Fabry Disease:
A Unique Disease — Uniquely Experienced

Fabry disease—
a significant burden with a devastating impact

Fabry disease is a progressive, multisystemic, X-linked lysosomal disorder affecting both males and females, caused by mutations or variants in the galactosidase alpha (*GLA*) gene.[1,2]

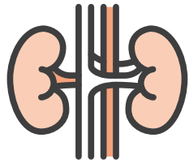
Fabry disease can have a devastating impact on people's lives. Although the disease may present differently in each affected individual, it can prove to be a significant burden regardless of presentation.[1,2]

The life expectancy of patients with Fabry disease is significantly shorter than that of the general population. Lifespans for people with Fabry disease may be shortened to ~50 years for untreated men and ~70 for untreated women—a 20- and 10-year reduction, respectively.[3]

LEADING CAUSES OF DEATH IN FABRY DISEASE[4]

Cardiovascular disease
(53.6% and 50.0% of male and female deaths, respectively)

Cerebrovascular complications
(12.5% of males)

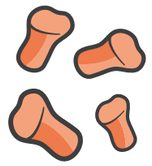


Renal disease
(10.7% of males)

As Fabry disease progresses, major organ system dysfunction may worsen. This may lead to a shortened lifespan and death[2,5], especially if left unmanaged.

Understanding the complexities of
Fabry disease and its symptoms

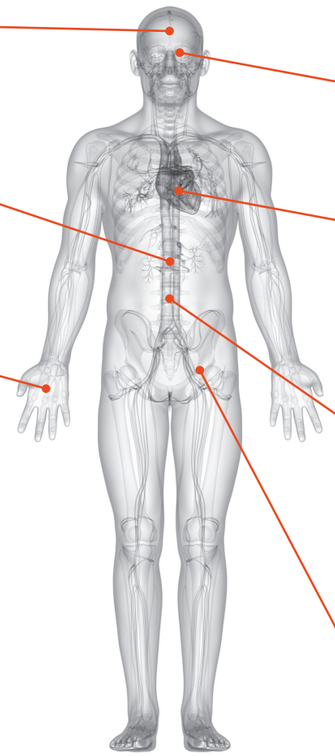
What causes Fabry disease?

Fabry disease is caused by mutations, or variants, in the *GLA* gene.[1,2]	These mutations can cause absent or deficient α-galactosidase A (α-Gal A).[3,6]	When α-Gal A is absent or deficient, globotriaosylceramide (GL-3), plasma globotriaosylsphingosine (lyso-Gb_3), and other disease substrates accumulate.[3,6]	This **leads to cell damage within affected parts of the individual's body** and causes the various pathologies seen in Fabry disease.[3,6]
			

Fabry disease symptoms are diverse and multisystemic

Fabry disease is characterised by multiple organ pathology.[3] Individuals with Fabry disease may experience a wide variety of signs and symptoms, including the following:

- Cerebrovascular symptoms, including dizziness or vertigo, transient ischaemic attacks, and stroke[1]
- Renal disease, typically requiring dialysis or transplantation after prolonged disease[1]
- Acroparaesthesia (abnormal tingling or burning sensation in the extremities)[3]
- Acute pain ("Fabry crises" often in hands and feet, accompanied by fever that may last hours to days)[1,3]
- Hypohidrosis (too little sweat, affecting regulation of body temperature)[1,3]



- Cornea verticillata (whorls in the cornea)[1,3]
- Cardiac disease, such as left ventricular hypertrophy, valvular disease, and rhythm disturbances[1]
- Gastrointestinal symptoms, such as abdominal pain, bloating, diarrhoea, constipation, and early satiety[2,3]
- Angiokeratomas (reddish-purple, non-blanching maculopapular lesions)[1,3]

Why *GLA* gene mutations matter in Fabry disease

To date, there are more than 1000 mutations of the *GLA* gene.[6] A variety of mutations in the *GLA* gene can give rise to Fabry disease, such as[3]:

- Missense mutations[7]
  - Compose ~60% of the *GLA* gene mutations known to cause Fabry disease
  - Cause the introduction of an incorrect amino acid into a protein through a mutation of a single nucleotide
- Splicing mutations
- Small deletions and insertions
- Large deletions

1000+
mutations

Many genetic mutations are specific to individual families affected by Fabry disease, whereas some are more widespread.[1]

Fabry disease is a unique disease, uniquely experienced. With more than 1000 known mutations of the *GLA* gene,[6] there is no single genotypic anomaly that causes Fabry disease.

