



Fabry Disease

Synonyms: Alpha-Galactosidase A Deficiency, Anderson-Fabry Disease

Atul Mehta, MA, MD, FRCP, FRCPath¹ and Derralynn A Hughes, MA, DPhil, FRCP, FRCPath²

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Summary

Clinical characteristics

Fabry disease is the most common of the lysosomal storage disorders and results from deficient activity of the enzyme alpha-galactosidase A (α -Gal A), leading to progressive lysosomal deposition of globotriaosylceramide and its derivatives in cells throughout the body. The classic form, occurring in males with less than 1% α -Gal A enzyme activity, usually has its onset in childhood or adolescence with periodic crises of severe pain in the extremities (acroparesthesia), the appearance of vascular cutaneous lesions (angiokeratomas), sweating abnormalities (anhidrosis, hypohidrosis, and rarely hyperhidrosis), characteristic corneal and lenticular opacities, and proteinuria. Gradual deterioration of kidney function to end-stage kidney disease (ESKD) usually occurs in men in the third to fifth decade. In middle age, most males successfully treated for ESKD develop cardiac and/or cerebrovascular disease, a major cause of morbidity and mortality. Heterozygous females typically have milder symptoms at a later age of onset than males. Rarely, females may be relatively asymptomatic throughout a normal life span or may have symptoms as severe as those observed in males with the classic phenotype.

In contrast, late-onset forms occur in males with greater than 1% α -Gal A activity. Clinical manifestations include cardiac disease, which usually presents in the sixth to eighth decade with left ventricular hypertrophy, cardiomyopathy, arrhythmia, and proteinuria; kidney failure, associated with ESKD but without the skin lesions or pain; or cerebrovascular disease presenting as stroke or transient ischemic attack.

Diagnosis/testing

Identification of deficient α -Gal A enzyme activity in plasma, isolated leukocytes, and/or cultured cells is the most efficient and reliable method of diagnosing Fabry disease in males. Identification of a hemizygous *GLA* pathogenic variant by molecular genetic testing confirms the diagnosis in a male proband. Identification of a

Author Affiliations: 1 Emeritus Professor, Department of Haematology, University College London School of Medicine, London, United Kingdom; Email: atul.mehta1@nhs.net. 2 Professor, Experimental Haematology, Lysosomal Storage Disorders Unit, Department of Haematology, Royal Free Hospital, University College London, London, United Kingdom; Email: rmgvdah@ucl.ac.uk.

heterozygous *GLA* pathogenic variant by molecular genetic testing establishes the diagnosis in a heterozygous female.

Management

Targeted therapies: Enzyme replacement therapy (ERT) with or without chaperone therapy (e.g., migalastat) to prevent and/or delay the progression of renal, cardiac, and cerebrovascular manifestations. Experts recommend that ERT be initiated as early as possible in all males with Fabry disease (including children and those with ESKD undergoing dialysis and kidney transplantation) and in females with clinical disease manifestations, as all are at high risk for renal, cardiac, and cerebrovascular complications.

Supportive care: Diphenylhydantoin, carbamazepine, or gabapentin to reduce pain (acroparesthesia); aspirin, lipid-lowering agents, and blood pressure control for cardiac ischemia; aspirin and/or other antiplatelet agents may be recommended for stroke prophylaxis; ACE inhibitors or angiotensin receptor blockers to reduce proteinuria; chronic hemodialysis and/or kidney transplantation for ESKD; rehabilitation and hearing aids for auditory and vestibular symptoms; management of psychiatric manifestations per psychologist.

Surveillance: Annual assessment for angiokeratomas, acroparesthesia, sweating abnormalities, and gastrointestinal, pulmonary, and vascular manifestations; annual cardiology assessment with EKG and echocardiogram as recommended by cardiologist from age 18 years in males, biannual cardiology assessments in females from age 18 years; annual neurologic assessment with brain MRI\MRA every two to three years beginning at age 18 years; assessment of renal function including blood urea nitrogen, creatinine, and urinalysis annually or more frequently as needed; annual audiology evaluations in males beginning at age 18 years and biannually in females; psychological assessment beginning at age 18 years annually or more frequently as needed.

Agents/circumstances to avoid: Smoking. Amiodarone may or may not have detrimental effects in individuals with Fabry disease; evidence is insufficient.

Evaluation of relatives at risk: Early identification of affected male and female relatives by molecular genetic testing (if the *GLA* pathogenic variant in the family is known) or, in males only, measurement of α -Gal A enzyme activity (if the *GLA* pathogenic variant in the family is not known) in order to initiate appropriate management as early as possible in affected individuals.

Genetic counseling

Fabry disease is inherited in an X-linked manner: hemizygous males are affected; heterozygous females may be as severely affected as males or asymptomatic throughout a normal life span. In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. If a male is the only affected family member, his mother is likely heterozygous for the *GLA* pathogenic variant; rarely, a single affected male in a family may have a *de novo* pathogenic variant. A heterozygous female has a 50% chance of transmitting the *GLA* pathogenic variant in each pregnancy. An affected male transmits the pathogenic variant to all his daughters and none of his sons. Once the *GLA* pathogenic variant has been identified in an affected family member, molecular genetic testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

GeneReview Scope

Fabry Disease: Included Phenotypes

- Classic Fabry disease
- Atypical & late-onset variants of Fabry disease

Diagnosis

Suggestive Findings

Fabry disease typically affects more than one organ system and **should be suspected** in males and females with the following clinical features, particularly if more than one is present:

- Vascular cutaneous lesions (angiokeratomas)
- Periodic crises of severe pain in the extremities (acroparesthesia)
- Sweating abnormalities (hypohidrosis, anhidrosis, or rarely hyperhidrosis)
- Cornea verticillata (characteristic corneal opacity) and lenticular opacities
- Unexplained left ventricular hypertrophy or cardiac arrhythmia
- Unexplained stroke
- Abdominal pain, nausea, and/or diarrhea of unknown etiology in young adulthood consistent with irritable bowel syndrome
- Renal insufficiency of unknown etiology including unexplained proteinuria or microalbuminuria

Family history is consistent with X-linked inheritance (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

Male proband. The diagnosis of Fabry disease **is established** in a male proband by:

- Identification of deficient alpha-galactosidase A (α -Gal A) enzyme activity in plasma, isolated leukocytes, and/or cultured cells. The test is a fluorometric assay and uses the substrate 4-methylumbelliferyl- α -D-galactopyranoside.
 - Males with classic Fabry disease have <1% α -Gal A enzyme activity.
 - Males with atypical Fabry disease have >1% α -Gal A enzyme activity.

Note: Both plasma and leukocyte enzyme activity should be assayed, as some pathogenic variants (e.g., p.Asn215Ser) affect intracellular trafficking or packaging/secretion of the enzyme, such that the reduction in enzyme activity in plasma is more marked than the reduction in enzyme activity in leukocytes.

- Identification of a hemizygous pathogenic (or likely pathogenic) variant in *GLA* by molecular genetic testing (see Table 1).

Female proband. The diagnosis of Fabry disease **is established** in a female proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *GLA* by molecular genetic testing (see Table 1).

(See also [ACMG ACT Sheet](#).)

Note: (1) Measurement of α -Gal A enzyme activity is unreliable for identification of heterozygous females. Although demonstration of markedly decreased α -Gal A enzyme activity in a female is diagnostic of the heterozygous state, some heterozygotes have α -Gal A activity in the normal range. (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (3) Identification of a hemizygous or heterozygous *GLA* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular Testing

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of Fabry disease has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

- **Single-gene testing.** Sequence analysis of *GLA* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Note: Targeted analysis can be performed first in individuals from Nova Scotia or individuals of Chinese ancestry with atypical presentation (see Molecular Genetics).

