Mol Ther*; 23:1138-48, 2015

Mechanism of action of chaperones



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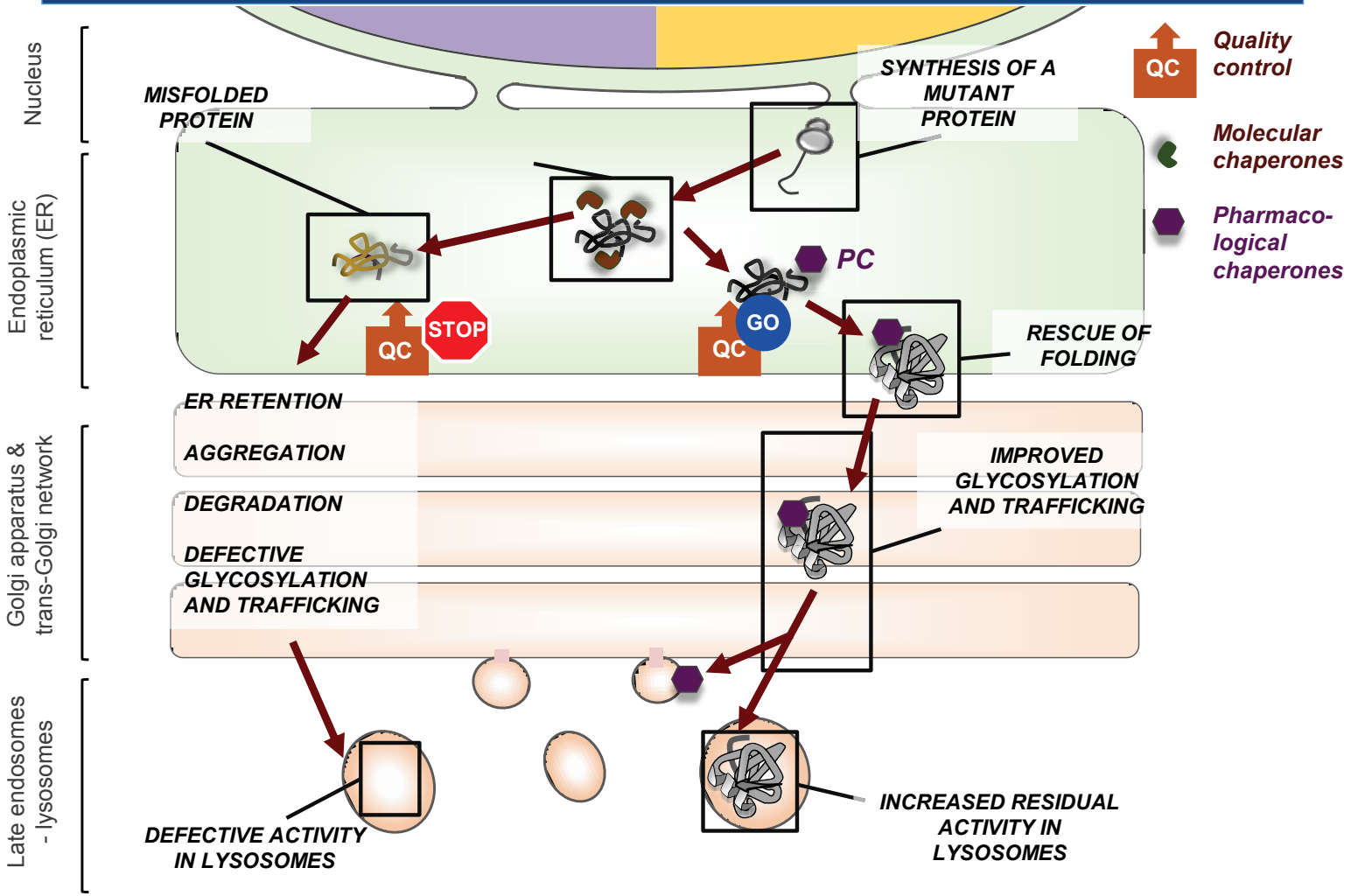
Mechanism of action of chaperones



