Hospital Central de la Cruz Roja San José y Santa Adela

SaludMadrid

Comunidad de Madrid

Grupo de Enfermedades Minoritarias

SEMI

SOCIEDAD ESPAÑOLA DE MEDICINA INTERNA

LA VISIÓN GLOBAL DE LA PERSONA ENFERMA

Consideraciones genéticas en la enfermedad de Fabry

Dra. Mónica López Rodríguez

Servicio Medicina Interna

DEFINICIÓN GENÉTICA

"La **Genética** es el estudio de la herencia, el proceso en el cual un padre le transmite ciertos genes a sus hijos."

MedlinePlus
Trusted Health Information for You

"La **Genética** es el campo de la biología que busca comprender la herencia biológica que se transmite de generación en generación.
El principal objeto de estudio la Genética son los **genes**, formados por segmentos de ADN (doble cadena) y ARN (cadena simple)."

WIKIPEDIA
The Free Encyclopedia

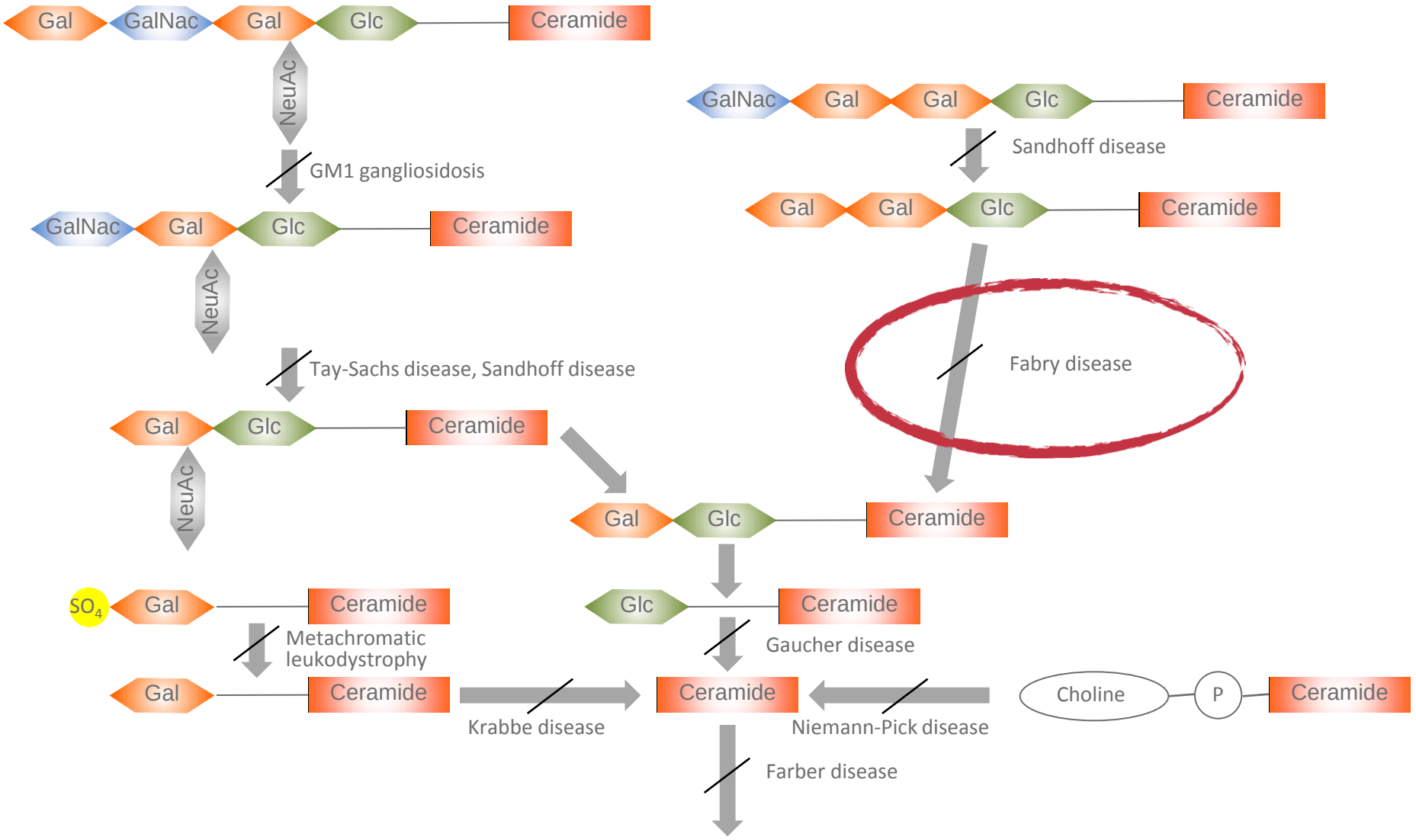
DEFINICIÓN

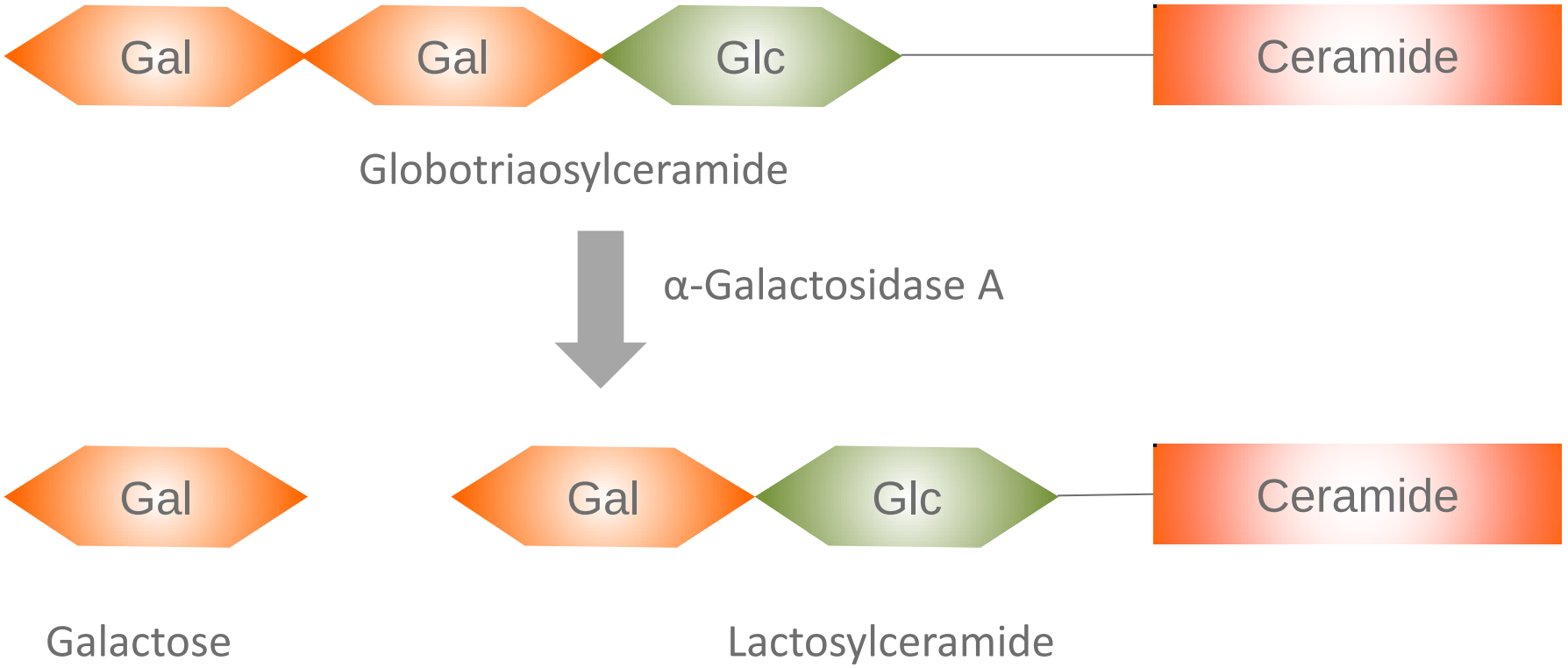
"La enfermedad de Fabry, también conocida como deficiencia de la alfa-galactosidasa-A, causa una acumulación de material graso en el sistema nervioso autónomo, los ojos, los riñones, y el sistema cardiovascular. La enfermedad de Fabry es la única enfermedad por almacenamiento de lípidos **ligado a X**."