- **A multigene panel** that includes *GLA* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

Option 2

When the diagnosis of Fabry disease has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

Table 1. Molecular Genetic Testing Used in Fabry Disease

Gene ¹	Method	Proportion of Pathogenic Variants ² Identified by Method
GLA	Sequence analysis ³	~95% ⁴
	Gene-targeted deletion/duplication analysis ⁵	~5% ^{4, 6}

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. Smid et al [2014]

Additional Testing

Biomarkers. Plasma globotriaosylsphingosine (lyso-Gb3) (the deacetylated derivative of the accumulated substrate) levels:

- Have been reported to correlate with disease severity [Aerts et al 2008] and organ involvement, particularly cardiac disease [Yogasundaram et al 2018, Weidemann et al 2019]; individuals with a novel variant and organ involvement consistent with Fabry disease had lyso-Gb3 levels ≥ 2.7 ng/mL; individuals with a novel *GLA* variant and no organ involvement had lyso-Gb3 levels < 2.7 ng/mL [Niemann et al 2014];
- Are higher in affected males than females [Yogasundaram et al 2018, Weidemann et al 2019];
- Can be used to distinguish between clinically relevant Fabry disease phenotypes (e.g., high risk versus low risk, classic versus late onset) [Nowak et al 2018, Maruyama et al 2019];
- Have been reported to correlate with treatment response [Aerts et al 2008]. Lower levels of lyso-Gb3 at initiation of treatment correlate with better long-term outcomes of pulmonary airflow limitation [Franzen et al 2018] and general clinical events [Arends et al 2017]. Cumulative exposure to lyso-Gb3 during a prolonged untreated period appears to predispose individuals with Fabry to worse long-term outcomes [Nowak et al 2022]. However, Bichet et al [2021a] found no significant correlations between baseline levels or changes in lyso-Gb3 and changes in left ventricular mass index, estimated glomerular filtration rate, or pain during treatment with the oral chaperone migalastat for ≥ 24 months.

Urinary levels of lyso-Gb3 derivatives also correlate with disease severity [Auray-Blais et al 2017, Effraimidis et al 2021].

Note: There are no universally recognized biomarkers of Fabry disease.

Tissue biopsy is not usually required and is not recommended as a diagnostic test.

- **Skin biopsy** [Liguori et al 2017] is relatively noninvasive and will demonstrate Gb3 deposits in skin structures in individuals with classic Fabry disease, but not in late-onset Fabry disease. Skin innervation is reduced but Gb3 deposits are not found within axons, suggesting that the damage is due to indirect mechanisms.
- **Kidney biopsy** is often diagnostic in individuals with kidney failure of unknown etiology. Histopathologic manifestations are well characterized [Warnock 2005] and scoring systems allow accurate staging [Fogo et al 2010] such that renal histopathology is frequently used to document treatment outcome in clinical trials. The diagnosis may be established by bedside stereomicroscopy [Svarstad et al 2018], but electron

microscopy (EM) should be performed to confirm the diagnosis. The characteristic zebra bodies seen on EM may be mimicked by drug-induced intralysosomal α -Gal A activity, such as hydroxychloroquine-induced renal phospholipidosis [de Menezes Neves et al 2017].

- **Endomyocardial biopsy.** Identification of characteristic globotriaosylceramide inclusions on endomyocardial biopsy can establish a diagnosis in an individual with left ventricular hypertrophy or heart failure and a *GLA* variant of uncertain significance [Hsu et al 2014, Linhart et al 2020].

Clinical Characteristics

Clinical Description

Fabry disease encompasses a spectrum of phenotypes ranging from the severe classic phenotype to atypical late-onset forms. The late-onset forms are more common than the classic phenotype. However, in registries and publications individuals with the classic phenotype are overrepresented.

Individuals with atypical Fabry disease present later in life and are underdiagnosed [Germain 2010]. Significant diagnostic delays are reported in the Fabry Outcome Survey (FOS) [Mehta et al 2004]; they are particularly common in females [Ellaway 2015] and may lead to avoidable complications [Reisin et al 2017].

The FOS and the Fabry Registry, multicenter international initiatives designed to examine the natural history of Fabry disease and the effects of enzyme replacement therapy (ERT), are an important source of long-term data on the disease [Giugliani et al 2016, Ortiz et al 2016, Ramaswami et al 2019a, Wanner et al 2020].

Table 2. Fabry Disease: Comparison of Phenotypes by Select Features

Feature	Classic	Late-Onset Variants	
Age at onset	4-8 yrs	>25 yrs	
Average age of death	41 yrs	>60 yrs	
Manifestation	Angiokeratoma	++	-
	Acroparesthesia	++	-/+
	Hypohidrosis/anhidrosis	++	-/+
	Corneal/lenticular opacity	+	-
	Cardiac disease	LVH/ischemia	LVH/cardiomyopathy
	Cerebrovascular disease	TIA/stroke	-
	Kidney disease	ESKD	Proteinuria or ESKD
	Residual α -Gal A enzyme activity	<1%	>1%

Mehta et al [2004], Eng et al [2007]

+ = present; - = absent; α -Gal A = alpha-galactosidase A; ESKD = end-stage kidney disease; LVH = left ventricular hypertrophy; TIA = transient ischemic attack

Classic Fabry Disease

This is usually seen in hemizygous males with <1% alpha-galactosidase A (α -Gal A) enzyme activity but may occasionally be seen in heterozygous females. Onset of symptoms usually occurs in childhood or adolescence with the appearance of angiokeratomas, periodic crises of severe pain in the extremities (acroparesthesia), hypohidrosis, and the characteristic corneal and lenticular opacities. Although proteinuria may be detected early, renal insufficiency usually occurs in the third to fifth decade of life. Death occurs from complications of kidney disease, cardiac involvement, and/or cerebrovascular disease.

Angiokeratomas are an early manifestation of Fabry disease, typically seen in children and young adolescents [Luna et al 2016]. They appear as clusters of punctate, dark red to blue-black angiectases in the superficial layers of the skin. The lesions may be flat or slightly raised and do not blanch with pressure. Slight hyperkeratosis is notable in larger lesions.

The clusters of lesions are most dense between the umbilicus and the knees; they most commonly involve the hips, back, thighs, buttocks, penis, and scrotum, and tend to be bilaterally symmetric. The oral mucosa, conjunctiva, and other mucosal areas are commonly involved. Wide variation in the distribution pattern and density of the lesions may occur. Examination of the skin, especially the scrotum and umbilicus, may reveal the presence of isolated lesions. Data from 714 affected individuals (345 males, 369 females) in the FOS [Orteu et al 2007] suggest that they are present in 66% of males (36% of females).

The number and size of these cutaneous vascular lesions progressively increase with age. The presence of angiokeratomas correlated with the severity of the systemic disease manifestations [Zampetti et al 2012].

Acroparesthesia occurs as episodic crises of agonizing, burning pain in the distal extremities that most often begin in childhood or early adolescence and signal clinical onset of the disease [Burand & Stucky 2021]. These crises last from minutes to several days and are usually triggered by exercise, fatigue, emotional stress, or rapid changes in temperature and humidity. Often the pain radiates to the proximal extremities and other parts of the body. Attacks of abdominal or flank pain may simulate appendicitis or renal colic.

