Fabry Disease

A guide to understanding
this rare lysosomal disease

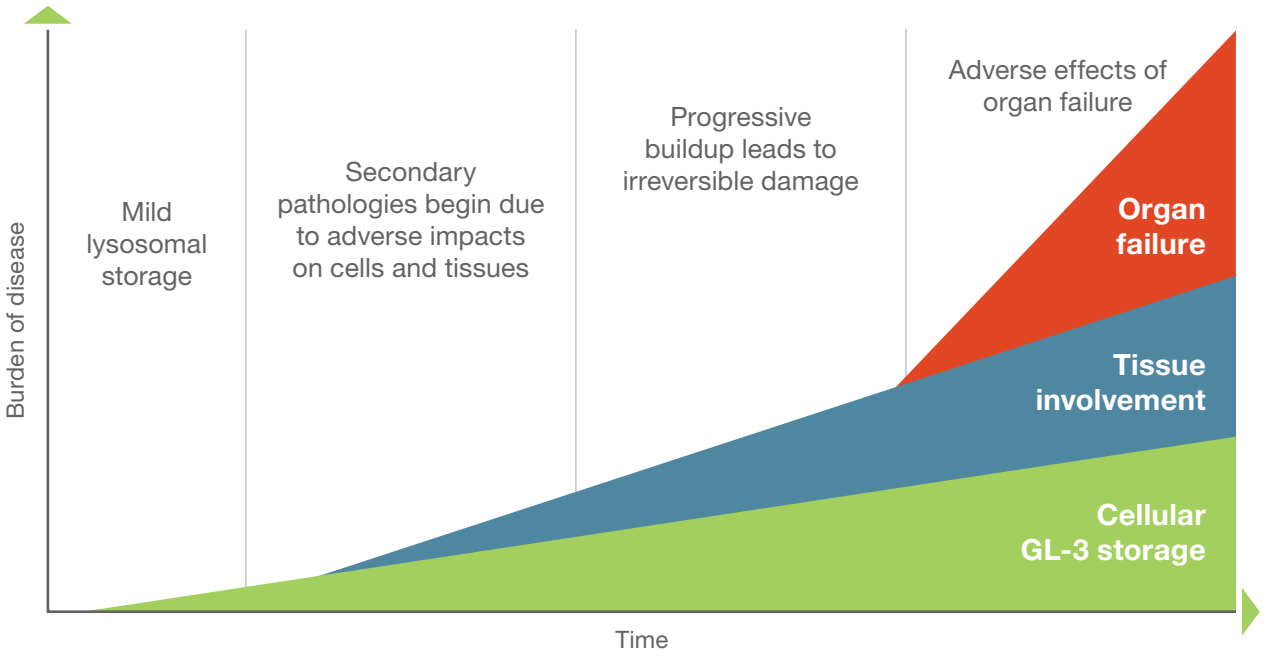
Understanding Fabry disease

Fabry disease is a rare, X-linked lysosomal disorder that can affect both males and females.[1,2] Fabry disease is caused by mutations (variants) in the galactosidase alpha gene (*GLA*), resulting in an absent or functionally deficient alpha-galactosidase A (alpha-Gal A) enzyme.[2] Functional deficiency may occur when improper protein folding reduces the stability of alpha-Gal A, often leading to enzyme degradation in the endoplasmic reticulum prior to normal transport to the lysosome.[3]

In healthy individuals, alpha-Gal A breaks down globotriaosylceramide (GL-3) and disease-causing substances. However, when alpha-Gal A is absent or deficient, GL-3 accumulates in the lysosome, leading to cellular damage within affected parts of the individual's body. This in turn causes the various pathologies seen in Fabry disease.[3,4]

Clinical progression and burden of Fabry disease over time

The accumulation of GL-3 begins in utero and progresses throughout life.[5,6]



Adapted with permission from Eng CM et al. *J Inherit Metab Dis*. 2007;30(2):184-192.[7]

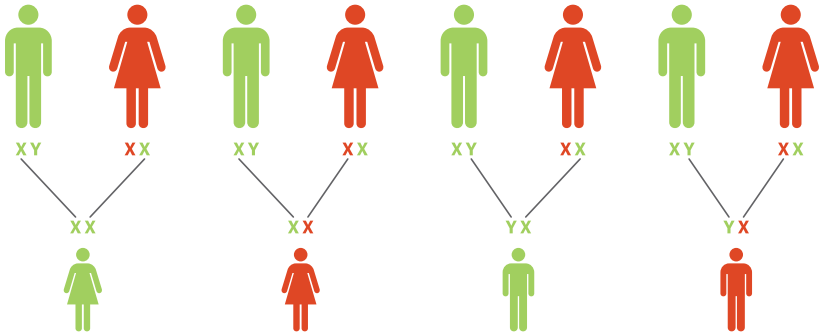
The X-linked inheritance pattern of Fabry disease[1]

The red **X** indicates an affected X chromosome.