MedlinePlus
Trusted Health Information for You

"La enfermedad de Fabry es una enfermedad de almacenamiento lisosómico **hereditaria ligada al cromosoma X** derivada de **mutaciones en el gen que codifica la enzima α-galactosidasa**."

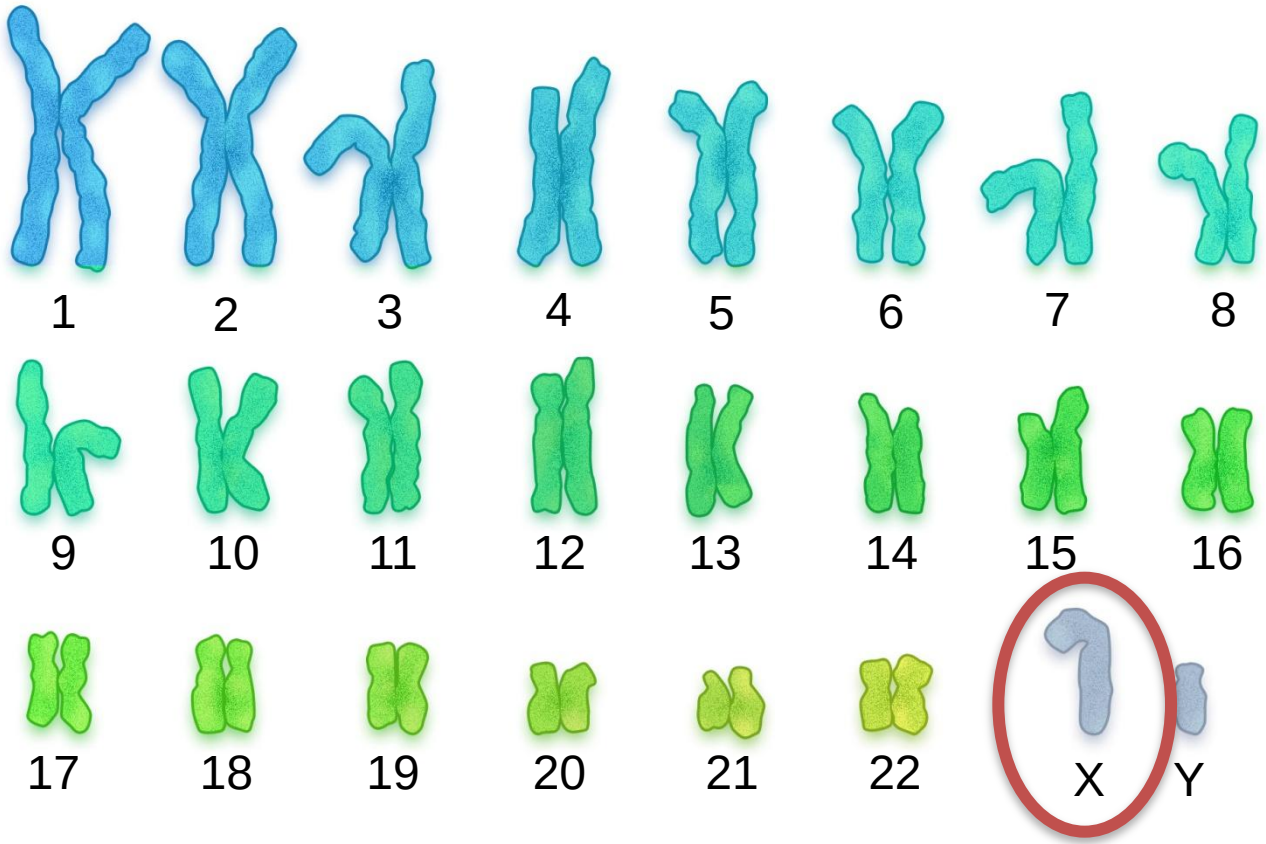
WIKIPEDIA
The Free Encyclopedia


Gal
GalNac
Gal
Glc
Ceramide
NeuAc
GM1 gangliosidosis
GalNac
Gal
Glc
Ceramide
NeuAc
Tay-Sachs disease, Sandhoff disease
Gal
Glc
Ceramide
NeuAc
GalNac
Gal
Gal
Glc
Ceramide
Sandhoff disease
Gal
Gal
Glc
Ceramide
Fabry disease
Gal
Glc
Ceramide
SO4
Gal
Ceramide
Metachromatic leukodystrophy
Glc
Ceramide
Gaucher disease
Gal
Ceramide
Krabbe disease
Ceramide
Niemann-Pick disease
Choline
P
Ceramide
Farber disease


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

Gen de la alfa-galactosidasa (GLA)

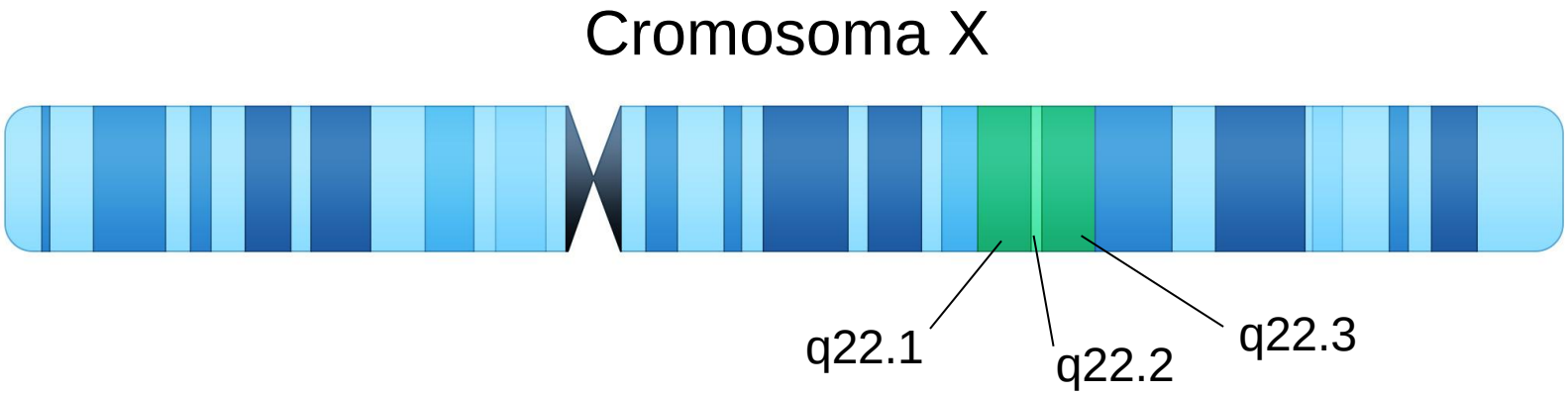
El gen *GLA* se encuentra en el cromosoma X[1]



[1]Gal 2006

El gen GLA en Xq22

El gen *GLA* se encuentra en la posición 22 del cromosoma X[1]