The crises usually decrease in frequency and severity with increasing age; however, in some affected individuals, the frequency increases and the pain can be so excruciating and incapacitating that the individual may contemplate suicide.

Nerve conduction studies show evidence of a small fiber neuropathy [Biegstraaten et al 2012] affecting small myelinated and unmyelinated neurons [Soliman et al 2016].

Hypohidrosis or **anhidrosis** is an early and almost constant finding. Hyperhidrosis also occurs; in the FOS it was seen in 12% of females and 6.4% of males [Lidove et al 2006].

Cornea verticillata, the characteristic corneal opacity that is observed only by slit-lamp microscopy, is found in affected males and most heterozygous females. The earliest corneal lesion is a diffuse haziness in the subepithelial layer. With time, the opacities appear as whorled streaks extending from a central vortex to the periphery of the cornea. The whorl-like opacities, typically inferior and cream colored, range from white to golden brown and may be very faint [Nguyen et al 2005]. In the FOS, cornea verticillata was present in 77% of females and 73% of males undergoing detailed ophthalmologic examination [Sodi et al 2007].

Lenticular changes are present in approximately 30% of affected males and include a granular anterior capsular or subcapsular deposit and a unique, possibly pathognomonic lenticular opacity (the "Fabry cataract"). The cataracts, which are best observed through a dilated pupil by slit-lamp examination using retroillumination, are whitish, spoke-like deposits of fine granular material on or near the posterior lens capsule. These lines usually radiate from the central part of the posterior cortex. The corneal and lenticular opacities do not interfere with visual acuity.

Other ocular features. Aneurysmal dilatation and tortuosity of conjunctival and retinal vessels also occur [Sivley et al 2018]; while not specific for Fabry disease, vessel tortuosity is observed more frequently in individuals with a higher disease severity score [Sodi et al 2007, Allen et al 2010]. Data from the FOS demonstrates that the ocular changes correlate well with overall disease severity and with genotype [Pitz et al 2015]. Ocular abnormalities, especially microaneurysms and posterior and anterior cataracts, persist and progress despite treatment with ERT [Michaud 2019].

Cardiac disease is present in most males with the classic phenotype by middle age and is the major cause of morbidity and mortality [Azevedo et al 2021, Pieroni et al 2021, Vardarli et al 2021].

Mitral insufficiency may be present in childhood or adolescence. Left ventricular enlargement and conduction abnormalities are early findings. Left ventricular hypertrophy (LVH), often associated with hypertrophy of the interventricular septum and appearing similar to hypertrophic cardiomyopathy (HCM), is progressive and occurs earlier in males than females [Kampmann et al 2005]. EKG changes including ST segment changes, T-wave inversion, and dysrhythmias such as a short PR interval and intermittent supraventricular tachycardias may be caused by infiltration of the conduction system. Echocardiography demonstrates an increased thickness of the interventricular septum and the left ventricular posterior wall [Yeung et al 2018]. Magnetic resonance studies using gadolinium demonstrated late enhancement areas, corresponding to myocardial fibrosis and associated with decreased regional functioning as assessed by strain and strain-rate imaging [Weidemann et al 2005]. T₁ mapping illustrates intramural fat deposition and posterior wall fibrosis [Sado et al 2013, Augusto et al 2021] which occurs prior to LVH. It has been hypothesized that a pre-storage myocardial phenotype might occur prior to T₁ lowering with microvascular dysfunction, impaired global longitudinal strain, and altered atrial depolarization and ventricular repolarization intervals [Augusto et al 2021].

Among 714 predominantly adult individuals in the FOS [Linhart et al 2007], angina, palpitations/arrhythmia, and exertional dyspnea were found in 23%-27% of males and 22%-25% of females. Hypertension, angina pectoris, myocardial ischemia and infarction, congestive heart failure, and severe mitral regurgitation are late signs. Hypertension was found in more than 50% of males and more than 40% of females in the FOS [Kleinert et al 2006].

Cerebrovascular manifestations result primarily from multifocal small vessel involvement and may include thrombosis, transient ischemic attacks (TIA), basilar artery ischemia and aneurysm, seizures, hemiplegia, hemianesthesia, aphasia, labyrinthine disorders, or frank cerebral hemorrhage [Burlina & Politei 2016]. Individuals with Fabry disease had increased basilar artery mean diameter and basilar artery linear length compared with controls [Fellgiebel et al 2011, Manara et al 2017]. White matter lesions are frequently found on MRI of individuals with Fabry; age and prior stroke independently predicted the burden of white matter hyperintensities [Rost et al 2016, Körver et al 2020b].

Renal involvement. Progressive glycosphingolipid accumulation in the kidney interferes with renal function, resulting in azotemia and renal insufficiency.

During childhood and adolescence, protein, casts, red cells, and birefringent lipid globules with characteristic "Maltese crosses" can be observed in the urinary sediment. Proteinuria, isosthenuria, and a gradual deterioration of tubular reabsorption, secretion, and excretion occur with advancing age. Polyuria and a syndrome similar to vasopressin-resistant diabetes insipidus occasionally develop.

Gradual deterioration of renal function and the development of azotemia occur in the third to fifth decade of life in approximately 50% of males with classic Fabry disease [Branton et al 2002], rising to almost 90% by the sixth decade; although end-stage kidney disease (ESKD) has been reported in the second decade. Death most often results from ESKD unless chronic hemodialysis or kidney transplantation is undertaken. The mean age at death of males not treated for ESKD is 41 years, but occasionally an untreated male with the classic phenotype survives into the seventh decade.

Renal sinus and parapelvic cysts are seen in up to half of individuals with Fabry disease, compared to fewer than 10% of controls [Ries et al 2004].

Other clinical features. In addition to the major clinical features described above, males and females with the classic phenotype may have gastrointestinal, auditory, pulmonary, and other manifestations.

- **Gastrointestinal.** Glycosphingolipid deposition in intestinal small vessels and in the autonomic ganglia of the bowel may cause episodic diarrhea, nausea, vomiting, bloating, cramping abdominal pain, and/or intestinal malabsorption [Hoffmann et al 2007, Politei et al 2016]. Symptoms resembling irritable bowel syndrome are reported in nearly 20% of individuals in the Fabry Registry [Eng et al 2007]. Achalasia and jejunal diverticulosis, which may lead to perforation of the small bowel, have been described. Radiographic studies may reveal thickened, edematous colonic folds, mild dilatation of the small bowel, a granular-appearing ileum, and the loss of haustral markings throughout the colon.
- **Pulmonary.** Several affected individuals have had pulmonary involvement, manifest clinically as chronic bronchitis, wheezing, or dyspnea. Primary pulmonary involvement has been reported in the absence of cardiac or renal disease. Pulmonary function studies may show an obstructive component which has been demonstrated to stabilize with ERT [Svensson et al 2015, Odler et al 2017, Franzen et al 2018].
- **Vascular.** Pitting edema of the lower extremities may be present in adulthood in the absence of hypoproteinemia, varices, or other clinically significant vascular disease. Although the pitting edema is initially reversible, progressive glycosphingolipid deposition in the lymphatic vessels and lymph nodes results in irreversible lymphedema requiring treatment with compression hosiery. Varicosities, hemorrhoids, and priapism have also been reported.
- **Cranial nerve VIII involvement.** High-frequency hearing loss, tinnitus, and vestibular disturbance with dizziness have been reported [Köping et al 2018]. Some studies indicate auditory involvement (including females and otherwise asymptomatic individuals) in up to 60% of individuals with Fabry disease [Eyer mann et al 2019].
- **Psychological.** Symptoms of depression have been reported in up to 60% of individuals with Fabry disease and appear to be unrelated to structural brain alterations [Schermuly et al 2011]. Anxiety, severe fatigue, and other psychosocial manifestations lead to decreased quality of life in many affected individuals [Ali et al 2018, Körver et al 2020a].