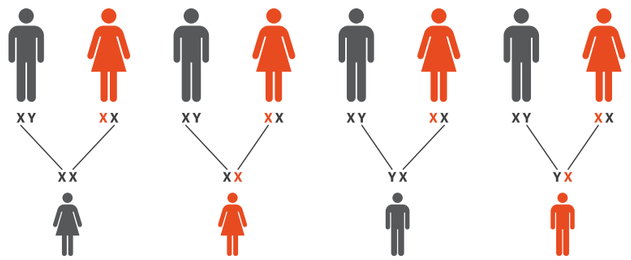
Understanding the X-linked inheritance pattern of Fabry disease[1]

The orange X indicates an affected X chromosome.

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

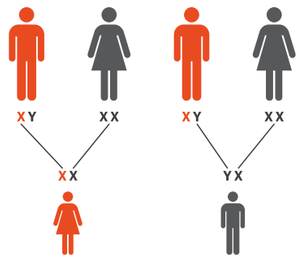
An individual **without** a gene mutation that causes Fabry disease

INHERITANCE THROUGH AN AFFECTED MOTHER[3]



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

INHERITANCE THROUGH AN AFFECTED FATHER[3]



The daughter will inherit the defective gene from her father.

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

Males with Fabry disease cannot transmit Fabry disease to their sons, but will always transmit the disease to their daughters[3]

Females with Fabry disease have a 50% chance of transmitting the disease to their sons and daughters[3]

Each Fabry disease mutation can present in a unique way

Three unique individuals

Manifestations of Fabry disease can differ significantly from individual to individual.[1,2] In one study, the functional effects of 3 different gene mutations that cause Fabry disease were studied. Each patient presented in a unique way.[7]

	AGE AT DIAGNOSIS	GENOTYPE	PHENOTYPE
 MICHAEL*	42	c.155G>A, p.C52Y	Prior to diagnosis, Michael experienced acroparaesthesia, hypohidrosis, and recurrent abdominal pain. Since being diagnosed, he has presented with multiple brain lesions and has experienced loss of mobility and cardiac disease.
 ANNE*	49	c.548G>C, p.G183A	Prior to diagnosis, Anne experienced mild hypertension and renal involvement. Anne has also presented with proteinuria (250 mg/h) and developing type 2 diabetes mellitus.
 GEORGE*	20	c.647A>G, p.Y216C	Prior to diagnosis, George experienced diffuse angiokeratoma, acroparaesthesia, pain, and limb edema. George has also presented with cardiac involvement.

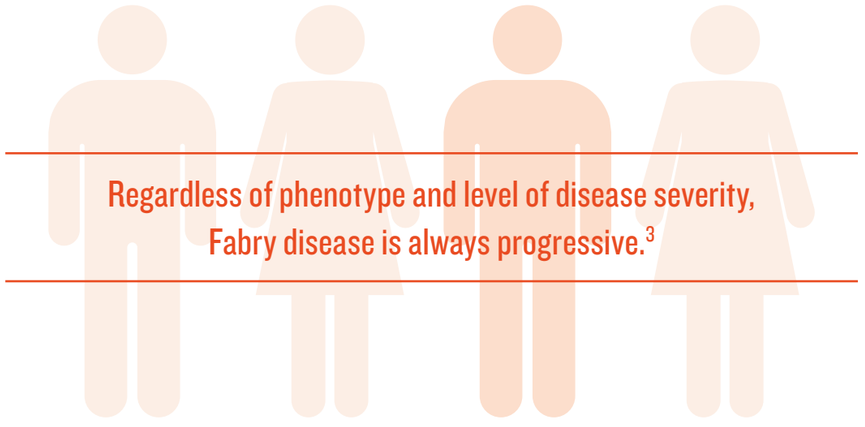
*Represent real examples from peer-reviewed literature; not actual patient names or images.

