Fabry Disease
Synonyms: Alpha-Galactosidase A Deficiency, Anderson-Fabry Disease
Atul Mehta, MA, MD, FRCP, FRCPath¹ and Derralynn A Hughes, MA, DPhil, FRCP, FRCPath²
Created: August 5, 2002; Updated: January 5, 2017.

Summary

Clinical characteristics
Fabry disease results from deficient activity of the enzyme alpha-galactosidase A (α-Gal A) and progressive lysosomal deposition of globotriaosylceramide (GL-3) 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 renal function to end-stage renal disease (ESRD) usually occurs in men in the third to fifth decade. In middle age, most males successfully treated for ESRD 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, they 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, males with greater than 1% α-Gal A activity may have: (1) a cardiac variant phenotype that usually presents in the sixth to eighth decade with left ventricular hypertrophy, cardiomyopathy and arrhythmia, and proteinuria, but without ESRD; or (2) a renal variant phenotype, associated with ESRD but without the skin lesions or pain; or (3) 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 heterozygous GLA pathogenic variant by molecular genetic testing confirms the diagnosis in a heterozygous female.
Management

Treatment of manifestations: Diphenylhydantoin, carbamazepine, or gabapentin to reduce pain (acroparesthesia); ACE inhibitors or angiotensin receptor blockers to reduce proteinuria; chronic hemodialysis and/or renal transplantation for ESRD.

Prevention of primary complications: The role of enzyme replacement therapy (ERT) in the long-term prophylaxis of renal, cardiac, and CNS manifestations is unproven; however, experts recommend that ERT be initiated as early as possible in all males with Fabry disease (including children and those with ESRD undergoing dialysis and renal transplantation) and in females with significant disease because all are at high risk for cardiac, cerebrovascular, and renal complications.

Prevention of secondary complications: Prophylaxis for renovascular disease, ischemic heart disease, and cerebrovascular disease as for the general population.

Surveillance: Annual or more frequent assessment of renal function; annual cardiology and audiology evaluations; biennial brain MRI/MRA.

Agents/circumstances to avoid: Smoking.

Evaluation of relatives at risk: Early identification of affected relatives by molecular genetic testing if the pathogenic variant in the family is known in order to initiate ERT as early as possible in affected individuals.

Genetic counseling

Fabry disease is inherited in an X-linked manner. In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). If only one male in a family is affected, his mother is likely heterozygous; 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 his pathogenic variant to all of his daughters. Heterozygote (carrier) testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the pathogenic variant in a family is known.

GeneReview Scope

Fabry Disease: Included Phenotypes

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

Diagnosis

Suggestive Findings

Fabry disease should be suspected in males and females with the following clinical features:

- Periodic crises of severe pain in the extremities (acroparesthesia)
- Vascular cutaneous lesions (angiokeratomas)
- Sweating abnormalities (anhidrosis, hypohidrosis, and rarely hyperhidrosis)
- Characteristic corneal and lenticular opacities
- Unexplained stroke
- Unexplained left ventricular hypertrophy
- Renal insufficiency of unknown etiology including unexplained proteinuria or microalbuminuria
Establishing the Diagnosis

A diagnostic algorithm is provided in Gal et al [2011] (see full text) and an approach to investigations of variants of unknown significance described in Smid et al [2014].

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 residual enzyme activity >1% of normal.

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 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 variant in GLA by molecular genetic testing (see Table 1).

Note: 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.

Molecular Testing

Molecular testing approaches can include single-gene testing, use of a multigene panel, and more comprehensive genomic testing:

- Single-gene testing. Sequence analysis of GLA is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.
  
  Targeted analysis for the p.Ala143Pro pathogenic variant can be performed first in individuals from Nova Scotia (incidence 1:15,000).
  
  Targeted analysis for the IVS4+919G>A pathogenic variant can be performed first in individuals of Chinese ancestry with atypical presentation (see Molecular Genetics) [Liu et al].

- 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 at the most reasonable cost 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.
More comprehensive genomic testing may be considered if single-gene testing (and/or use of a multigene panel) has not confirmed a diagnosis in an individual with features of Fabry disease. Such testing may include exome sequencing, genome sequencing, and mitochondrial sequencing.