Fabry disease in children. Males generally present with the classic phenotype from age three to five years. Abdominal pain, acroparesthesia, hearing loss, cataract, skin rash, and fatigue are common features [Ramaswami et al 2006, Germain et al 2019b].

Heterozygous Females

The clinical manifestations in heterozygous females range from asymptomatic throughout a normal life span to as severe as affected males. Variation in clinical manifestations is attributed to random X-chromosome inactivation [Deegan et al 2006]. More severely affected females are more likely to express the X chromosome with the *GLA* pathogenic variant in affected organs [Echevarria et al 2016].

Most heterozygous females from families in which affected males have the classic phenotype have a milder clinical course and better prognosis than affected males.

Mild manifestations include the characteristic cornea verticillata (70%-90%) and lenticular opacities that do not impair vision; acroparesthesia (50%-90%); angiokeratomas (10%-50%) that are usually isolated or sparse; hypohidrosis; and chronic abdominal pain.

With advancing age, heterozygotes may develop mild-to-moderate LVH and valvular disease. More serious manifestations include significant LVH, cardiomegaly, myocardial ischemia, infarction, and cardiac arrhythmias [Deegan et al 2006, Wilcox et al 2008, Lenders et al 2016a].

The occurrence of cerebrovascular disease including transient ischemic attacks and cerebrovascular accidents is consistent with the microvascular pathology of the disease [MacDermot et al 2001].

Renal findings in heterozygotes include isosthenuria; the presence of erythrocytes, leukocytes, and granular and hyaline casts in the urinary sediment; and proteinuria. According to the United States and European dialysis and

transplantation registries, approximately 10% of heterozygotes develop kidney failure requiring dialysis or transplantation.

Excessive guilt, fatigue, occupational difficulty, suicidal ideation, and depression have been noted in heterozygotes [Sadek et al 2004].

Late-Onset Variants of Fabry Disease

Cardiac manifestations. Males and females with cardiac disease are asymptomatic during most of their lives and typically present in the sixth to eighth decade of life with LVH, HCM, conduction disturbances, and arrhythmias. Screening of males with "late-onset" HCM found that 6.3% who were diagnosed at or after age 40 years and 1.4% of males who were diagnosed before age 40 years had Fabry disease confirmed by identification of low α -Gal A enzyme activity and a *GLA* hemizygous pathogenic variant [Sachdev et al 2002]. Magnetic resonance imaging of the heart typically shows late enhancement of the posterior wall with gadolinium reflecting posterior wall fibrosis demonstrated in postmortem specimens [Moon et al 2003]. The incidence of cardiac complications is similar in individuals with the atypical Fabry cardiac variant and individuals with classic Fabry disease [Patel et al 2015]. Females may develop myocardial fibrosis without apparent LVH [Mundigler et al 2011].

Individuals with the cardiac variant exhibit mild-to-moderate proteinuria with normal renal function for age. Renal pathology is limited to glycosphingolipid deposition in podocytes, which is presumably responsible for their proteinuria. They generally do not develop kidney failure except in the presence of an additional etiology or risk factor and kidney biopsy should be considered for all individuals with a pathogenic variant predictive of late-onset cardiac disease who develop renal impairment.

Renal manifestations. Renal variants were identified among individuals of Japanese ancestry on chronic hemodialysis in whom ESKD had been misdiagnosed as chronic glomerulonephritis [Nakao et al 2003]. Of note, five of the six individuals did not have angiokeratoma, acroparesthesia, hypohidrosis, or corneal opacities, but did have moderate-to-severe LVH. These observations indicated that the early symptoms of classic Fabry disease may not occur in individuals with the renal variant who develop renal insufficiency, and that the renal variant may be underdiagnosed. The prevalence of Fabry disease among individuals receiving dialysis has been estimated in other studies as 0.12% to 0.7% [Mallett et al 2020].

Classic and Late-Onset Fabry Disease

Cerebrovascular manifestations. FOS data indicate that stroke or TIA occur in approximately 13% of all affected individuals (15% males, 11.5% females), including those with classic Fabry and late-onset cerebrovascular disease [Ginsberg et al 2006]. The Fabry Registry has reported that cerebrovascular manifestations are often a presenting feature of Fabry disease and may be more frequent than previously recognized [Sims et al 2009]. Rolfs et al [2005] reported that in Germany a *GLA* pathogenic variant was identified in 21 of 432 males (4.9%) and seven of 289 females (2.4%) age 18-55 years suffering cryptogenic stroke. However, other studies have not confirmed such a high prevalence [Brouns et al 2010, Wozniak et al 2010, Rolfs et al 2013]. Thromboembolic events are more common among individuals with Fabry disease who also have the factor V Leiden variant [Lenders et al 2015].

Other manifestations

- Individuals with Fabry disease showed slower gait and transfer speed, poorer fine manual dexterity, and slower hand speed than controls.
- Affected individuals had an increased incidence of depression, pain, and daytime sleepiness but did not exhibit extrapyramidal motor features or signs of significant cognitive impairment [Löhle et al 2015].
- Movement disorders including Parkinson disease are reported [Wise et al 2017, Gago et al 2020].

Life expectancy and cause of death. Based on data from the Fabry Registry, 75 of 1,422 males and 12 of 1,426 females were reported to have died. The 87 deceased individuals were diagnosed at a much older age than other individuals in the Fabry Registry. The life expectancy of males with Fabry disease was 58.2 years, compared with 74.7 years in the general population of the United States. The life expectancy of females with Fabry disease was 75.4 years, compared with 80.0 years in the United States general population. The most common cause of death among both sexes was cardiovascular disease [Waldek et al 2009]. Most individuals (57%) who died of cardiovascular disease had previously received kidney replacement therapy (e.g., dialysis or transplantation). In the FOS, the principal causes of death among 181 affected relatives (most of whom had died before 2001) were kidney failure in males (42%) and cerebrovascular disease in females (25%) [Mehta et al 2009]. In contrast, of the 42 individuals enrolled in the FOS whose deaths were reported between 2001 and 2007, cardiac disease was the main cause of death in both males (34%) and females (57%). The possible effect of ERT on life expectancy is discussed in Management, Targeted Therapies.

Genotype-Phenotype Correlations

Efforts to establish genotype-phenotype correlations have been limited because most families with Fabry disease have a private pathogenic variant, and significant phenotypic variability exists even among individuals with the same pathogenic variant.