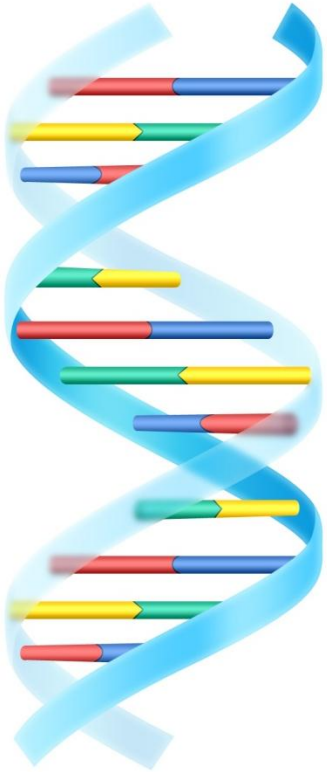


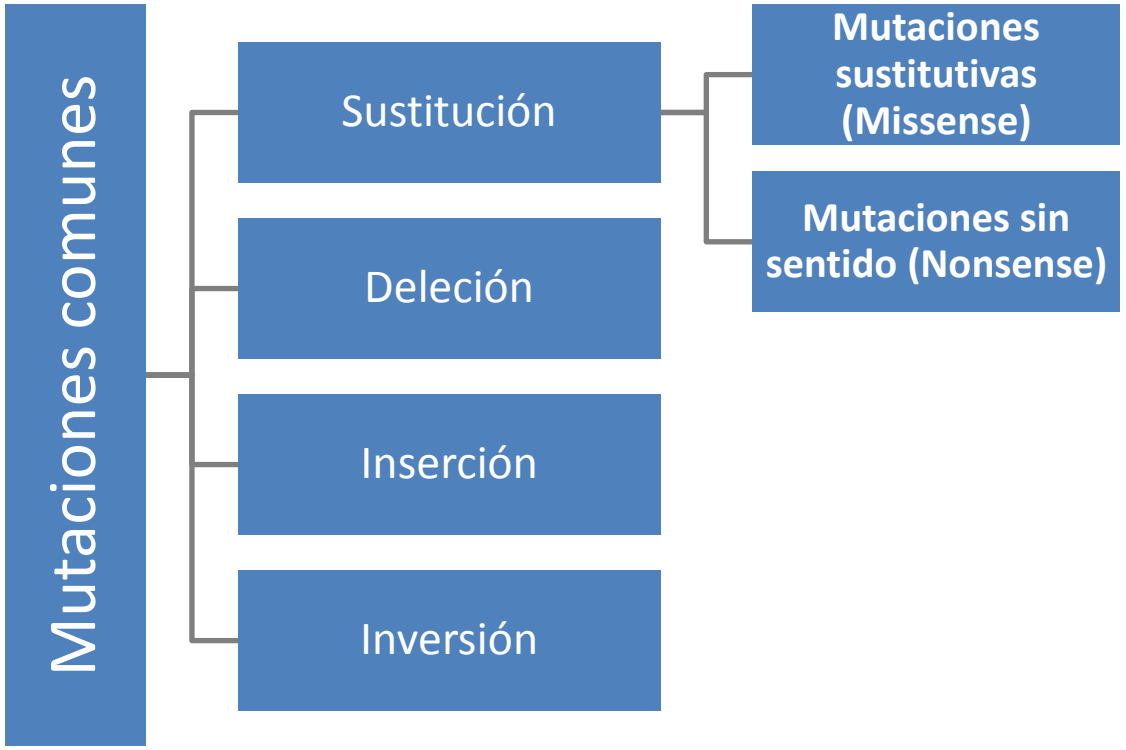
En la enfermedad de Fabry, el gen *GLA* está ausente o es deficiente[2]

[1]Gal 2006; [2]Fauci 2008

Mutaciones genéticas

Son cambios permanentes en el ADN

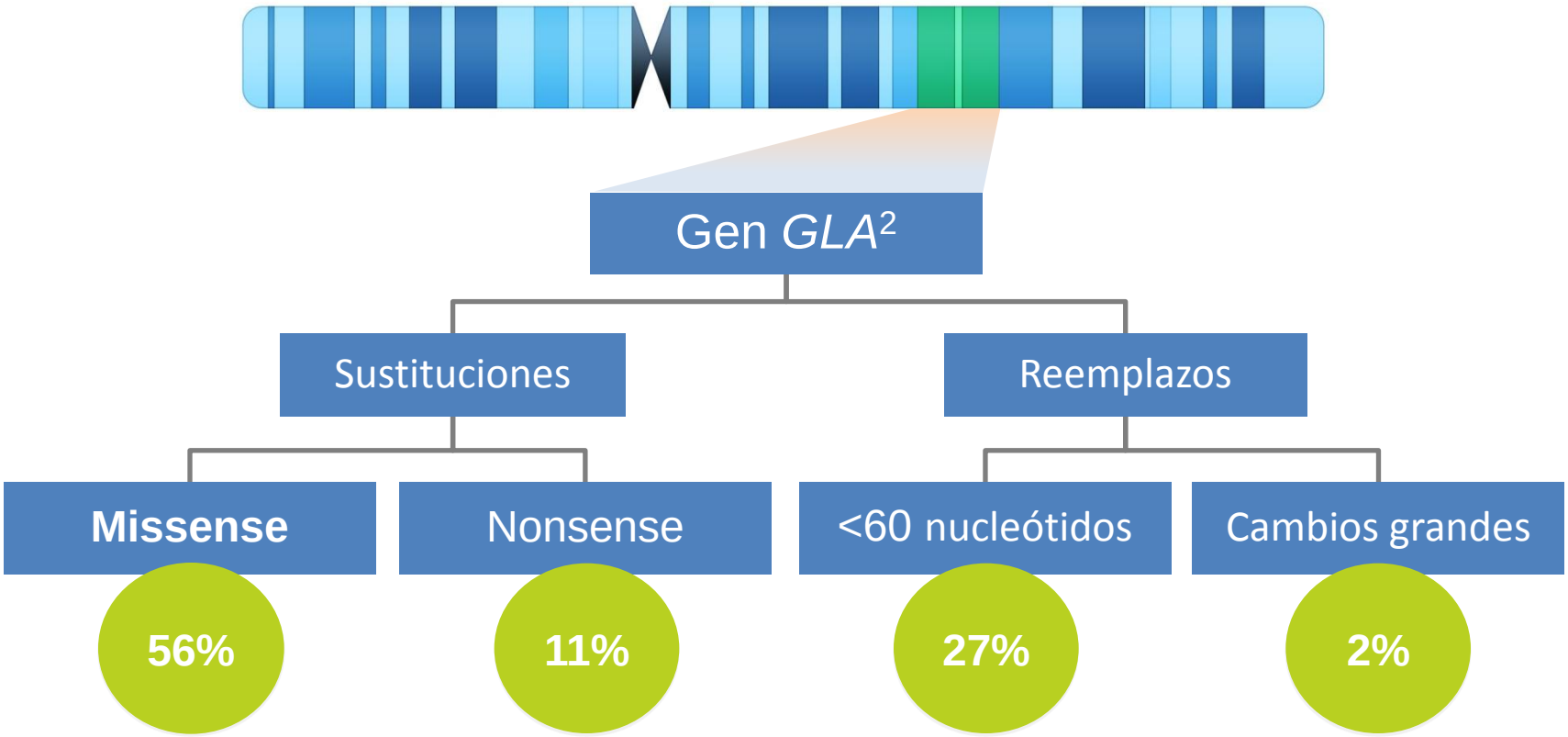




[1]Gal 2006; [2]Evans 2008

Mutaciones genéticas en la enfermedad de Fabry

>500 mutaciones en el gen *GLA* en la enfermedad de Fabry[1]



[1]Benjamin 2009; [2]Gal 2006

MUTACIONES GEN GLA

Biochemical and Molecular Genetic Basis of Fabry Disease

GREGORY M. PASTORES,* YEONG-HAU H. LIEN†

**Neurogenetics Program, Department of Neurology and Pediatrics, New York University School of Medicine, New York, New York; and †Department of Medicine, University of Arizona Health Sciences Center, Tucson, Arizona.*