An individual **with** a gene mutation that causes Fabry disease

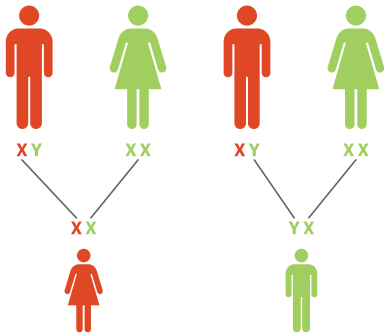
An individual **without** a gene mutation that causes Fabry disease

INHERITANCE THROUGH AN AFFECTED MOTHER[3]



There is a 50% chance that an affected mother with a heterozygous genotype will pass the mutated gene to any of her children.

INHERITANCE THROUGH AN AFFECTED FATHER[3]



The daughter will always inherit the mutated gene from her father.

The son will not inherit the mutated gene from his father.

As a progressive, multisystemic disease, Fabry disease can[1]:

- Have a devastating impact on people's lives
- Have a wide spectrum of symptoms
- Present differently in each affected individual
- Prove to be a significant burden regardless of presentation

In families affected by Fabry disease, targeted mutational analysis is important as it can be used to diagnose at-risk individuals who may not yet exhibit the phenotypic characteristics of the disease.[8]

Diagnosing Fabry disease

Fabry disease diagnosis is challenging, as symptoms are diverse, varied, and affect multiple organs[3,9]

While Fabry disease is considered "rare," many of its signs and symptoms are seen with more common disorders. As a result of the multiorgan pathology often seen in patients with Fabry disease and the number of conditions that mimic the signs and symptoms of the disease, diagnosis may be difficult.[3,9]

The road to a Fabry disease diagnosis can be long and difficult

It is estimated that patients visit an average of 10 different specialists before a Fabry disease diagnosis is confirmed, leading to a delay of ~15 years in men and women from the onset of first symptoms to diagnosis.[10,11]

GLA gene sequencing confirms a diagnosis of Fabry disease[10]

In addition, gene sequencing helps:

- Establish the disease phenotype[12]
- Provide additional information regarding disease prognosis and treatment[13]
- Permit the testing of at-risk family members[12]

NOTE: In males with the suspected classic phenotype, an absence or low levels of alpha-Gal A activity in blood cells or dried blood spots is sufficient to make the diagnosis. However, *GLA* gene sequencing is required for women.[10]

The patient's disease phenotype and genetic variant should inform treatment decisions.[12]

Onset, symptoms, and progression in Fabry disease

Highly variable but progressive course

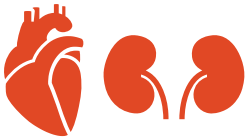
Fabry disease symptoms are often classified into classic and nonclassic phenotypes. However, Fabry disease is most appropriately considered as having a heterogeneous, progressive spectrum of disease.[3] Because inheritance is X-linked, the disease course is especially variable in females, in whom one of the two copies of the *GLA* gene is randomly inactivated in different tissues.[3]

Fabry disease presents along a spectrum[3,14]

Males often show symptoms very early, before age 10[3]

Symptoms in females can present during childhood or later and range in severity from mild to severe[3]

A late-onset phenotype exists in both males and females[14]



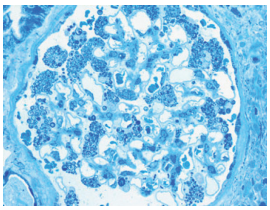
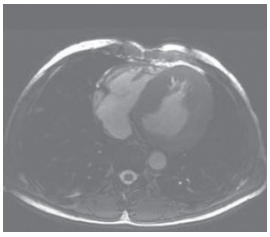
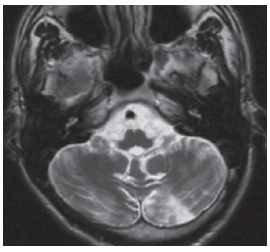
Cardiac and renal variants cause symptoms predominantly in those organ systems[3]

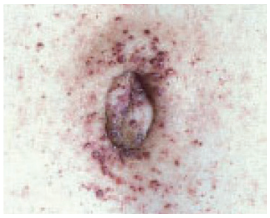
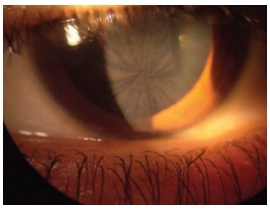
Patients with Fabry disease demonstrate wide variability with regard to age at presentation, symptoms, disease severity, and predictability of disease course[3,14]

Signs and symptoms of Fabry disease

As a progressive, multisystem, multiorgan disease, Fabry disease has a wide spectrum of symptoms.[15] Although Fabry disease has different phenotypes and presents differently in each individual, it can prove to be a significant burden regardless of presentation.[1]