Adapted from: Parenti G, Andria G, Valenzano K, *Mol Ther*; 23:1138-48, 2015

Results

- **Methodology of the 2 phase 3 studies**
- Kidney
- Heart
- Surrogate markers
- Safety

Results

- Methodology of the 2 phase 3 studies
- **Kidney**
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Results

- Methodology of the 2 phase 3 studies
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- Methodology of the 2 phase 3 studies
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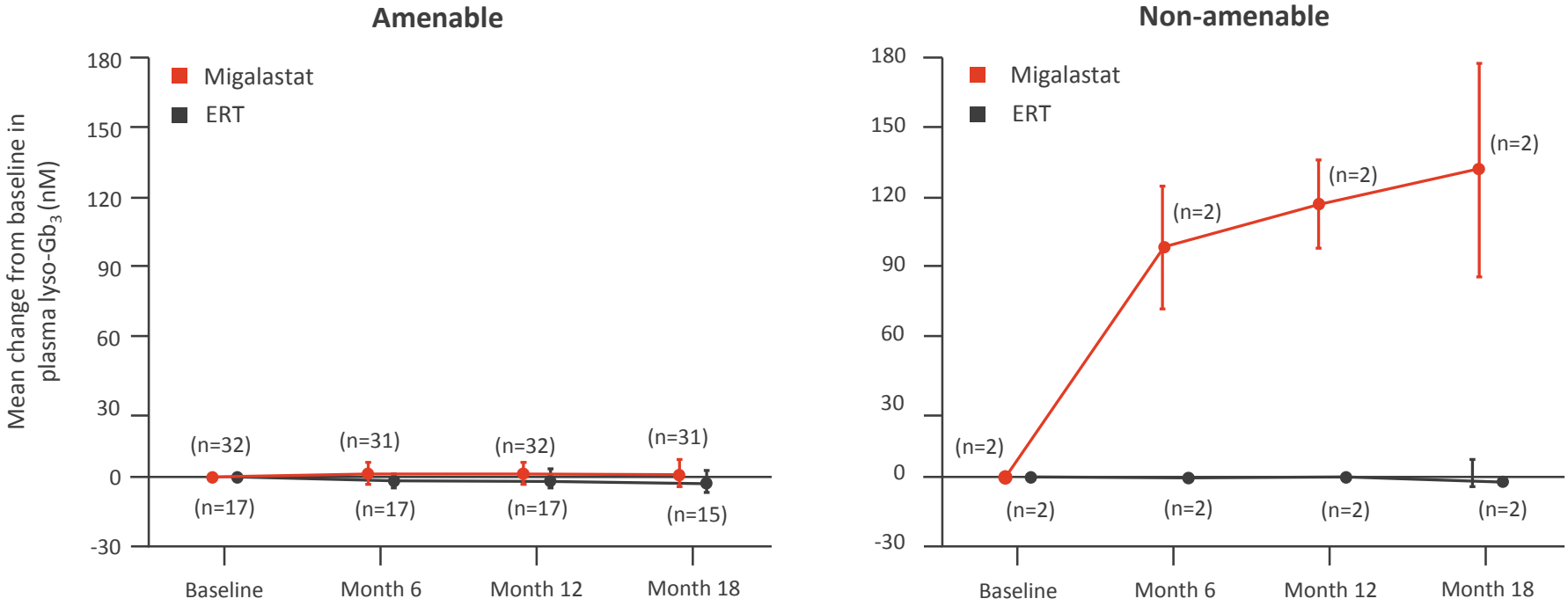
Results

- Methodology of the 2 phase 3 studies
- Kidney
- Heart
- Surrogate markers
- **Safety**

ATTRACT: Plasma lyso-Gb_3 levels

Secondary endpoint

- Plasma lyso-Gb_3 levels slightly increased but remained low in patients with amenable mutations treated with migalastat for 30 months; levels also remained low in patients on ERT for up to 18 months*
- In patients with non-amenable mutations, plasma lyso-Gb_3 increased following treatment switch compared with patients who remained on ERT



*mITT population
ERT, enzyme-replacement therapy; lyso-Gb_3, globotriaosylsphingosine; mITT, modified intention-to-treat

Nicholls K, et al. Poster presented at: Kidney week November 2014,Philadelphia,PA; GALAFOLD (migalastat hydrochloride) [Summary of product characteristics].2017

Ministère de la Santé
et des Solidarités

Carte de soins et d'urgence

Emergency Healthcare Card

Maladie de Fabry

Fabry disease

La maladie de Fabry est une maladie génétique héréditaire de surcharge (groupe des maladies lysosomales) caractérisée par une atteinte pluri-viscérale, principalement cérébrale, cardiaque et rénale.