J Am Soc Nephrol 13: S130–S133, 2002

M1T	S65T	G128E	C202Y	N215S	Q279E	A377D
M1I	E66Q	Y134S	P205T	Y216D	Q279H	W340R
P6X	IVS G-T	G138R	W209X	R220X	Q280H	W340X
A20P	M72V	C142Y	Ex4-SD	G258R	M284T	R342Q
A31V	Y86C	A143T	613D9	P259R	W287C	R342X
L32P	L89P	S148R	IVS4 +1	G260A	L294X	R356W
P40S	I91T	A156V	IVS4 +2	N263S	M296I	E358K
W44X	D92Y	G163V	IVS4 +4	V269A	M298K	G361R
H46R	C94S	L166V		N272K	N298H	R363H
H46Y	C94Y	D170V		W277X	N298S	Y365X
W47G	W95S	409D1		239D2	N301G	G373S
R49P	A97V	520DT		240ins2	R301Q	A377D
C52R	R100T			241ins1	R301X	P409A
125D13	R112C			256D1	D313Y	P409T
154DT	F113L			257D2	N329K	777D1
DE358	F113S			M267I	G328R	
Complex	304D1			G358R	898*ins1	
	Complex			P259R	987D1	

J Am Soc Nephrol 13: S130–S133, 2002

MUTACIONES GEN GLA

Mutaciones en los 7 exones

93% de los genotipos se corresponden con variante clásica de la EF

18 genotipos asociados con variante cardiaca de la EF.

Gran heterogeneidad en los genotipos

Variante clásica: R220X, R227Q, E398X…

Variante renal: S78X, C126-127, CATG, A352D,…

Variante cardiaca: R112H, R301Q, G328R, R404,…

J Am Soc Nephrol 13: S130–S133, 2002

Lysosomal Disease Network's 10th Annual WORLD Symposium 2014

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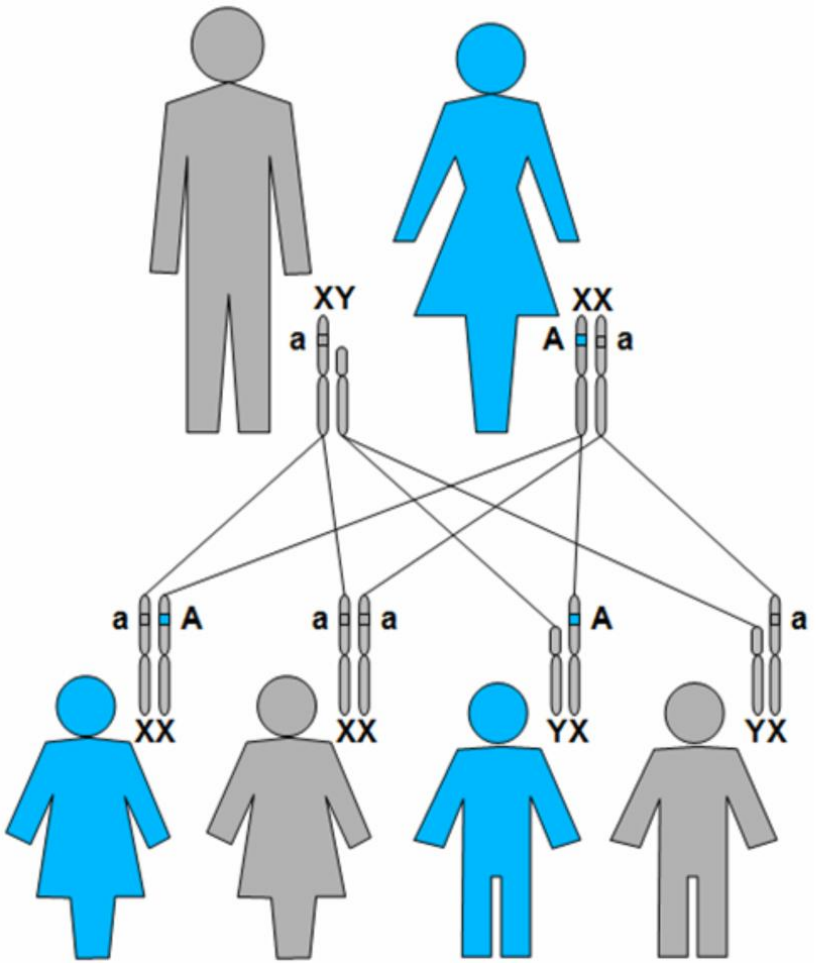
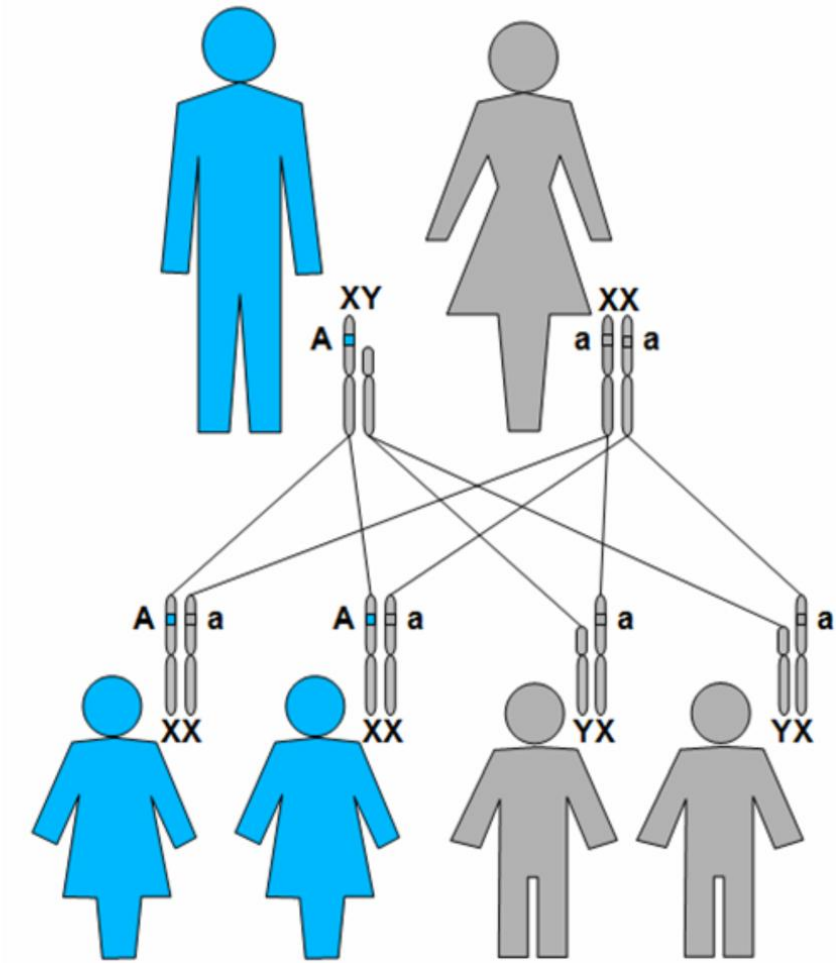
The demographics and prevalence of the most frequently reported α-galactosidase A mutations in Fabry patients: data from the Fabry Registry

Dawn A. Laney, *Emory, Decatur, GA, USA*

- **Fabry Registry. Genotipo de más de 3200 pacientes**
- **15 mutaciones más repetidas: 10 *missense*.**
- **La más repetida (4,8%): N215S.**
- **La mayoría: mutaciones familiares exclusivas o *de novo*.**
- **Gran heterogeneidad en los genotipos**