- Males with the classic phenotype have a variety of *GLA* variants including large and small gene rearrangements, splicing defects, and missense or nonsense variants [Desnick et al 2001, Schaefer et al 2005, [Human Gene Mutation Database](#)].
- Individuals with later-onset atypical Fabry disease (renal, cardiac, or cerebrovascular disease) have missense or splicing variants that express residual α -Gal A enzyme activity [Rolfs et al 2005].
- A number of pathogenic variants including p.Arg112His, p.Arg301Gln, and p.Gly328Arg have been identified in individuals with both the classic phenotype and the cardiac variant phenotype, suggesting that other modifying factors are involved in disease expression [Ashton-Prolla et al 2000].
- The c.427G>A (p.Ala143Thr) variant has been reported as benign [Terry et al 2013]. A comprehensive cardiac study of a pedigree with this variant - including relevant biopsy and imaging data - demonstrates conclusively the pathogenicity of this variant [Fuller & Mehta 2020, Valtola et al 2020].
- Individuals with the p.Asn215Ser pathogenic variant have overall less severe disease than age-matched individuals with Fabry disease caused by pathogenic variants associated with classic disease, as assessed in cohorts from single centers [Oder et al 2017, Reuter & Platt 2017, Lavalley et al 2018] and from registry studies [Germain et al 2018]. These individuals generally have predominant cardiac disease, though ESKD is reported [Sugarman et al 2018].
- Newborn screening in Taiwan has revealed a high prevalence (~1:1,600 males) of individuals with the c.640-801G>A pathogenic variant where older family members with late-onset cardiac features have been found [Lin et al 2009].

Prevalence

Fabry disease is found among all ethnic, racial, and demographic groups. The incidence of classic Fabry disease has been estimated at 1:50,000 to 1:117,000 males [Meikle et al 1999, Desnick et al 2001].

Targeted screening programs evaluating individuals on dialysis and those with HCM and newborn screening (NBS) of enzyme activity in dried blood spots suggests that atypical later-onset Fabry disease that primarily affects the cardiovascular, cerebrovascular, or renal system is more common than previously recognized [Linthorst et al 2010, Maruyama et al 2013].

NBS in northern Italy found an incidence of 1:7,879 newborns; all individuals had the later-onset or an unclassified variant of Fabry disease [Graganiello et al 2021]. The incidence in Washington State and in Illinois

was similar at 1:6,000-1:9,000 males [Scott et al 2013, Burton et al 2017]; while the incidence in Missouri was 1:2,913-1:3,277 individuals [Hopkins et al 2015, Hopkins et al 2018]. The incidence in Hungary, Austria, and Spain was 1:3,000-1:4,000 [Mechtler et al 2012, Wittmann et al 2012, Colon et al 2017].

Enzyme-based NBS in the Taiwan Chinese population found a high prevalence (~1:1,600 males) of the cardiac-variant Fabry-causing pathogenic variant c.640-801G>A as well as in individuals diagnosed with idiopathic HCM [Lin et al 2009]. These findings were confirmed and extended by a DNA-based study of 10,499 neonates, which found an incidence of 1:875 male infants and 1:395 females [Chien et al 2012].

In Japan the incidence of *GLA* pathogenic variants is approximately 1:12,000 (males and females) [Inoue et al 2013, Sawada et al 2020].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *GLA*.

Differential Diagnosis

Common misdiagnoses in individuals with Fabry disease are summarized in Table 3.

Table 3. Common Misdiagnoses in Individuals with Fabry Disease

Fabry-Related Manifestation / Concern	Common Misdiagnoses
Systemic symptoms	"Growing pains"
	Early-onset stroke ¹
	Juvenile arthritis
	Multiple sclerosis ²
	Petechiae
	Raynaud syndrome
	Rheumatic fever
	Rheumatoid arthritis
Pain assoc w/low-grade fever & ↑ erythrocyte sedimentation rate	Systemic lupus erythematosus
	Erythromelalgia
	Neurosis
Cardiovascular	Rheumatic fever
	Hypertrophic cardiomyopathy
Renal	End-stage kidney disease ³
	Familial Mediterranean fever (assoc w/both pain & renal involvement) ⁴

1. Cabrera-Salazar et al [2005], Rolfs et al [2005]

2. Callegaro & Kaimen-Maciel [2006]

3. Bekri et al [2005], Ichinose et al [2005], Tanaka et al [2005]

4. Lidove et al [2012], Zizzo et al [2013]

Differential diagnosis of the cutaneous lesions must exclude the angiokeratoma of Fordyce spots, angiokeratoma of Mibelli, and angiokeratoma circumscriptum (see Table 4) – none of which has the typical histologic or ultrastructural lysosomal storage pathology of the Fabry lesion — and angiokeratomas associated other

lysosomal storage diseases. Angiokeratomas associated with the latter may be similar to or indistinguishable in clinical appearance and distribution from the cutaneous lesions seen in individuals with Fabry disease (see Table 5 for selected examples of such disorders).

Table 4. Differential Diagnosis of Cutaneous Lesions: Other Types of Angiokeratoma

Angiokeratoma Type	Characteristics
Angiokeratoma of Fordyce	<ul style="list-style-type: none"> Spots similar in appearance to those of Fabry disease but limited to scrotum Usually appear after age 30 yrs
Angiokeratoma of Mibelli	<ul style="list-style-type: none"> Warty lesions on extensor surfaces of extremities in young adults Assoc w/erythematous subcutaneous swellings (chilblains)
Angiokeratoma circumscriptum or naeviforme	<ul style="list-style-type: none"> Can occur anywhere on body Clinically & histologically similar to angiokeratoma of Fordyce Not assoc w/chilblains

Table 5. Differential Diagnosis of Cutaneous Lesions: Angiokeratomas Associated with Autosomal Recessive Lysosomal Storage Disorders

Gene	Disorder
<i>AGA</i>	Aspartylglucosaminuria
<i>FUCA1</i>	Fucosidosis (OMIM 230000)
<i>GLB1</i>	Adult-type β -galactosidase deficiency (See <i>GLB1-Related Disorders</i> .)
<i>MANBA</i>	β -mannosidase deficiency (OMIM 248510)
<i>NAGA</i>	Adult-onset α -galactosidase B deficiency (Schindler disease) (OMIM 609241)
<i>NEU1</i>	Sialidosis (α -neuraminidase deficiency \pm β -galactosidase deficiency) (OMIM 256550)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Fabry disease, the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with Fabry Disease

System/Concern	Evaluation	Comment
General	Assess for angiokeratomas, acroparesthesia, sweating abnormalities, abdominal pain, other GI symptoms, pulmonary & vascular manifestations.	
Eyes	Ophthalmologic eval for ocular manifestations of Fabry disease	
Cardiac	<ul style="list-style-type: none"> Cardiac eval EKG Echocardiography Cardiac MRI to evaluate for low T₁ & fibrosis 	
Neurologic	Neurologic assessment	
	Brain MRI/MRA	In adulthood or earlier if symptomatic
Renal	Renal function studies incl BUN, creatinine, & urinalysis	
Hearing	Formal audiologic assessment	
Psychiatric	Assess for mood disturbance, anxiety, & depression (using hospital anxiety & depression scale).	

Table 6. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals ¹	To inform affected persons & families re nature, MOI, & implications of Fabry disease to facilitate medical & personal decision making

BUN = blood urea nitrogen; GI = gastrointestinal; MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Targeted Therapies

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Enzyme Replacement Therapy (ERT)

The two ERTs using recombinant or gene-activated human α -Gal A enzyme that have been evaluated in clinical trials are Fabrazyme® (agalsidase beta 1 mg/kg every 2 weeks; see [prescribing information](#)) and Replagal® (agalsidase alfa 0.2 mg/kg every 2 weeks; see [summary of product characteristics](#)). Both were approved in 2001 by the European Agency for Evaluation of Medical Products; only Fabrazyme® was approved by the FDA for use in the United States.

No differences were found with regard to the clinical efficacy of agalsidase alfa or agalsidase beta [Sirrs et al 2014; M West, personal communication].