[illegible]

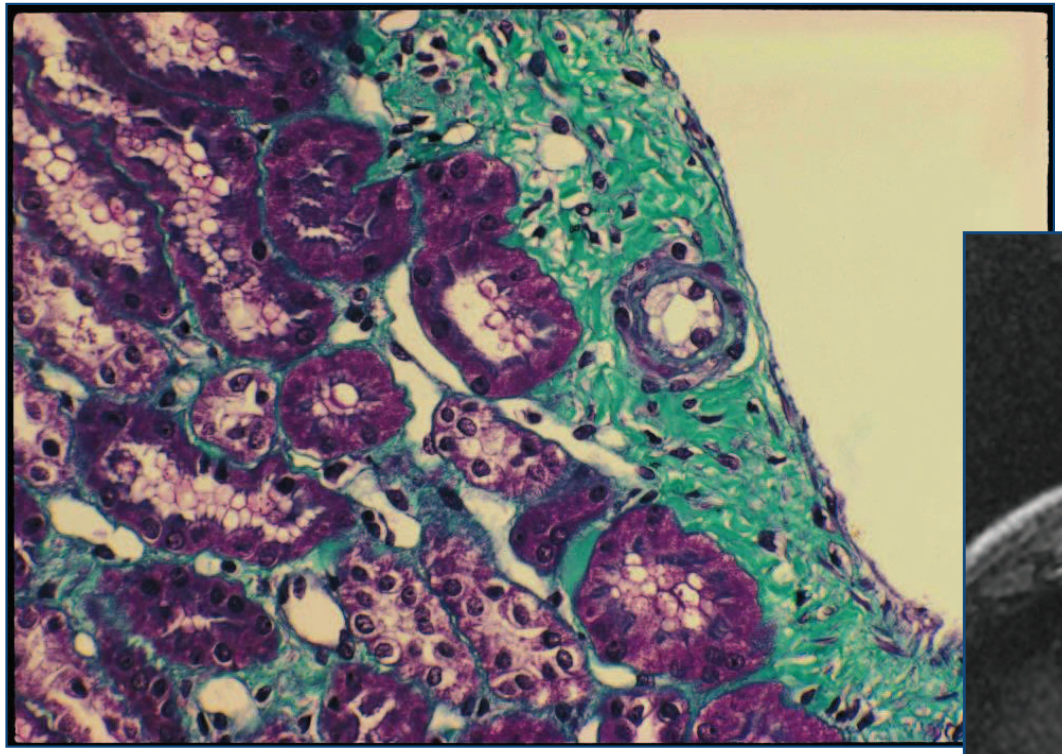
Cette carte est remplie et mise à jour par le médecin, en présence et avec l'accord du malade qui en est le propriétaire.

Ce document est confidentiel et soumis au secret médical.