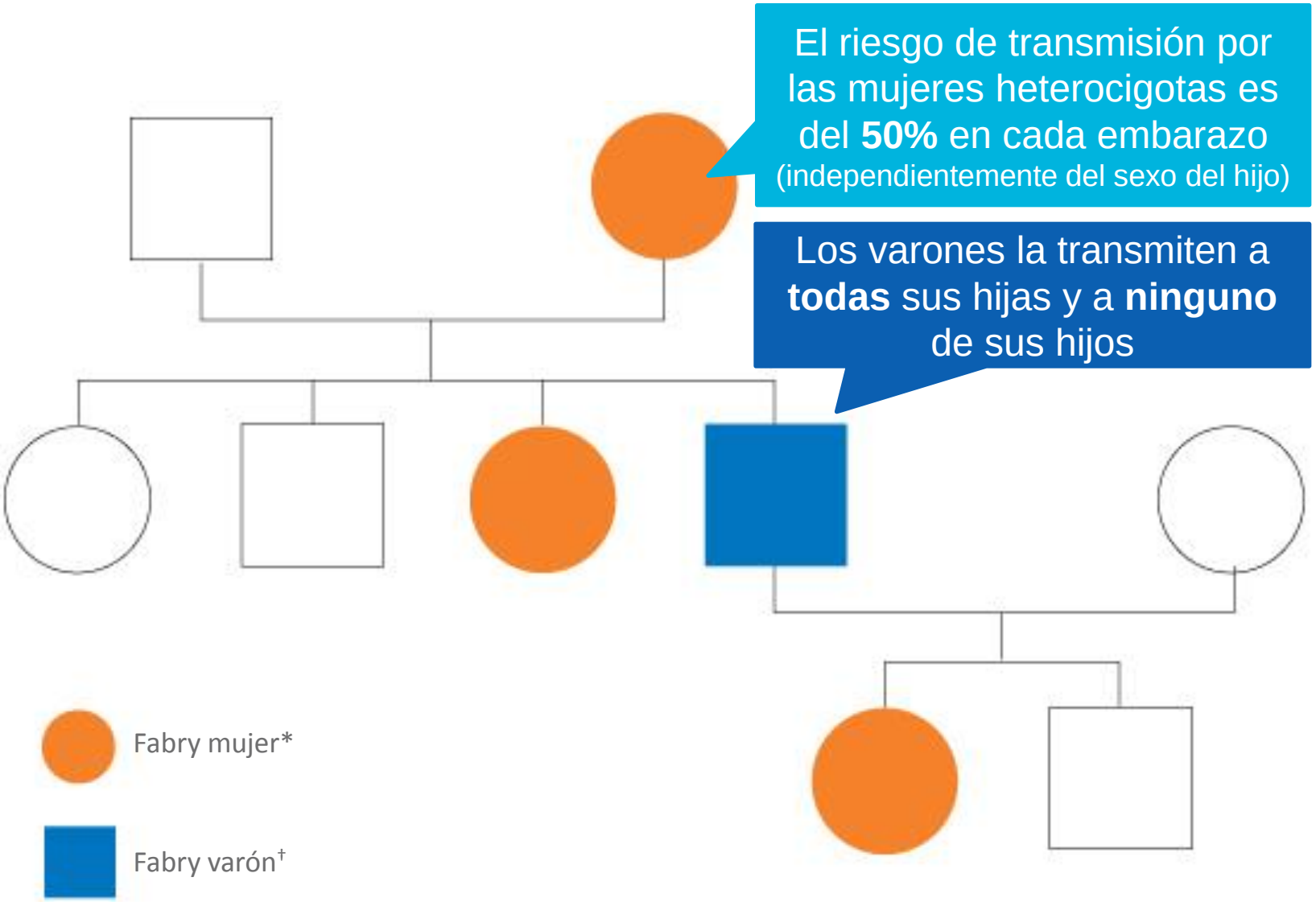
Herencia ligada al X (NO RECESIVA)



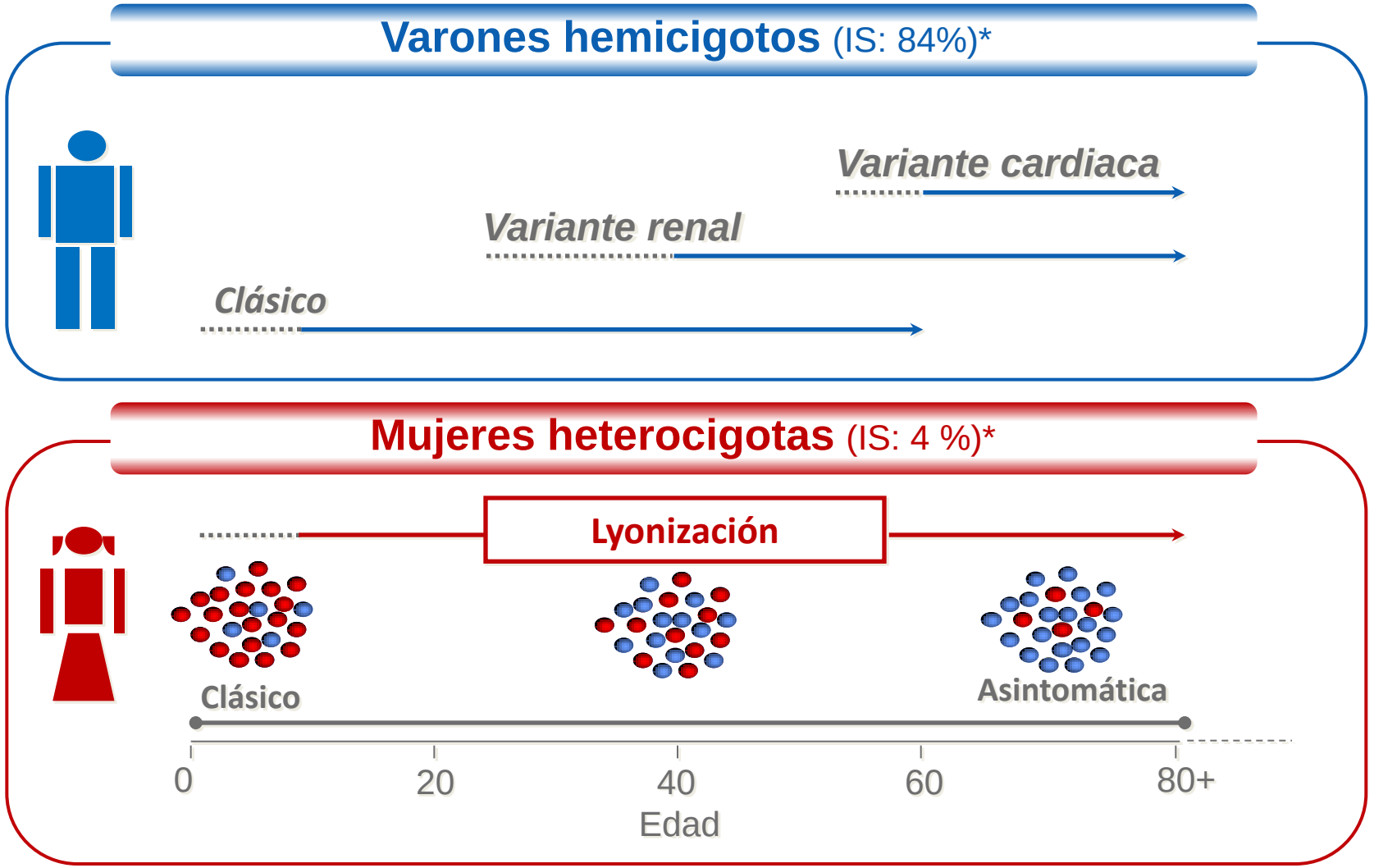


Am J Med Genet 2004;129A:136.