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Method</th>
<th>Proportion of Probands with a Pathogenic Variant Detectable by Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLA</td>
<td>Sequence analysis</td>
<td>~95%</td>
</tr>
<tr>
<td></td>
<td>Gene-targeted deletion/duplication analysis</td>
<td>~5%</td>
</tr>
</tbody>
</table>

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include 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. Deletion/duplication analysis can be used (a) to confirm a putative exon/whole-gene deletion in males after failure to amplify by PCR in sequence analysis and (b) to identify partial- and whole-gene deletions in females.
7. Bernstein et al [1989], Kornreich et al [1990]

### Additional Testing

#### Biomarkers
- Plasma globotriaosylsphingosine (lyso-Gb3) (the lyso derivative of the accumulated substrate) levels appear to correlate with disease severity and to decline with enzyme replacement therapy [Aerts et al 2008].
- Urinary levels of lyso-Gb3 derivatives also correlate with disease severity [Auray-Blais et al 2015].
- Plasma lyso-Gb3 levels are higher in affected males than females.
- Identification of elevated plasma and urinary lyso-Gb3 can confirm the diagnosis in an individual with a GLA variant of uncertain significance identified by molecular genetic testing or late-onset disease manifestations. Niemann et al [2014] reported that individuals with a novel variant and organ involvement consistent with Fabry disease had lyso-Gb3 levels ≥2.7ng/mL; Individuals with a novel GLA variant and no organ involvement had lyso-Gb3 levels <2.7 ng/mL.

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

**Endomyocardial biopsy.** Identification of characteristic globotriaosylceramide (GL-3) inclusions on endomyocardial biopsy can establish a diagnosis in an individual with left ventricular hypertrophy and a GLA variant of uncertain significance [Hsu et al 2014].
Clinical Characteristics

Clinical Description

Fabry disease encompasses a spectrum of phenotypes ranging from the severe classic phenotype to atypical forms. The classic phenotype is probably the most common, although atypical forms of the disease, which present later in life, may be underdiagnosed [Sachdev et al 2002, Nakao et al 2003].

The Fabry Outcome Survey (FOS) and the Fabry Registry, multicenter international initiatives designed to examine the natural history of Fabry disease and the effects of enzyme replacement therapy, are an important source of new data on the disease [Mehta et al 2004, Eng et al 2007].

Table 2. Major Manifestations in Classic and Atypical Fabry Disease

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Classic</th>
<th>Renal Variant</th>
<th>Cardiac Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>4-8 yrs</td>
<td>&gt;25 yrs</td>
<td>&gt;40 yrs</td>
</tr>
<tr>
<td>Average age of death</td>
<td>41 yrs</td>
<td>&gt;60 yrs</td>
<td>&gt;60 yrs</td>
</tr>
<tr>
<td>Angiokeratoma</td>
<td>++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Acroparesthesia</td>
<td>++</td>
<td>–/+</td>
<td>–</td>
</tr>
<tr>
<td>Hypohidrosis/anhidrosis</td>
<td>++</td>
<td>–/+</td>
<td>–</td>
</tr>
<tr>
<td>Corneal/lenticular opacity</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>LVH/ischemia</td>
<td>LVH</td>
<td>LVH/cardiomyopathy</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>TIA/stroke</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Renal disease</td>
<td>ESRD</td>
<td>ESRD</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Residual α-Gal A enzyme activity</td>
<td>&lt;1%</td>
<td>&gt;1%</td>
<td>&gt;1%</td>
</tr>
</tbody>
</table>

Mehta et al [2004], Eng et al [2007]
+ = present; – = absent; α-Gal A = alpha-galactosidase A; ESRD = end-stage renal disease; LVH = left ventricular hypertrophy; TIA = transient ischemic attack

Classic Fabry Disease

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 renal disease, cardiac involvement, and/or cerebrovascular disease.

Angiokeratomas are often one of the earliest manifestations of Fabry disease. 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. A 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 angiokeratoma 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. 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.

**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; 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].

**Cardiac disease.** Mitral insufficiency may be present in childhood or adolescence. Left ventricular enlargement and conduction abnormalities are early findings. Left ventricular hypertrophy, 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]. Cardiac disease is present in most males with the classic phenotype by middle age and is the major cause of morbidity and mortality in those who have undergone dialysis or transplantation for treatment of end-stage renal disease (ESRD).

ECG 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 [Pieroni et al 2006]. 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 [Moon et al 2003, Weidemann et al 2005]. T1 mapping illustrates intramural fat deposition and posterior wall fibrosis [Sado et al 2013].

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 [Politei & Capizzano 2006]. FOS data indicate that stroke or TIA occur in approximately 13% of affected individuals overall (15% males, 11.5% females) [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].