Agalsidase alfa improves pain and quality of life, reduces the natural rate of decline of renal and cardiac function in males and females with Fabry disease [Mehta et al 2009], and may improve life expectancy [Beck et al 2015]. The enzyme is safe in children [Ramaswami et al 2006]. In persons with advanced kidney disease, weekly administration of 0.2 mg/kg agalsidase alfa may be associated with a slower decline in renal function [Schiffmann et al 2007, Schiffmann et al 2015]. Individuals with normal renal function or left ventricular mass index (LVMI) at baseline treated with agalsidase alfa for ten years remained largely stable while those with abnormal renal function or cardiac hypertrophy prior to treatment had modest disease progression [Ramaswami et al 2019a].

Agalsidase beta increased clearance of globotriaosylceramide (GL-3) from the endothelial cells of the kidney, heart, and skin among treated individuals [Eng et al 2001]. After up to five years of treatment, males with classic Fabry disease reported significantly fewer gastrointestinal symptoms (pain and diarrhea) [Hopkin et al 2020]. In another cohort, cardiac hypertrophy did not progress compared to the pre-treatment period and the rate of renal decline was within normal range [Wanner et al 2020].

A Phase IV extension study showed that the risk of major clinical events (a combination of death, myocardial infarction, stroke, and development of ESKD or a 33% increase in serum creatinine concentration) was reduced by 53% with agalsidase beta treatment after adjustment for baseline proteinuria ($P = 0.06$) [Banikazemi et al 2007]. In a ten-year follow up 49/52 were alive and 42/52 (81%) did not experience any severe clinical events during the ten-year treatment interval [Germain et al 2015]. Disease progression was most likely to be observed in individuals who initiated treatment after age 40 years and/or had advanced kidney disease at baseline. A meta-analysis of ten Phase III and IV studies of agalsidase beta demonstrated that individuals receiving

agalsidase beta had a slower rate of decline of renal function than comparable individuals who were untreated [Ortiz et al 2020].

Lubanda et al [2009] have shown in a small study of 21 individuals that those who have been "stabilized" with agalsidase beta at 1 g/kg can thereafter be safely treated with a maintenance dose of 0.3 g/kg every other week. A study of lower-dose agalsidase beta in children did not show consistent benefit at the low dose of 0.5 mg/kg [Ramaswami et al 2019b].

ERT in females. A systematic review of ERT in females with Fabry disease suggested that ERT had a beneficial effect on substrate levels, cardiac outcomes, and quality of life [Germain et al 2019a]. Note: Many studies of Fabry disease include both males and females.

Antibody formation has been reported with both agalsidase alfa and agalsidase beta in males, but not females [Linthorst et al 2004, Wilcox et al 2012] with no difference between agalsidase alfa and agalsidase beta with regard to the development of serum inhibitors. Lenders et al [2016b] reported that 40% of males on ERT have evidence of serum-mediated inhibition of agalsidase activity. They further reported that inhibition-positive individuals have worse clinical outcomes and higher levels of globotriaosylsphingosine (lyso-Gb3) than inhibition-negative individuals. Nonsense and frameshift variants in *GLA*, higher plasma lyso-Gb3, and agalsidase beta as first treatment have been associated with antibody formation [van der Veen et al 2020]. There is a suggestion that saturating the anti-drug antibodies by modulating the dose of infused enzyme may be protective but risks increasing antibody titers [Lenders et al 2018]. A reference antibody to measure anti-drug antibody titers in individuals with Fabry disease has been generated [Lenders et al 2021].

There is an emerging consensus that ERT has, at best, a limited effect on the long-term outcome of Fabry disease. Studies from individual centers suggest that cardiac, renal, and cerebrovascular outcomes are comparable among treated and untreated cohorts [Rombach et al 2013, Weidemann et al 2013]. A Cochrane review highlighted the generally poor quality of evidence in favor of ERT for Fabry disease [El Dib et al 2016].

Despite these reservations, experts endorse the original recommendation that ERT be initiated as early as possible in all males with Fabry disease, including children and those with ESKD undergoing dialysis and kidney transplantation, and in heterozygous females with significant disease [Desnick et al 2003, Eng et al 2007], because all are at high risk for cardiac and neurologic complications including transient ischemic attacks and strokes. The treatment initiation guidelines from a group of European physicians are generally more conservative [Biegstraaten et al 2015]; they recommend starting ERT before the onset of irreversible complications (e.g., irreversible organ damage). ERT should be discontinued if it is not improving organ function and compliance should be closely monitored. In a recent analysis from the Fabry Outcome Survey (FOS), individuals initiating agalsidase alfa within 24 months of symptom onset had a significantly lower risk of cardiac or renal events than those with delayed initiation [Hughes et al 2021]. In another FOS cohort, the presence of LVH and/or reduced renal function at the time of agalsidase alfa initiation was associated with a significantly higher risk for a cardiovascular or renal event [Feriozzi et al 2020, Hughes et al 2021].

Chaperone Therapy

Chaperone therapy uses small molecules designed to enhance the residual enzyme activity by protecting the mutated enzyme from misfolding and degradation in the cell [Desnick & Schuchman 2002]. A pharmacogenetic assay has been developed to identify the α -Gal A mutated enzymes amenable to chaperone therapy (e.g., migalastat) [Benjamin et al 2017]. In 2016 migalastat received approval in the European Union; it was approved in the United States in 2018.

In a Phase III study, individuals previously treated with ERT were randomized to ongoing ERT or migalastat [Hughes et al 2017]. LVMI decreased significantly with migalastat while there was no significant change with ERT [Hughes et al 2017]. Migalastat has been found to reduce podocyte lyso-Gb3 [Mauer et al 2017]. Another

Phase III study assessed renal histopathology after treatment with migalastat or placebo; 41% (13/32) who received migalastat and 28% (9/32) who received a placebo had a response ($\geq 50\%$ reduction in the number of GL-3 inclusions per kidney interstitial capillary) ($P = 0.30$). The median change in interstitial capillary GL-3 from baseline was -40.8% with migalastat and -5.6% with placebo ($P = 0.10$) [Germain et al 2016]. Other reports demonstrate improvement in gastrointestinal symptoms and stable long-term renal function [Schiffmann et al 2018, Bichet et al 2021b]. Chaperone therapy in adults with Fabry disease is reviewed in Nowicki et al [2024].

Criteria for assessment of safety and treatment response from migalastat in females have been established [Giugliani et al 2013] (see [Galafold®](#) - prescribing information).

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields.

Acroparesthesia [Schuller et al 2016]

- **Diphenylhydantoin.** The severe pain of such episodes in affected males and heterozygous females often responds to low-maintenance doses of diphenylhydantoin by reducing the frequency and severity of the periodic crises of excruciating pain and constant discomfort. A potential side effect of diphenylhydantoin is gingival hypertrophy.
- **Carbamazepine** has similar effects. The combination of the two drugs may also significantly reduce the frequency and severity of the pain. Dose-related autonomic complications with carbamazepine include urinary retention, nausea, vomiting, and ileus.
- **Gabapentin** has been demonstrated to improve pain [Ries et al 2003].

Cardiovascular disease. Although evidence as to the effect on long-term outcomes is lacking, use of aspirin, lipid-lowering agents, and optimal blood pressure control are recommended in persons with symptoms of cardiac ischemia [Eng et al 2006].

Neurovascular disease. Aspirin and/or other anti-platelet agents such as clopidogrel may be recommended for stroke prophylaxis.

Renal disease. Renal insufficiency is the most serious late complication in males with the classic phenotype. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be used in those with evidence of renal involvement, especially to reduce proteinuria [Waldek & Feriozzi 2014, Warnock et al 2015]. Blood pressure control should be optimized and cholesterol normalized [Waldek & Feriozzi 2014].