Herencia ligada al X (NO RECESIVA)



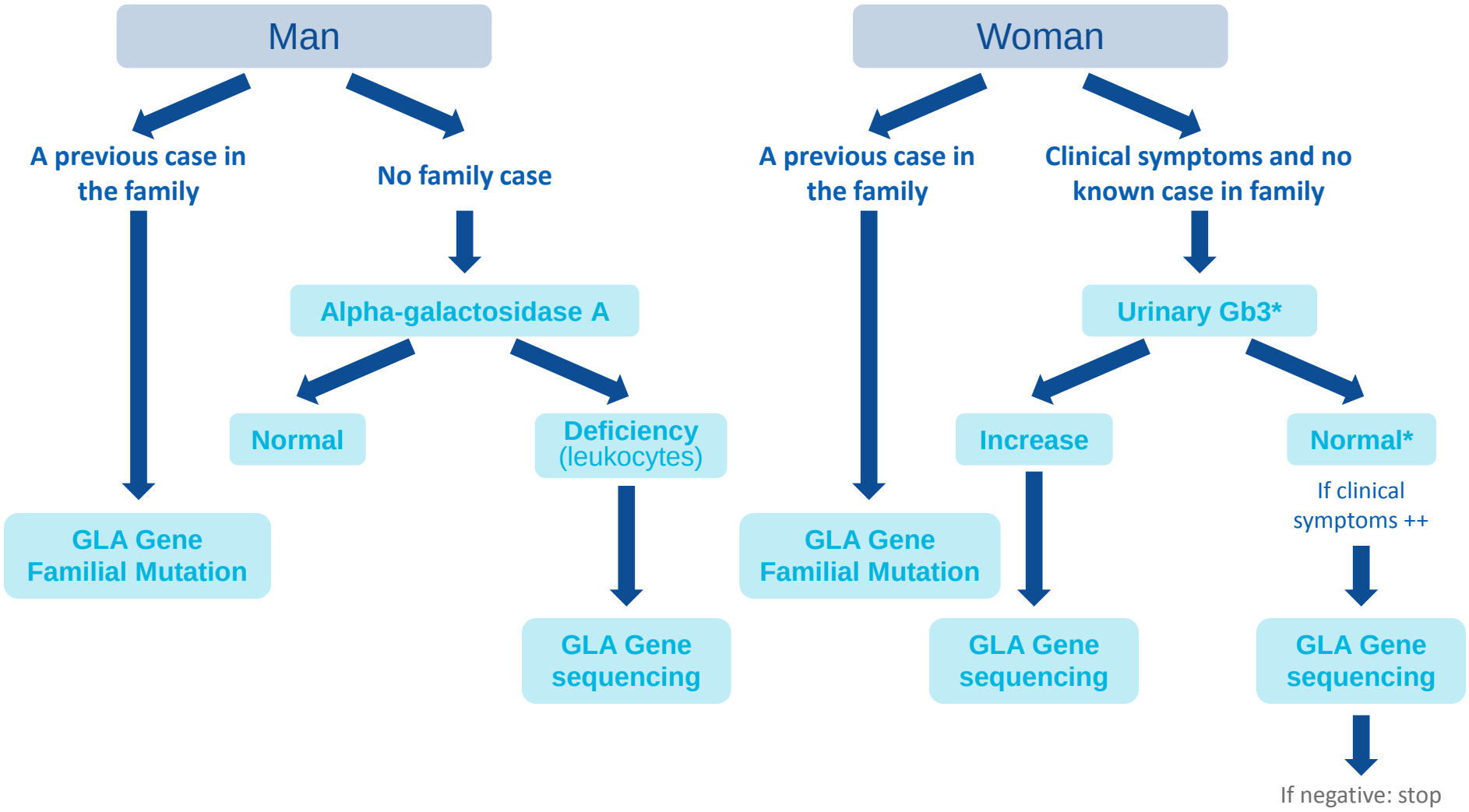
Herencia ligada al X (NO RECESIVA)



*IS: Índice de Severidad.

Am J Med Genet 2004;129A:136.

¿ESTUDIO ENZIMÁTICO, MOLECULAR,…?



*Urinary Gb3 excretion (men and women) always normal in Fabry disease with certain mutations (and after kidney transplantation).

¿LysoGb3?

How well does urinary lyso-Gb_3 function as a biomarker in Fabry disease?

Christiane Auray-Blais [a,*], Aimé Ntwari [a], Joe T.R. Clarke [a], David G. Warnock [b], João Paulo Oliveira [c], Sarah P. Young [d], David S. Millington [d], Daniel G. Bichet [e], Sandra Sirrs [f], Michael L. West [g], Robin Casey [h], Wuh-Liang Hwu [i], Joan M. Keutzer [j], X. Kate Zhang [j], René Gagnon [a]

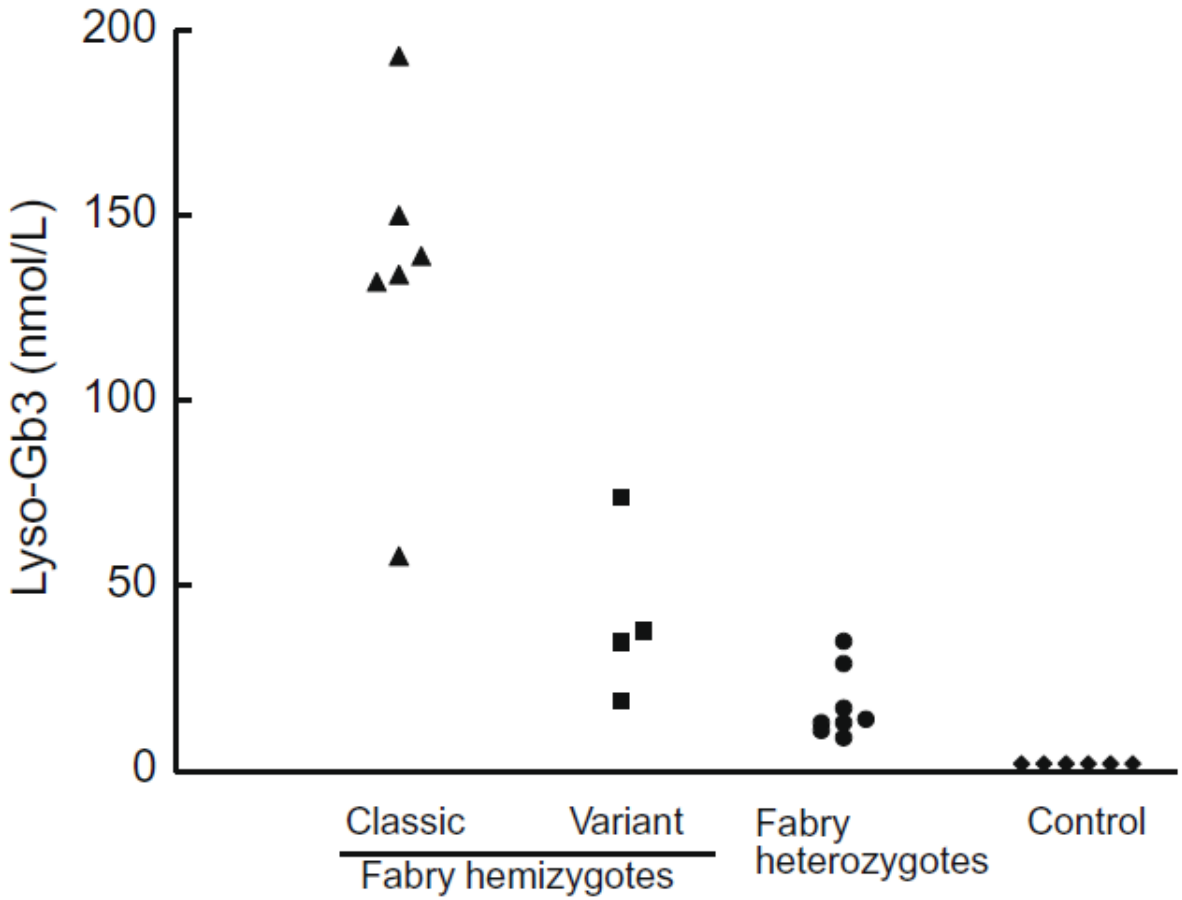
Clinica Chimica Acta 411 (2010) 1906–1914

Plasma globotriaosylsphingosine as a biomarker of Fabry disease

Tadayasu Togawa [a], Takashi Kodama [a], Toshihiro Suzuki [a], Kanako Sugawara [b], Takahiro Tsukimura [a], Toya Ohashi [c], Nobuyuki Ishige [d], Ken Suzuki [d], Teruo Kitagawa [d], Hitoshi Sakuraba [a,b,*]

Molecular Genetics and Metabolism 100 (2010) 257–261

LysoGb3 como biomarcador



Molecular Genetics and Metabolism 100 (2010) 257–261

LysoGb3 como biomarcador

- ↑↑↑ en varones forma clásica
- ↑ (respecto controles) en variantes atípicas y mujeres heterocigotas
- Respuesta más sensible que Gb3 al TSE.