In addition, a distinct neurologic phenotype including decreased motor performance and nonmotor neurologic manifestations has been described. 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].

**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 usually occur in the third to fifth decade of life, although ESRD has been reported in the second decade. Death most often results from ESRD unless chronic hemodialysis or renal transplantation is undertaken. The mean age at death of males not treated for ESRD is 41 years, but occasionally an untreated male with the classic phenotype survives into the seventh decade.

**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]. 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 [Magage et al 2007] which has been demonstrated to stabilize with enzyme replacement therapy (ERT) [Odler et al 2017].

- **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 dizziness have been reported [Hegemann et al 2006].
- **Psychological.** Depression, anxiety, severe fatigue, and other psychosocial manifestations lead to decreased quality of life in many affected individuals [Cole et al 2007].

**Heterozygous (Carrier) 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; and hypohidrosis. In addition, heterozygotes may have chronic abdominal pain and diarrhea [Gupta et al 2005].

With advancing age, heterozygotes may develop mild to moderate enlargement of the left heart (left ventricular hypertrophy) and valvular disease. More serious manifestations include significant left ventricular hypertrophy, cardiomegaly, myocardial ischemia, infarction, and cardiac arrhythmias [Shah et al 2005, Deegan et al 2006, Wilcox et al 2008].

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, Whybra et al 2001, Galanos et al 2002].

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 renal failure requiring dialysis or transplantation.

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

**Life expectancy and cause of death.** Based on data from the Fabry Registry, 75 of 1422 males and 12 of 1426 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 genders was cardiovascular disease [Waldek et al 2009]. Most individuals (57%) who died of cardiovascular disease had previously received renal 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 renal 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 impact of ERT on life expectancy is discussed in Management, Prevention of Primary Manifestations.
Atypical Variants of Fabry Disease

Cardiac variant. 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 left ventricular hypertrophy, hypertrophic cardiomyopathy (HCM), conduction disturbances and arrhythmias. Screening of males with "late-onset" hypertrophic cardiomyopathy (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].

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 renal failure.

Renal variant. Renal variants were identified among individuals of Japanese ancestry on chronic hemodialysis in whom ESRD 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 left ventricular hypertrophy. 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. Therefore, it is appropriate to test individuals on renal dialysis and/or undergoing renal transplantation without a confirmed etiology of renal disease for Fabry disease.

Genotype-Phenotype Correlations

Efforts to establish genotype-phenotype correlations have been limited because most families with Fabry disease have a private pathogenic variant, and there is significant phenotypic variability 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, Schäfer et al 2005, Human Gene Mutation Database].
- Individuals with later-onset atypical variants (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].
- An analysis of the Fabry Outcome Survey (FOS) showed that disease manifestations in individuals with the p.Asn215Ser pathogenic variant were less severe than in age-matched individuals with Fabry disease caused by pathogenic variants associated with classic disease [Schaefer et al 2005].
- Newborn screening in Taiwan has revealed a high prevalence (~1:1600 males) of individuals with the IVS4+919G>A pathogenic variant where older family members with late-onset cardiac features have been found [Lin et al 2009].

Prevalence

The incidence of Fabry disease is estimated at 1:50,000 to 1:117,000 males [Meikle et al 1999, Desnick et al 2001]. Recent studies suggest that milder forms of the disease that present later in life and primarily affect the cardiovascular, cerebrovascular, or renal system may be more common and may be underdiagnosed.
A newborn screening study from Italy shows an incidence as high as 1:3,100, with an 11:1 ratio of persons with the later-onset/classic phenotypes [Spada et al 2006]. The incidence of Fabry disease among nearly 35,000 neonates screened in Austria is 1:3859 [Mechtler et al 2012].

In a study of the Taiwan Chinese population an unexpected high prevalence of the cardiac-variant Fabry-causing pathogenic variant c.640-801G>A (also known as IVS4+919G>A and c.639+919G>A) was found among newborns (~1:1600 males) as well as individuals with idiopathic hypertrophic cardiomyopathy [Lin et al 2009].

Fabry disease is found among all ethnic, racial, and demographic groups.

**Genetically Related (Allelic) Disorders**

No phenotypes other than those discussed in this GeneReview have been associated with pathogenic variants in GLA.

**Differential Diagnosis**

The pain of Fabry disease may be associated with a low-grade fever and an elevated erythrocyte sedimentation rate; these symptoms have frequently led to the misdiagnosis of rheumatic fever, neurosis, or erythromelalgia.