Chronic hemodialysis and kidney transplantation have become lifesaving procedures. The engrafted kidney remains histologically free of glycosphingolipid deposition because the normal alpha-galactosidase A (α -Gal A) enzyme activity in the allograft catabolizes endogenous renal glycosphingolipid substrates. Therefore, successful kidney transplantation corrects renal dysfunction and is an option for end-stage kidney disease (ESKD) [Ersözlü et al 2018]. Survival of grafts is comparable to individuals without Fabry disease, with long-term graft survival being limited by Fabry-related cardiac disease. Ten- and 25-year graft survival rate of 92% (15 individuals) and 22% (4 individuals) have been reported with a ten- and 25-year patient survival rate of 100% (17 individuals) and 25% (4 individuals) [Capelli et al 2020].

Note: (1) Immune function in males with Fabry disease is similar to that in other individuals with uremia, obviating any immunologic contraindication to transplantation. Autoimmune conditions have, however, been reported to occur at an increased frequency in individuals with Fabry disease [Martinez et al 2007]. (2) Transplantation of kidneys from female heterozygotes should be avoided, as the organs may already contain

significant substrate deposition; all related potential donors must be evaluated to exclude affected males and heterozygous females.

Hearing impairment. Auditory and vestibular symptoms should be managed promptly with rehabilitation and hearing aids, when necessary, to limit the effect on quality of life [Suntjens et al 2015].

Psychiatric manifestations. There is no specific therapy for neuropsychiatric symptoms associated with Fabry disease. However, as these symptoms contribute to poor quality of life, early expert intervention and inclusion of a psychologist in the multidisciplinary team is recommended [Müller 2006].

Surveillance

The following are general guidelines, and the frequency of evaluations should be adjusted based on disease severity and needs of the affected individual. Individuals receiving ERT are typically evaluated more frequently (e.g., every 6 months).

Table 7. Recommended Surveillance for Individuals with Fabry Disease

System/Concern	Evaluation	Frequency
General	Assess for angiokeratomas, acroparesthesia, sweating abnormalities, & gastrointestinal manifestations.	Annually starting by age ~7 yrs or earlier if symptomatic
	Assess for pulmonary & vascular manifestations.	Annually starting by age 18 yrs or earlier if symptomatic
Cardiac	<ul style="list-style-type: none"> • Cardiology eval • EKG • Echocardiogram 	<ul style="list-style-type: none"> • Annually in males beginning at age 18 yrs • Every 2 yrs in females from age 18 to ~35 yrs
Neurologic	Neurologic assessment	Annually
	Brain MRI/MRA	Every 2-3 yrs beginning at age 18 yrs (more frequently if symptomatic)
Renal	Renal function studies incl BUN, creatinine, & urinalysis	Annually beginning at age 18 yrs or more frequently as needed
Hearing	Audiologic eval	<ul style="list-style-type: none"> • Annually in males beginning at age 18 yrs • 2x/yr in females from age 18 to 35 yrs (more frequently if symptomatic)
Psychiatric	Psychologic assessment	Annually beginning at age 18 yrs (or more frequently as needed)

BUN = blood urea nitrogen

Agents/Circumstances to Avoid

The obstructive lung disease that has been documented in older hemizygous males and heterozygous females is more severe in smokers; therefore, affected individuals should be discouraged from smoking.

Amiodarone has been reported to induce cellular and biochemical changes resulting in a phenocopy in particular of the keratopathy of Fabry disease [Whitley et al 1983]. Given potential effects on cellular levels of α -Gal A enzyme activity, it has been contraindicated in persons with Fabry disease. However, little evidence of a detrimental effect in this specific group exists and the relative benefit in individuals with cardiac arrhythmia should be considered.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger at-risk male and female relatives of an affected individual in order to identify as early as possible those who would benefit from initiation of treatment (ERT) and preventive measures [Germain et al 2021]. ERT should be initiated as early as possible in all males with Fabry disease and in heterozygous females with significant disease [Desnick et al 2003, Eng et al 2006] because all are at high risk for cardiac, cerebrovascular, and neurologic complications including transient ischemic attacks and strokes (see Targeted Therapies), and emerging evidence indicates improved benefit to individuals who start disease-specific treatment promptly after symptom onset or diagnosis. Evaluations can include the following:

- Molecular genetic testing capable of detecting the familial *GLA* pathogenic variant
- If the *GLA* pathogenic variant in the family is not known:
 - **Males.** Measure α -Gal A enzyme activity.
 - **Females.** Measurement of α -Gal A enzyme activity is unreliable in females although demonstration of decreased α -Gal A enzyme activity is diagnostic of the heterozygous state. If α -Gal A enzyme analysis is uninformative (i.e., if α -Gal A enzyme activity is in the normal range), perform molecular genetic testing first by *GLA* sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Gene replacement therapy has been investigated in the mouse model of Fabry disease [Ziegler et al 1999, Ziegler et al 2002, Ziegler et al 2004]. Trials of *ex vivo* gene therapy via autologous stem cell transplantation [Khan et al 2021] and *in vivo* gene therapy using adeno-associated virus vectors are being studied in Europe and elsewhere [Tuttolomondo et al 2019]. Systemic mRNA therapy is also being investigated [Zhu et al 2019].

Alternative enzyme therapy. A PEGylated version of recombinant α -Gal A with a longer circulating half-life is currently in a Phase III trial. A Phase II study of 16 individuals revealed an extended plasma half-life, reduction in peritubular capillary Gb3 inclusions, and stable renal function. Three individuals who initially developed anti-drug antibodies did not have detectable antibodies by one year of therapy [Schiffmann et al 2019].

Substrate reduction therapy for Fabry disease with lucerastat and venglustat is under evaluation in clinical trials.

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Fabry disease is inherited in an X-linked manner: hemizygous males are affected; heterozygous females may be as severely affected as males or asymptomatic throughout a normal life span.

Risk to Family Members

Parents of a male proband

- The father of a male proband will not have the disorder nor will he be hemizygous for the *GLA* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives and the *GLA* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother of the affected male is likely heterozygous for the *GLA* pathogenic variant. Rarely, an affected male may have a *de novo* *GLA* pathogenic variant (in which case the mother is not a heterozygote) or the mother may have somatic/germline mosaicism.
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a *GLA* pathogenic variant, the chance of transmitting it in each pregnancy is 50%:
 - Males who inherit the pathogenic variant will be affected. Although the specific pathogenic variant segregating in a family and the manifestations of the disorder in other family members with the pathogenic variant can give some indication of likely clinical manifestations, accurate clinical prediction in a sib found to have a *GLA* pathogenic variant is not possible.
 - Females who inherit the pathogenic variant will be heterozygotes. Heterozygous females may be asymptomatic throughout a normal life span or may have symptoms as severe as those observed in males with the classic phenotype. See Clinical Description, **Heterozygous females**.
- If the proband represents a simplex case and if the *GLA* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the possibility of maternal germline mosaicism [Pianese et al 2019].

Offspring of a male proband. Affected males transmit the *GLA* pathogenic variant to all of their daughters and none of their sons. See **Sibs of a male proband**.

Parents of a heterozygous female

- A heterozygous female may have inherited the *GLA* pathogenic variant from either her mother or her father or the pathogenic variant may be *de novo*.
- Detailed evaluation of the parents and review of the extended family history may help distinguish females with a *de novo* pathogenic variant from those with an inherited pathogenic variant. Molecular genetic testing of the parents can help to determine if the pathogenic variant was inherited.