Molecular Genetics and Metabolism 100 (2010) 257–261

- Medición, con espectrometría de masas, de Lyso-Gb3 en orina
- Presencia de Lyso-Gb3 en orina es exclusiva de enfermedad de Fabry
- No Lyso-Gb3 en orina de pacientes con diagnóstico molecular de EF (R363H y R118C)

Clinica Chimica Acta 411 (2010) 1906–1914

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The Fabry genotype-phenotype database: an international expert consortium

Robert J. Desnick[a], Dana O. Doheny[b], Dominique P. Germain[c], Yoshikatsu Eto[d,e], Frank Weidemann[f], Hitoshi Sakuraba[g], Rong Chen[a], David F. Bishop[a], [a]*Icahn School of Medicine at Mount Sinai, New York, NY, USA,* [b]*Icahn School of Medicine at Mount Sinai, New York, NJ, USA,* [c]*University of Versailles and Hopital Raymond Poincare, Garches, France,* [d]*Advance Clinical Research Center and Asian LSD Center, Kawasaki, Japan,* [e]*Tokyo Jikei University School of Medicine, Tokyo, Japan,* [f]*University of Wurzburg, Wurxburg, Germany,* [g]*Meiji Pharmaceutical University, Tokyo, Japan*

- **www.hgmd.org, www.fabry-database.org, otros "registros Fabry"**
- **School of Medicine at Mount Sinai**
- **Acceso libre.**
- **Implicaciones en seguimiento, relación con el fenotipo, decisión de TSE…**

GENOTIPO y LysoGb3

Original Article

Gene Mutations Versus Clinically Relevant Phenotypes
Lyso-Gb3 Defines Fabry Disease

Markus Niemann, MD; Arndt Rolfs, MD; Stefan Störk, MD, PhD; Bart Bijnens, PhD; Frank Breunig, MD; Meinrad Beer, MD; Georg Ertl, MD; Christoph Wanner, MD; Frank Weidemann, MD

Background—Currently, no method is available to identify α-galactosidase A (agalA) mutations determining clinically relevant Fabry disease. In our largest European Fabry cohort, we investigated whether a biomarker, specific for the defect, could stratify persons at risk.

Methods and Results—A total of 124 individuals with agalA mutations were investigated with a comprehensive clinical workup, genetic analysis, and laboratory testing, including measurements of agalA activity and lyso-Gb3 (degradation product of the accumulating Gb3). Additionally, an extensive family screening with a clinical workup of relatives was performed. The patient population was divided into 2 samples: previously described mutations (n=72) and novel mutations (n=52). The patients with previously described mutations were subdivided into 2 groups: classical mutations, which were known to cause the classic type of Fabry disease with specific symptoms and a high risk for major events in all 3 main organs (heart, kidney, and central nervous system), and atypical mutations without the typical presentation. All patients with atypical mutations (n=17) had lower lyso-Gb3 levels than any of the patients with classical Fabry disease (n=55). A cutoff value of 2.7 ng/mL separated the 2 groups. Six out of 52 patients with novel mutations showed a lyso-Gb3 level <2.7 ng/mL. Clinical investigation, blinded to lyso-Gb3 results, revealed no classic organ involvement in these patients or their relatives. In contrast, the characterization of patients with lyso-Gb3≥2.7ng/mL suggested classical Fabry mutations in most of the patients (93%).

Conclusions—Our data show that the biomarker lyso-Gb3 may identify the clinically relevant agalA mutations leading to Fabry disease. (***Circ Cardiovasc Genet*. 2014;7:8-16.**)

GENOTIPO y LysoGb3

GENOTIPO:

- **<u>Mutación clásica</u>:**

  Afectación de al menos 2 de 3 órganos (corazón, riñón, SNC)

  Síntomas específicos cualquier órgano + 1 evento mayor (IRC est III-IV, HVI severa, ictus)

- **<u>Variantes atípicas</u>: resto**

124 pacientes con genotipo de EF. De ellos, 23 pacientes con Lyso-Gb3<2,7 ng/mL:

17/23 mujeres

5/23 con polimorfismos

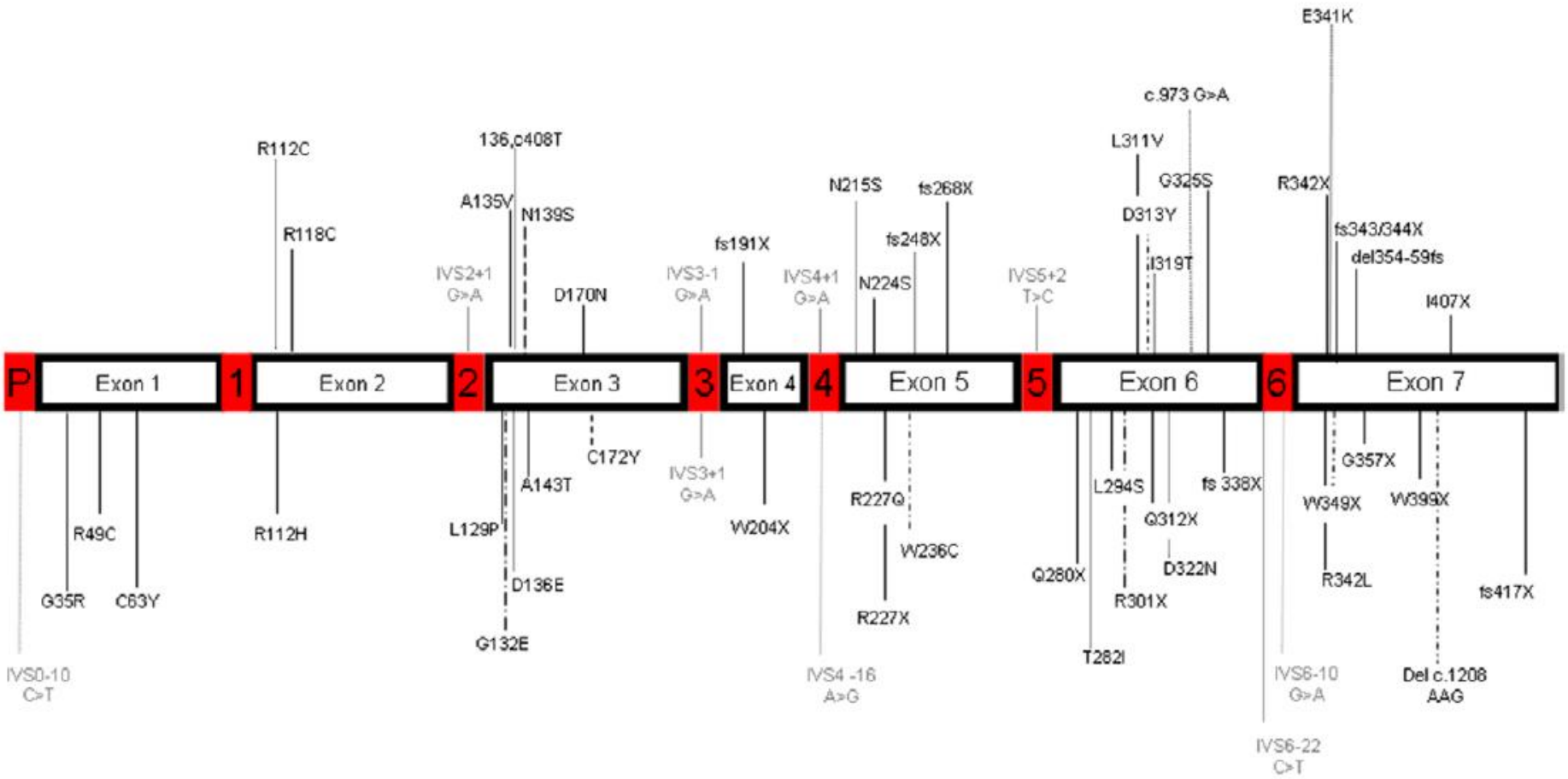
0/23 HVI

2/23 IRC (1 caso HTA, 1 caso sarcoidosis renal)

3/23 ictus (1 cardioembólico, 2 criptogénicos)

Circ Cardiovasc Genet. 2014;7:8-16.

GENOTIPO y LysoGb3



Circ Cardiovasc Genet. 2014;7:8-16.

GENOTIPO y LysoGb3

Hombres *vs* Mujeres

Table 1. Clinical Baseline Characteristics of the Patients With agalA Mutations Subdivided by Sex

	Men n=51	Women n=73	*P* Value
Age, y	39±13	41±14	0.30
Alpha-galactosidase activity, nmol/min per mg protein	0.06±0.11	0.32±0.36	<0.0001
Lyso-Gb3, ng/mL	67.8±35.9	6.3±4.7	<0.0001

Mutaciones típicas *vs* Atípicas

Table 3. Clinical Baseline Characteristics of All Patients With Typical and Atypical agalA Mutations

	Typical n=101	Atypical n=23	*P* Value
Men/women	45/56 (45%,55%)	6/17 (24%,76%)	0.08
Age, y	40±14	40±14	0.95
Alpha-galactosidase activity, nmol/min per mg protein	0.2±0.1	0.5±0.6	0.02
Lyso-Gb3, ng/mL	38.7±39.1	0.8±0.9	<0.001

Circ Cardiovasc Genet. 2014;7:8-16.

Mutaciones típicas *vs* Atípicas

Table 3. Clinical Baseline Characteristics of All Patients With Typical and Atypical agalA Mutations

	Typical n=101	Atypical n=23	*P* Value
General symptoms			
Abnormal sweating (n)	51 (51%)	2 (9%)	<0.001
Heat or cold intolerance (n)	58 (58%)	4 (17%)	<0.001
Chronic diarrhea (n)	32 (32%)	4 (17%)	0.13
Sudden deafness (n)	21 (21%)	2 (9%)	0.15
Angiokeratomata (n)	41 (41%)	0	<0.001
Neurology			
Stroke (n)	11 (11%)	3 (13%)	0.50
Chronic pain syndrome (n)	33 (33%)	1 (4%)	0.003
Acroparaesthesia (n)	68 (68%)	4 (17%)	<0.001
Heart			
Cardiomyopathy (n)	49 (49%)	0 (0%)	<0.001
LV mass, g	153±59	100±28	<0.001
Kidney			
Kidney transplantation (n)	7 (7%)	0 (0%)	0.22
Dialysis (n)	6 (6%)	0 (0%)	0.28
Serum creatinin, mg/dL	1.1±1.3	0.8±0.2	0.28
Serum urea, mg/dL	31±19	27±7	0.33
DTPA clearance, ml/min	91±36	111±23	0.003
Medication			
Beta blocker (n)	16 (16%)	4 (17%)	0.53
Calcium channel blocker (n)	3 (3%)	1 (4%)	0.57
ACE inhibitor (n)	33 (33%)	5 (22%)	0.22
Aspirin (n)	22 (22%)	4 (17%)	0.44
Disease severity score	9±6	4±4	<0.001

GENOTIPO y LysoGb3

CLINICAL PERSPECTIVE

The current study suggests that the biomarker lyso-Gb3 can differentiate classical Fabry disease from atypical agalA mutations. This is especially helpful when the clinical information about a new mutation is limited and in women patients with an agalA activity level in the gray zone. The data question the current practice to establish the diagnosis of Fabry disease: it seems that the measurement of agalA activity in combination with genotyping is not sufficient for diagnosing Fabry disease. Fabry disease might be redefined based on three criteria: (1) information about the agalA mutation, (2) the level of lyso-Gb3, and (3) the typical Fabry symptoms and organ involvement. If a patient has an agalA mutation and an elevated lyso-Gb3 level and typical symptoms or organ involvement, this combination may be labeled classical Fabry disease. In patients exhibiting an agalA mutation plus elevated lyso-Gb3 levels who are still asymptomatic and free of organ involvement, this constellation may be labeled classical Fabry mutation. Finally, in patients with an agalA mutation but a normal lyso-Gb3 level, it may be labeled atypical α-galactosidase A mutation.

***Circ Cardiovasc Genet*. 2014;7:8-16.**

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A case series study on diagnostic dilemmas in Fabry disease

Bouwien Smid[a], Carla Hollak[a], Ben Poorthuis[a], Janneke Timmermans[b], Gabor Linthorst[a], [a]*Academic Medical Centre, Amsterdam, Netherlands*, [b]*UMC St. Radboud, Nijmegen, Netherlands*

conclude, a misdiagnosis of FD may occur in subjects with a GLA variant and isolated non specific findings, such as HCM or stroke. To prevent misdiagnoses, inappropriate counselling and costly therapy, a structured diagnostic approach is mandatory. Other causes need to be excluded, including concomitant disease and risk factors and the use of medication causing similar inclusion bodies on histology. Certain GLA variants might be interpreted as risk factors for developing FD complications rather than directly disease causing and decisions for treatment should be made with caution. Determination of plasma lysoGb3 might be an important tool to discriminate between non Fabry and non-classical FD patients.

CONSEJO GENÉTICO

J Genet Counsel (2013) 22:555–564
DOI 10.1007/s10897-013-9613-3

PROFESSIONAL ISSUES

Fabry Disease Practice Guidelines: Recommendations of the National Society of Genetic Counselors

Dawn A. Laney · Robin L. Bennett · Virginia Clarke · Angela Fox · Robert J. Hopkin · Jack Johnson · Erin O'Rourke · Katherine Sims · Gerald Walter

Mutaciones: http://www.hgmd.cf.ac.uk/ac/index.php

- Aprox 500 mutaciones descritas.

- La mayoría, únicas ("mutaciones privadas")

CONSEJO GENÉTICO

1. **Remitir a especialista en metabolopatías y consejo genético**
2. **Riesgo de afectación familiar**
3. **Elaboración árbol genealógico completo**
4. **Identificación familiares “en riesgo”**
5. **Evaluación preconcepcional (especialista clínico)**
6. **Opciones:**

    Donantes de gametos / adopción

    Tests genéticos (preimplantacionales, bx coriónica, amniocentesis)

TAKE-HOME MESSAGES

- **Herencia lig X (lyonización)**
- **Gran heterogeneidad en las mutaciones**
- **Predominan mutaciones *missense***
- **Genotipo y Lyso-Gb3: implicación clínica**
- **Lyso-Gb3 como biomarcador de enfermedad**
- **Consejo genético especializado**