Symptoms in individuals with Fabry disease are similar to those of other disorders including rheumatoid arthritis, juvenile arthritis, rheumatic fever, systemic lupus erythematosus (SLE), “growing pains,” petechiae, Raynaud syndrome, early-onset stroke [Cabrera-Salazar et al 2005, Rolfs et al 2005] and multiple sclerosis [Callegaro & Kaimen-Maciel 2006].

Males with Fabry disease may be unrecognized in cardiac clinics, where they are diagnosed with hypertrophic cardiomyopathy, and in nephrology clinics, where they are diagnosed with end-stage renal disease [Bekri et al 2005, Ichinose et al 2005, Tanaka et al 2005].

Two studies have indicated that several individuals with familial Mediterranean fever, which can also cause pain and renal involvement, have been misdiagnosed as having Fabry disease [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, none of which has the typical histologic or ultrastructural lysosomal storage pathology of the Fabry lesion:

- **Angiokeratoma of Fordyce** is characterized by spots similar in appearance to those of Fabry disease but limited to the scrotum and usually appearing after age 30 years.
- **Angiokeratoma of Mibelli** is characterized by warty lesions on the extensor surfaces of extremities in young adults and associated with erythematous subcutaneous swellings (chilblains).
- **Angiokeratoma circumscriptum or naeviforme** can occur anywhere on the body, is clinically and histologically similar to angiokeratoma of Fordyce, and is not associated with chilblains.

Angiokeratomas, in clinical appearance and distribution reportedly similar to or indistinguishable from the cutaneous lesions seen in individuals with Fabry disease, have been described in individuals with other lysosomal storage diseases, including fucosidosis, sialidosis (α-neuraminidase deficiency with or without β-galactosidase deficiency), adult-type β-galactosidase deficiency, aspartylglucosaminuria, adult-onset α-galactosidase B deficiency, β-mannosidase deficiency, and a lysosomal disorder with intellectual disability and some features of the mucopolysaccharidoses [Desnick et al 2001].
Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Fabry disease, the following evaluations are recommended:

- Careful history for evidence of acroparesthesia, sweating abnormalities (i.e., hypohidrosis), or other manifestations of the disorder
- Renal function studies, including BUN, creatinine, and urinalysis
- Cardiac evaluation, including echocardiography
- Examination of the skin for angiokeratomas
- Formal audiology assessment
- Ophthalmologic evaluation
- Neurologic assessment
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Acroparesthesia

- 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].

Renal disease. Renal insufficiency is the most frequent and serious late complication in males with the classic phenotype. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should be used in those with evidence of renal involvement, especially to reduce proteinuria [Waldek & Feriozzi 2014, Warnock et al 2015]. Chronic hemodialysis and/or renal 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 renal transplantation corrects renal function.

Reviews of the registries of the European Renal Association-European Dialysis and Transplantation Association and the United States Renal Data System support excellent outcomes for renal transplantation in individuals with Fabry disease. For example, during the ten-year period from 1988 to 1998, 93 individuals who underwent renal transplantation were reported to the US registry. Compared to a matched control group, recipients with Fabry disease had equivalent five-year life survival (82% vs 83%) and graft survival (67% vs 75%), respectively.

Note: (1) Immune function in males with Fabry disease is similar to that in other individuals with uremia, obviating any immunologic contraindication to transplantation in this disease. 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.


**Prevention of Primary Manifestations**

**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) and Replagal™ (agalsidase alfa 0.2 mg/kg every 2 weeks). 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.

The following is a summary of some of the clinical trials for each drug:

- Single-center double-blind placebo-controlled studies of agalsidase alfa have shown a beneficial effect of ERT on neuropathic pain [Schiffmann et al 2001] and left ventricular hypertrophy [Hughes et al 2008]. Data from the Fabry Outcome Survey (FOS) suggest that ERT with 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 renal 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].

- A double-blind, randomized, placebo-controlled study of agalsidase beta demonstrated increased clearance of globotriaosylceramide (GL-3) from the endothelial cells of the kidney, heart, and skin among treated subjects [Eng et al 2001].

- A Phase IV extension study showed that the risk of major clinical events (a combination of death, myocardial infarction, stroke, development of ESRD, 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 of these individuals, with additional data from the Fabry Registry, Germain et al [2015] reported that 49 of 52 were alive and 42/52 (81%) did not experience any severe clinical events during the ten-year treatment interval. Disease progression was most likely to be observed in those individuals who initiated treatment after age 40 years and/or had advanced renal disease at baseline. A study of cardiac outcomes from the Fabry Registry of 115 males treated with agalsidase beta for at least two years reports that treated individuals fared better than 48 untreated males. Left ventricular mass fell at a slope of -3.6 g/year in 31 males aged 18-30 years but rose by 9.5 g/year in 15 males who were not treated [Germain et al 2013].