Sibs of a heterozygous female. The risk to sibs depends on the genetic status of the parents:

- If the mother has a *GLA* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. See **Sibs of a male proband**.
- If the father has a *GLA* pathogenic variant, he will transmit it to all his daughters and none of his sons.
- If the heterozygous female represents a simplex case and if the *GLA* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs remains greater than that of the general population because of the possibility of parental germline mosaicism. Parental germline mosaicism has been demonstrated in this condition [Dobrovolný et al 2005, Pianese et al 2019].

Offspring of a heterozygous female. Women with a *GLA* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child. See **Sibs of a male proband**.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *GLA* pathogenic variant, the parent's family members may be at risk and should be offered clinical examination, genetic counseling, and molecular genetic testing.

Heterozygote Detection

Molecular genetic testing to identify female heterozygotes requires either prior identification of the *GLA* pathogenic variant in the family or, if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Measurement of alpha-galactosidase A (α -Gal A) enzyme activity is unreliable for heterozygote detection. Although demonstration of decreased α -Gal A enzyme activity in a female is diagnostic of the heterozygous state, some heterozygotes have α -Gal A enzyme activity in the normal range.

Related Genetic Counseling Issues

Fabry disease practice guidelines are available. See [Fabry Disease Practice Guidelines: Recommendations of the National Society of Genetic Counselors](#) [Laney et al 2013] and [Fabry Disease Practice Resource: Focused Revision](#) [Henderson et al 2020].

See [Management, Evaluation of Relatives at Risk](#) for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are heterozygous, or are at risk of being heterozygous.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *GLA* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Note: Although the specific pathogenic variant segregating in a family and the manifestations of the disorder in male and female family members with the pathogenic variant can give some indication of likely clinical manifestations, accurate clinical prediction in a fetus found to have a *GLA* pathogenic variant is not possible.

Biochemical testing. If the karyotype is 46,XY, α -Gal A enzyme activity can be measured in fetal cells. (If the *GLA* pathogenic variant has been identified in an affected family member, the diagnosis can be confirmed by molecular genetic testing of fetal DNA.)

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **Fabry Support and Information Group (FSIG)**
108 NE 2nd Street
Suite C
PO Box 510
Concordia MO 64020
Phone: 660-463-1355
Fax: 660-463-1356
Email: info@fabry.org
www.fabry.org
- **Medical Home Portal**
[Fabry Disease](#)
- **MedlinePlus**
[Fabry disease](#)
- **National Fabry Disease Foundation (NFDF)**
4301 Connecticut Avenue Northwest
Suite 404
Washington DC 20008-2369
Phone: 800-651-9131 (toll-free)
Fax: 800-651-9135 (toll-free)
Email: info@fabrydisease.org
www.fabrydisease.org
- **Canadian MPS Society for Mucopolysaccharidoses and Related Diseases**
Canada
Phone: 800-667-1846
Email: info@mpssociety.ca
www.mpssociety.ca
- **MPS Society**
United Kingdom
Phone: 0345 389 9901
Email: mps@mpssociety.org.uk
www.mpssociety.org.uk
- **National Tay-Sachs and Allied Diseases Association, Inc. (NTSAD)**

Phone: 617-277-4463

Email: info@ntsad.org

www.ntsad.org

- **RegistryNXT!**

Phone: 888-404-4413

Email: RegistryNXTHelpDesk@nof1health.com

www.registrynxt.com

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Fabry Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>GLA</i>	Xq22.1	Alpha-galactosidase A	GLA @ LOVD CCHMC - Human Genetics Mutation Database (GLA)	GLA	GLA

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

Table B. OMIM Entries for Fabry Disease ([View All in OMIM](#))

300644	GALACTOSIDASE, ALPHA; GLA
301500	FABRY DISEASE

Molecular Pathogenesis

GLA encodes alpha-galactosidase A (α -Gal A), a lysosomal exoglycosidase. normally responsible for removal of terminal galactose from globotriosylceramide, which along with its deacetylated derivative globotriaosylsphingosine (lyso-Gb3) accumulates in the relative absence of the enzyme.

Pathogenic mechanisms have been extensively reviewed [Kok et al 2021, Tuttolomondo et al 2021]. Enzyme deficiency leads to accumulation of Gb3 and particularly its deacylated form, lyso-Gb3 and its various isoforms, in plasma, urine, and lysosomes in a wide range of cells and tissues including the autonomic nervous system, dorsal root ganglia, kidney epithelial cells, vascular system cells, and myocardial cells. Lysosomal dysfunction leads to dysregulation of cell signaling pathways, which may disturb specific cellular functions (e.g., in podocytes) or calcium metabolism, or may trigger inflammatory pathways [Rozenfeld & Feriozzi 2017, Yogasundaram et al 2018, Braun et al 2019].

Impaired mitochondrial function and energy metabolism may not only contribute to cardiomyopathy and kidney disease but also disturb the autophagy-lysosomal pathway. Substrate accumulation also promotes endothelial dysfunction and structural changes in the vasculature, which contribute to cerebrovascular and cardiovascular complications.

Mechanism of disease causation. Reduction in enzyme activity. For example, some missense variants affect active site residues (functional variants), some missense variants affect folding of the enzyme (structural variants), and insertions/deletions, frameshift, and nonsense variants result in absent or very low residual α -Gal

A activity. Missense variants may result in a misfolded enzyme with residual α -Gal A activity. Misfolded enzymes do not undergo normal processing from endolysosomal compartments into lysosomes and may be sequestered away from lysosomes.

Table 8. Notable *GLA* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias ¹)	Predicted Protein Change	Comment [Reference]
NM_000169.3 NP_000160.1	c.272T>C	p.Ile91Thr	Assoc w/late-onset cardiac disease [Patel et al 2015]
	c.335G>A	p.Arg112His	
	c.337T>C	p.Phe113Leu	
	c.352C>T	p.Arg118Cys	VUS; reported to \uparrow risk of cerebrovascular disease [Ferreira et al 2015]
	c.427G>A	p.Ala143Thr	VUS; reported assoc w/kidney failure, stroke, & LVH [Terry et al 2013]
	c.427G>C	p.Ala143Pro	Founder variant in Nova Scotia [Kirkilionis et al 1991]
NM_000169.3	c.640-801G>A (IVS4+919G>A; c.639+919G>A)	--	Founder variant in Taiwan & China; assoc w/late-onset cardiac disease [Liu et al 2015]
NM_000169.3 NP_000160.1	c.644A>G	p.Asn215Ser	Assoc w/late-onset cardiac disease [Patel et al 2015]
	c.888G>A	p.Met296Ile	
	c.902G>A	p.Arg301Gln	
	c.982G>A	p.Gly328Arg	

LVH = left ventricular hypertrophy; VUS = variant of uncertain significance

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See [Quick Reference](#) for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions.

Chapter Notes

Author History

Kenneth H Astrin, PhD; Mount Sinai School of Medicine (2001-2008)

Robert J Desnick, PhD, MD; Mount Sinai School of Medicine (2001-2008)

Derralynn A Hughes, MA, DPhil, FRCP, FRCPath (2008-present)

Atul Mehta, MA, MD, FRCP, FRCPath (2008-present)

Revision History

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- 26 February 2008 (me) Comprehensive update posted live
- 27 August 2004 (me) Comprehensive update posted live

- 5 August 2002 (me) Review posted live
- 17 September 2001 (rd) Original submission

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