Two unique family members

Even when family members share an identical mutation, their disease presentation may be completely different.[1,8,9] One study examined the effects of a W226X mutation in 2 male relatives, showing that although both individuals had an identical mutation, each experienced a unique presentation.[9]

	AGE AT DIAGNOSIS	GENOTYPE	PHENOTYPE
 BILL*	18	W226X	Bill was diagnosed with Fabry disease after being evaluated due to severe growth retardation, skeletal dysplasia, and delayed puberty.†
 MARC*	11	W226X	Marc was diagnosed with Fabry disease after being referred for evaluation due to a family history of Fabry disease. He experienced acroparaesthesia, hypohidrosis, and discomfort. He was previously diagnosed with celiac disease.

*Represent real examples from peer-reviewed literature; not actual patient names or images.
†Clinical presentation is not typical of Fabry disease.

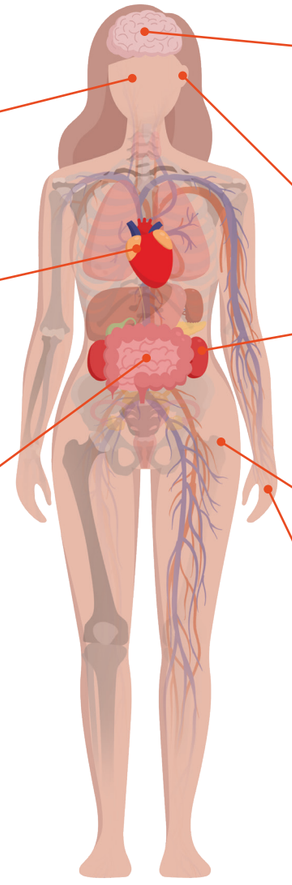


Regardless of phenotype and level of disease severity, Fabry disease is always progressive.[3]

Heterozygous women are not just carriers

It is a common misconception that females are just carriers of a defective *GLA* gene. Heterozygous women with Fabry disease can experience a variable presentation, ranging from asymptomatic or mild symptoms to symptoms that are just as severe and multisystemic as those experienced by male patients, such as cardiac, renal, and cerebrovascular complications.[1,5,10]

Common symptoms in women with Fabry disease[11]



CNS, central nervous system;
eGFR, estimated glomerular filtration rate.

Symptom variability may be due to X-chromosome inactivation

Variability of symptoms and presentation in women with Fabry disease may be explained through X-chromosome inactivation, or lyonisation. This takes place when 1 of the 2 X-chromosomes becomes inactivated inside female embryonic cells. This causes affected females with Fabry disease to have a mix of both normal and mutant cells, thus causing varied expression of the disease.[3,11]

Women with Fabry disease experience more than just physical symptoms

Pain and QoL

The pain experienced with Fabry disease is different from other neuropathic pain conditions.[12] According to one study, 52% of women reported experiencing pain at some point in their lifetime.[12] A vast majority described their pain as "burning."[12]

When it comes to pain intensity, location, and frequency, a large international study found that the data were comparable between men and women.[13]

In addition, pain has a severe impact on quality of life. In general, women with Fabry disease have a decreased quality of life (QoL) compared to the general population.[14]

Depression and QoL

Depression is often an underdiagnosed, under-reported problem in Fabry disease and reduces QoL. In general, 46% of patients have depression.[3]

In another study, about one-third of women living with Fabry disease admitted to feelings of depression, anxiety, fatigue, and frustration.[15]

Diagnosis of Fabry disease can be challenging and often delayed[3]

Fabry disease is "often seen, rarely diagnosed"[16]