- The largest comparative study is the Canadian Fabry Disease initiative. Sirrs et al [2014] have reported five-year follow-up data on 362 subjects for a composite endpoint (death, neurologic or cardiovascular events, development of ESRD, or sustained increase in serum creatinine of 50% from baseline). Ninety-two of 178 individuals treated with ERT were randomly allocated to either agalsidase alfa or agalsidase beta. No differences were found with regard to the clinical efficacy of the two medications, and individuals who switched from agalsidase beta to agalsidase alfa during the time of Fabrazyme® shortage were stable. In comparison with the placebo group in the Banikazemi study individuals treated with ERT had a significant reduction in clinical events, which occurred at an older age. The eight-year follow-up data continued to suggest that the two medications are equivalent at their standard doses [M West, personal communication].

- Antibody formation has been reported with both agalsidase alfa and agalsidase beta in males, but not females [Linthorst et al 2005, Wilcox et al 2012]. Lenders et al [2015] reported that 40% of 68 males with Fabry disease 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 lyso-Gb3 than inhibition-negative individuals. There appeared to be no difference between agalsidase alfa and beta with regard to the development of serum inhibitors. The impact of antibody formation on the overall efficacy of treatment is currently unknown.

- During 2009-2012, a shortage of agalsidase beta resulted in the substitution of agalsidase alfa for agalsidase beta in several cohorts of affected individuals. Reports thus far have not indicated any significant

- 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 has been conducted in children (FIELD study [Wijburg et al 2015]); it will be interesting to observe if lower doses of agalsidase beta are equally efficacious in children.

There is an emerging consensus that ERT has, at best, a limited impact on the long-term outcome of Fabry disease. Studies of consecutive affected persons 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 recent Cochrane review has also highlighted the generally poor quality of evidence in favor of ERT for Fabry disease.

Despite these emerging data, a panel of physician experts have recommended that ERT be initiated as early as possible in all males with Fabry disease, including children and those with ESRD undergoing dialysis and renal transplantation, 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. The treatment initiation guidelines from a group of European physicians are generally more conservative [Biegstraaten et al 2015]. They emphasize the need to start ERT before the advent of irreversible complications and suggest that initiation of ERT after irreversible organ damage has occurred is to be avoided. ERT should be discontinued if it is making no impact on organ function in an individual; and compliance should be closely monitored.

**Prevention of Secondary Complications**

The prophylaxis for renovascular disease, ischemic heart disease, and cerebrovascular disease in persons with Fabry disease is the same as for the general population.

- Proteinuria/microalbuminuria should be minimized with ACE inhibitors/ARBs [Tahir et al 2007]; blood pressure control optimized; and cholesterol normalized [Waldek & Feriozzi 2014].
- Aspirin and other anti-platelet agents such as clopidogrel may be recommended for the prophylaxis of stroke.
- Although evidence as to the effect on long-term outcomes is lacking, use of aspirin and lipid-lowering agents and optimal blood pressure control are recommended in persons with symptoms of cardiac ischemia [Eng et al 2006].

The role of ERT in the long-term prophylaxis of renal, cardiac, and CNS manifestations is unproven; however, on the basis of stabilization of organ function in persons with more advanced disease, some have suggested the initiation of ERT in early disease stages: at first sign of disease manifestations in boys; at age 12-13 years in asymptomatic boys; and at the time of diagnosis in adult males [Eng et al 2006]. Studies indicate that late initiation of therapy when renal or cardiac manifestations are significant is associated with less effect than initiation earlier in the disease course [Germain et al 2015, Ortiz et al 2016].

**Surveillance**

The following are appropriate:

- Annual or more frequent renal function studies
- Annual cardiology evaluation
- Annual audiology evaluation
- Biennial brain MRI/MRA
Agents/Circumstances to Avoid

The obstructive lung disease, which 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.

Evaluations can include:

- Molecular genetic testing if the pathogenic variant in the family is known.
- If the 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. Ophthalmologic examination for the characteristic whorl-like corneal opacities by slit-lamp microscopy can be considered if enzyme analysis is uninformative. However, only 80%-90% of heterozygous females have the corneal lesions.

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]. A trial of gene therapy via autologous stem cell transplantation is currently in progress in Canada.