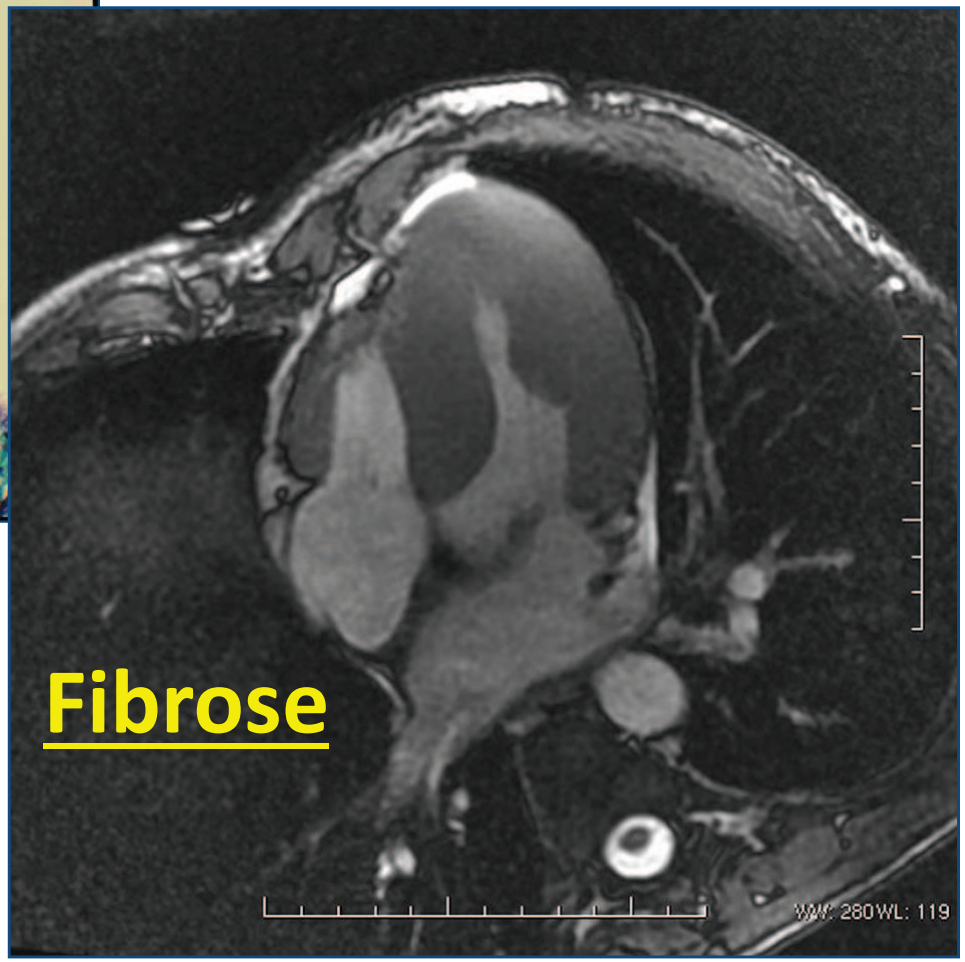
Nul ne peut en exiger la communication sans autorisation du titulaire ou de son représentant légal.

Maladie de Fabry : brûlures des extrémités, présentes ou passées, à examen clinique et EMG normal