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 from symptom onset to diagnosis.[17,18]

Gene testing can inform Fabry disease diagnosis and management

Genotype alone does not determine disease progression in Fabry disease—the etiology is complex, and there is great variability in the manifestation and progression of disease.[17,19] Even when disease presentation is asymptomatic or mild, the accumulation of disease substrates (including GL-3 and lyso-Gb_3) can contribute to long-term damage of organs and tissues.[3,20] If there is suspicion of Fabry disease, gene testing is generally recommended to confirm diagnosis.[3,21]

DIAGNOSIS IN MALES *VS* FEMALES IS DIFFERENT

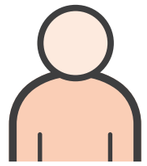
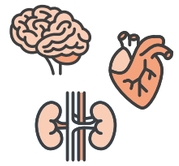
		
In males, an absence or low levels of α-Gal A activity in blood cells or dried blood spots is sufficient to make the diagnosis.[17]	However, *GLA* gene sequencing is required for women, as α-Gal A activity can appear normal.[17,22]	For families affected by Fabry disease, targeted mutational analysis can be used to diagnose at-risk individuals who may not yet exhibit the phenotypic characteristics of the disease.[22]

Gene testing can be an important diagnostic tool to enhance our understanding of each patient's unique disease and lead to a more personalised approach to disease management.[23,24]

Many factors should be considered when managing Fabry disease

When treating a progressive, multisystemic disorder such as Fabry disease[1,2], it is important to attune any management strategy to the diverse pathologies and the variable severity seen and to tailor management strategies specifically for each patient.

Managing such a disease relies on several key factors, such as:

			
Initiating treatment early before irreversible organ damage occurs[1]	Carefully monitoring multiple organ systems[3,25]	Individualising management (ie, specific genetic mutation/ variant, symptoms, and presentation of disease)[3,25]	Stabilising disease progression in various organ systems[26,27]

Clinical vigilance and regular monitoring are vital

Even if no apparent symptoms are present at baseline or at follow-up appointments, complications involving the organs can still occur.[25] For this reason, routine assessments and monitoring are key in the management of Fabry disease. In addition, baseline values should always be obtained.[25]

For recommendations on assessing and monitoring specific organs affected by Fabry disease, please refer to the following guidelines:


Molecular Genetics and Metabolism

Fabry disease revisited: Management and treatment recommendations for adult patients

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.

Also available for download at: www.ncbi.nlm.nih.gov/pubmed/29530533.

Help patients feel in control of their disease

With a lifestyle-oriented management program, patients can be encouraged to take an active role in their disease management.[28] A personalised program can empower patients to feel that they are in control of their disease and to live their lives as they wish—WITH CHOICE.

Fabry disease fast facts

Fabry disease is a progressive, multisystemic, X-linked lysosomal disorder caused by mutations, or variants, in the *GLA* gene, which encodes the α-Gal A enzyme[1,2]

Regardless of phenotype and level of disease severity, Fabry disease is always progressive[3]

Accumulation of disease substrates (including GL-3 and lyso-Gb_3) can contribute to long-term damage of organs and tissues[3,6]

In males, an absence or low levels of α-Gal A activity in blood cells or dried blood spots is sufficient to make the diagnosis. However, *GLA* gene sequencing is required for women[17,22]

Patients visit an average of 10 different specialists before a Fabry disease diagnosis is confirmed[17]

Patients with Fabry disease have a delay of ~15 years from symptom onset to diagnosis[18]

For more information about Fabry disease, please visit
[INSERT YOUR LOCAL WEBSITE OR RESOURCE HERE].