How Fabry disease symptoms can affect organ systems

Organ system	Symptoms	
Renal[3]	• Podocyte damage, glomerular sclerosis • Proteinuria • Decreased renal function • Kidney failure	 **Kidney biopsy showing GL-3 deposition in podocytes.** Image courtesy of Dr. Anthony Chang.
Cardiovascular[3]	• Irregular heartbeat • Left ventricular hypertrophy (LVH) • Heart failure • Myocardial infarction (MI)	 **Cardiac MRI showing left ventricular hypertrophy.** Image from Germain DP. *Orphanet J Rare Dis.* 2010;5:30.[3]
Central nervous system and neurologic[3]	• Acute pain crises, especially in hands/feet, which may be severe • Chronic neuropathic pain • Hypohidrosis, leading to intolerance of heat and exercise • Stroke/transient ischemic attack (TIA)	 **Axial brain MRI section showing stroke of the left cerebellar hemisphere.** Image from Germain DP. *Orphanet J Rare Dis.* 2010;5:30.[3]
Neuropsychiatric[3,16]	• Depression • Anxiety	

Organ system	Symptoms	
Dermatologic[3]	• Angiokeratoma	 **Angiokeratomas around the belly button of a patient with Fabry disease.** Image used with permission from Desnick RJ et al. *Ann Intern Med.* 2003;138(4):338-346.[1]
Ophthalmologic[3]	• Corneal whorling (cornea verticillata) • Cataracts	 **Cornea of a female patient heterozygote for Fabry disease.** Image from Germain DP. *Orphanet J Rare Dis.* 2010;5:30.[3]
Pulmonary[3]	• Dyspnea with exertion • Airway obstruction	
Gastrointestinal[3]	• Nausea, vomiting, cramping, diarrhea • Pain/bloating after eating; early fullness • Difficulty gaining weight	
Ear, nose, throat[3]	• Hearing loss, tinnitus, vertigo	

Impact on organ systems

As Fabry disease progresses, major organ system dysfunction may worsen. This may lead to a shortened lifespan and death, most often from cardiovascular complications, cerebrovascular complications, or renal failure.[15,17]

Fabry disease at a glance

- Fabry disease is a rare, X-linked lysosomal disorder that can affect both males and females[1,2]
- Diagnosis is challenging, as symptoms are diverse, varied, and affect multiple organs[3,9]
- The course of Fabry disease is highly variable, but it is progressive regardless of sex or age at presentation[3,14]
- Fabry disease has a wide spectrum of symptoms[3,15] and presents differently in each individual, proving to be a significant burden regardless of presentation[1]

References: 1. Desnick RJ, Brady R, Barranger J, et al. Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. *Ann Intern Med.* 2003;138(4):338-346. **2.** Filoni C, Caciotti A, Carraresi L, et al. Functional studies of new GLA gene mutations leading to conformational Fabry disease. *Biochim Biophys Acta.* 2010;1802(2):247-252. **3.** Germain DP. Fabry disease. *Orphanet J Rare Dis.* 2010;5:30. **4.** Tuttolomondo A, Simonetta I, Duro G, et al. Inter-familial and intra-familial phenotypic variability in three Sicilian families with Anderson-Fabry disease. *Oncotarget.* 2017;8(37):61415-61424. **5.** Vedder AC, Strijland A, vd Bergh Weerman MA, et al. Manifestations of Fabry disease in placental tissue. *J Inherit Metab Dis*. 2006;29(1):106-111. **6.** Thurberg BL, Politei JM. Histologic abnormalities of placental tissues in Fabry disease: a case report and review of the literature. *Hum Pathol.* 2012;43(4):610-614. **7.** Eng CM, Fletcher J, Wilcox WR, et al. Fabry disease: baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. *J Inherit Metab Dis.* 2007;30(2):184-192. **8.** Yousef Z, Elliott PM, Cecchi F, et al. Left ventricular hypertrophy in Fabry disease: a practical approach to diagnosis. *Eur Heart J.* 2013;34(11):802-808. **9.** Hoffmann B, Mayatepek E. Fabry disease-often seen, rarely diagnosed. *Dtsch Arztebl Int.* 2009;106(26):440-447. **10.** Rozenfeld PA. Fabry disease: treatment and diagnosis. *IUBMB Life.* 2009;61(11):1043-1050. **11.** Wilcox WR, Oliveira JP, Hopkin RJ, et al. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. *Mol Genet Metab.* 2008;93(2):112-128. **12.** Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: Management and treatment recommendations for adult patients. *Mol Genet Metab.* 2018;123(4):416-427. **13.** Gal A, Hughes DA, Winchester B. Toward a consensus in the laboratory diagnostics of Fabry disease - recommendations of a European expert group. *J Inherit Metab Dis.* 2011;34(2):509-514. **14.** El-Abassi R, Singhal D, England JD. Fabry's disease. *J Neurol Sci.* 2014;344(1-2):5-19. **15.** Mehta A, Beck M, Eyskens F, et al. Fabry disease: a review of current management strategies. *QJM.* 2010;103(9):641-659. **16.** Laney DA, Gruskin DJ, Fernhoff PM, et al. Social-adaptive and psychological functioning of patients affected by Fabry disease. *J Inherit Metab Dis.* 2010;33(suppl 3):S73-S81. **17.** Mehta A, Clarke JTR, Giugliani R, et al, for the FOS Investigators. Natural course of Fabry disease: changing pattern of death in FOS – Fabry Outcome Study. *J Med Genet.* 2009;46(8):548-552.

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