Représentations Fabry

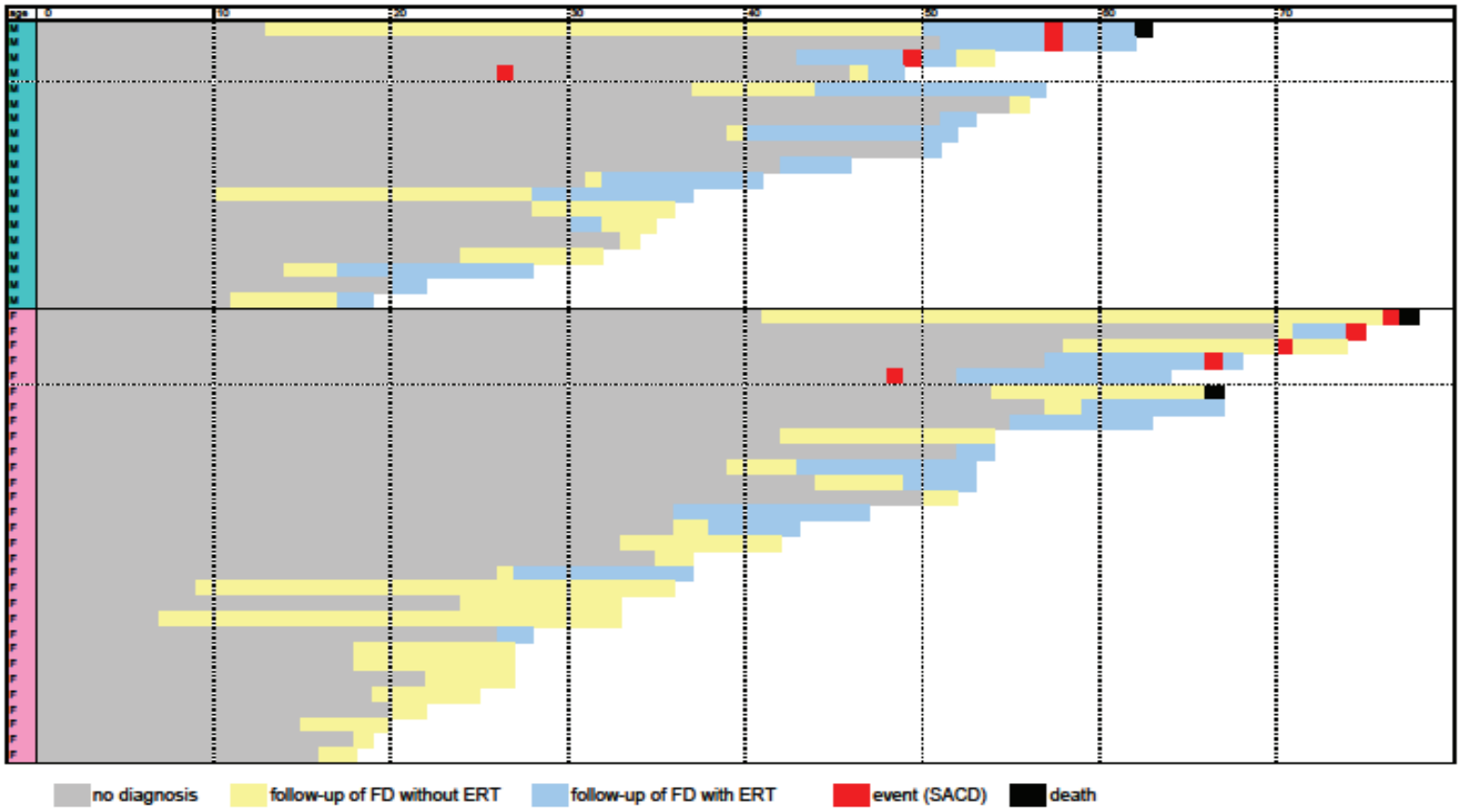


Ischémie



Fibrose

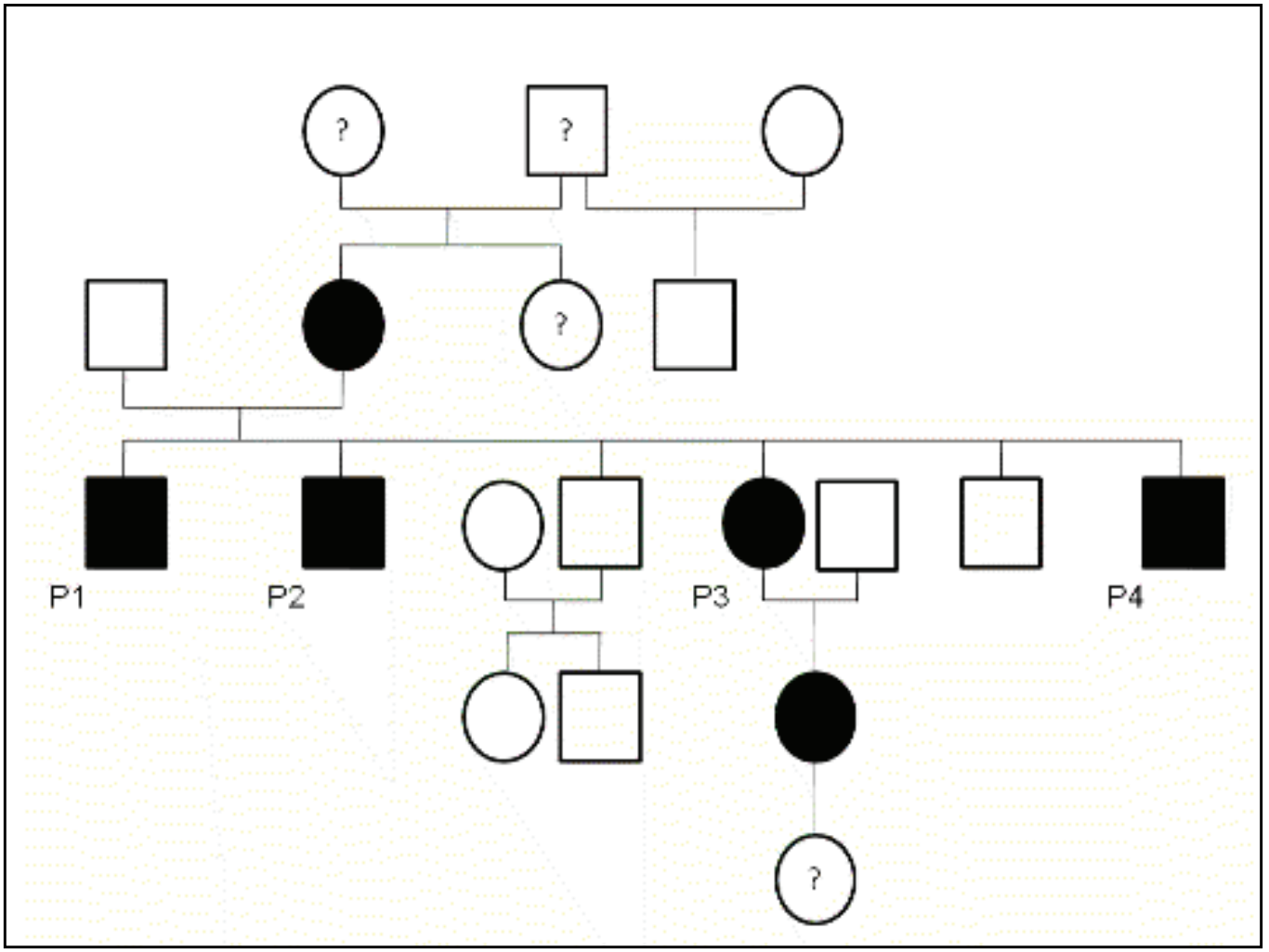
Cardiac device implantation in Fabry disease