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.** Mehta A, Beck M, Eyskens F, et al. Fabry disease: a review of current management strategies. *QJM.* 2010;103(9):641-659. **3.** Germain DP. Fabry disease. *Orphanet J Rare Dis.* 2010;5:30. **4.** Waldek S, Patel MR, Banikazemi M, Lemay R, Lee P. Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry. *Genet Med.* 2009;11(11):790-796. **5.** Mehta A, Clarke JT, Giugliani R, et al. Natural course of Fabry disease: changing pattern of causes of death in FOS – Fabry Outcome Survey. *J Med Genet.* 2009;46(8):548-552. **6.** 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. **7.** 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. **8.** Militaru S, Adam R, Dorobantu L, et al. Rare presentation and wide intrafamilial variability of Fabry disease: A case report and review of the literature. *Anatol J Cardiol.* 2019;22(3):154-158. **9.** Knol IE, Ausems MG, Lindhout D, et al. Different phenotypic expression in relatives with Fabry disease caused by a W226X mutation. *Am J Med Genet.* 1999;82(5):436-439. **10.** Guffon N. Clinical presentation in female patients with Fabry disease. *J Med Genet.* 2003;40(4):e38. **11.** Perretta F, Antongiovanni N, Jaurretche S. Major organic involvement in women with Fabry disease in Argentina. *ScientificWorldJournal.* 2018;2018:6515613. **12.** Üçeyler N, Ganendiran S, Kramer D, Sommer C. Characterization of pain in Fabry disease. *Clin J Pain.* 2014;30(10):915-920. **13.** Morand O, Johnson J, Walter J, et al. Symptoms and quality of life in patients with Fabry disease: results from an international patient survey. *Adv Ther.* 2019;36(10):2866-2880. **14.** Arends M, Körver S, Hughes DA, Mehta A, Hollak CE, Biegstraaten M. Phenotype, disease severity and pain are major determinants of quality of life in Fabry disease: results from a large multicenter cohort study. *J Inherit Metab Dis.* 2018;41(1):141-149. **15.** MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *J Med Genet.* 2001;38(11):769-775. **16.** Hoffmann B, Mayatepek E. Fabry disease—often seen, rarely diagnosed. *Dtsch Arztebl Int.* 2009;106(26):440-447. **17.** Rozenfeld PA. Fabry disease: treatment and diagnosis. *IUBMB Life.* 2009;61(11):1043-1050. **18.** 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. **19.** Eng CM, Germain DP, Banikazemi M, et al. Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. *Genet Med.* 2006;8(9):539-548. **20.** Namdar M, Gebhard C, Studiger R, et al. Globotriaosylsphingosine accumulation and not alpha-galactosidase-A deficiency causes endothelial dysfunction in Fabry disease. *PLoS One.* 2012;7(4):E36373. **21.** Laney DA, Bennett RL, Clarke V, et al. Fabry disease practice guidelines: recommendations of the National Society of Genetic Counselors. *J Genet Couns.* 2013;22(5):555-564. **22.** 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. **23.** Branton MH, Schiffmann R, Sabnis SG, et al. Natural history of Fabry renal disease: influence of alpha-galactosidase A activity and genetic mutations on clinical course. *Medicine (Baltimore).* 2002;81(2):122-138. **24.** Schaefer E, Mehta A, Gal A. Genotype and phenotype in Fabry disease: analysis of the Fabry Outcome Survey. *Acta Paediatr Suppl.* 2005;94(447):87-92; discussion 79. **25.** 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. **26.** Mignani R, Pieruzzi F, Berri F, et al. FAbry STabilization indEX (FASTEX): an innovative tool for the assessment of clinical stabilization in Fabry disease. *Clin Kidney J.* 2016;9(5):739-747. **27.** Wanner C, Arad M, Baron R, et al. European expert consensus statement on therapeutic goals in Fabry disease. *Mol Genet Metab.* 2018;124(3):189-203. **28.** Coulter A, Roberts S, Dixon A. Delivering better services for people with long-term conditions. The King's Fund website. www.kingsfund.org.uk/sites/files/kf/field/field_publication_file/delivering-better-services-for-people-with-long-term-conditions.pdf. Accessed March 26, 2020.

Amicus Therapeutics

NP-NN-ALL-00040420
Date of preparation: June 2020