SACD: severe arrhythmia or conduction defect

Sené T, Lidove O *et al. Medicine* 2016;95:e4996.

Un patient = Une famille



J. Fabry

W. Anderson

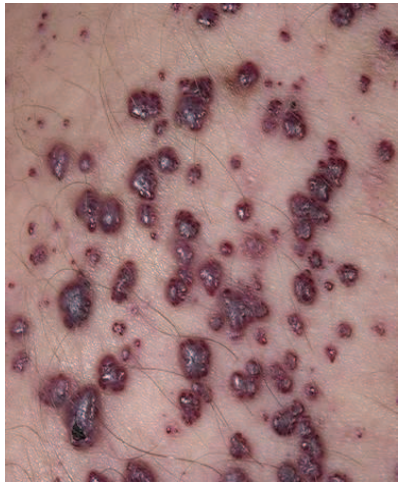
C. De Duve

K. Hashimoto

R. Brady

1898 **1950** **1965** **1967** **2000** **2015-16** **……**

Angiokeratoma corporis diffusum



Lysosome

Nobel 1974

Fabry = Lysosomal disease

Defect in α- Galacto Sidase

Are female affected?

Enzyme Replacement Therapy

Fabrazyme®, Replagal®

Female are affected!

Chaperone Therapy

Galafold®

Substrate reduction therapy?

-

Gene Therapy?

-

Combination therapies?

With Courtesy W Mauhin

Conclusions

- **Maladie de Fabry = maladie systémique**
  - **Transmission liée à l'X**
  - **Phénotype très variable**
  - **Les femmes sont parfois sévèrement atteintes**
  - **Diagnostic fait trop tardivement (> 30 ans)**
  - **Cas index : nécessite une enquête généalogique**

« Surcharge lysosomale »

- Fabry
- **Gaucher**
- **Niemann-Pick B**

Remerciements

- **Patients et familles**
- **Associations de patients :**
  - **APMF**
  - **VML**
- **CRML**
- **Co-auteurs des travaux**
  - Groupe collaboratif français
- **Collaborateurs**
  - **Cliniciens**
  - **Biochimistes**
  - **Généticiens**

APMF
Association des Patients de la Maladie de Fabry

VAINCRE LES MALADIES LYSOSOMALES
VML
RARE MAIS PAS SEUL !

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CRML
Centre de Référence des Maladies Lysosomales