Chaperone therapy, a novel approach, 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 report of chaperone therapy in a male with the cardiac variant demonstrated the "proof of concept" for this therapeutic strategy for Fabry disease [Frustaci et al 2001].

Phase I trials have demonstrated elevation of plasma α-Gal A levels in healthy volunteers [Fan et al 1999, Ishii et al 2004]. Phase III trials are now in progress in males and females with Fabry disease with a pharmacologic chaperone (1-deoxygalactonojirimycin; DGJ; Migalastat Amicus Therapeutics, NJ, USA). DGJ has been demonstrated to enhance trafficking of mutated α-Gal A to lysosomes of fibroblasts derived from persons with Fabry disease and to increase enzyme activity while reducing GL-3 substrate in tissues of a transgenic/knockout animal model of Fabry disease. In 2016 Migalastat received marketing approval in the European Union.

Alternative enzyme therapy. A PEGylated version of recombinant α-Gal A with a longer circulating half-life is currently in a Phase II trial.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.
Other

Substrate reduction therapy for Fabry disease has a biochemical rationale. Clinical trials of substrate reduction therapy will be commencing soon.

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.

Risk to Family Members

Parents of an affected male proband

- The father of an affected male 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 individual 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, maternal germline mosaicism should be considered as a possible explanation.
- If only one individual in the family is affected, the mother of the affected male is likely heterozygous for the GLA pathogenic variant. Rarely, an affected male may have a de novo pathogenic variant, in which case the mother is not a carrier.

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

- If the mother of the proband has a pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and may be symptomatic. See Clinical Description, Heterozygous (Carrier) Females.
- If the proband represents a simplex case (i.e., a single occurrence in a family) 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 theoretic possibility of maternal germline mosaicism.

Sibs of a (symptomatic or asymptomatic) heterozygous female

- If the father of the proband has a GLA pathogenic variant, he will transmit it to all his daughters and none of his sons.
- 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; females who inherit the pathogenic variant will be heterozygotes (carriers) and may be symptomatic. See Heterozygous (Carrier) Females.
Paternal germline mosaicism has been demonstrated in this condition [Dobrovolný et al 2005]. Thus, even if the GLA pathogenic variant has not been identified in paternal leukocyte DNA, female sibs of a heterozygous female may still be at increased risk of inheriting the pathogenic variant.

**Offspring of an affected male.** Affected males transmit the GLA pathogenic variant to:
- All of their daughters who will be heterozygotes and may be symptomatic. See Heterozygous (Carrier) Females.
- None of their sons.

**Offspring of a (symptomatic or asymptomatic) heterozygous female.** Women with a GLA pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child:
- Males who inherit the pathogenic variant will be affected.
- Females who inherit the pathogenic variant will be heterozygotes and may be symptomatic. See Heterozygous (Carrier) Females.

**Other family members.** The proband’s maternal aunts may be at risk of being heterozygotes and the aunts’ offspring, depending on their gender, may be at risk of being heterozygotes and/or of being affected. At-risk females should be offered clinical examination, genetic counseling, and molecular genetic testing.

**Heterozygote (Carrier) Detection**

**Molecular genetic testing** of at-risk female relatives to determine their genetic status is most informative if the GLA pathogenic variant has been identified in the proband.

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

**Ophthalmologic examination** for the characteristic whorl-like corneal opacities by slit-lamp microscopy can be considered if enzyme analysis is uninformative and the specific GLA pathogenic variant in the family has not been identified by molecular genetic testing. However, only 80%-90% of heterozygous females have the corneal lesions.

**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].

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, clarification of genetic status, and discussion of the availability of prenatal 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 carriers, or are at risk of being carriers.

**DNA banking** is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.
Prenatal Testing and Preimplantation Genetic Testing

**Molecular genetic testing.** Once the GLA pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are 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, a biochemical diagnosis can be confirmed by molecular genetic testing of fetal DNA.)

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](http://www.fabry.org)

- **MedlinePlus**
  Fabry disease

- **My46 Trait Profile**
  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](http://www.fabrydisease.org)

- **Canadian MPS Society**
  #218-2055 Commercial Drive
  Vancouver British Columbia V5N 0C7
  Canada
  **Phone:** 800-667-1846; 604-924-5130
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

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

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)

<table>
<thead>
<tr>
<th>OMIM ID</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>300644</td>
<td>GALACTOSIDASE, ALPHA; GLA</td>
</tr>
<tr>
<td>301500</td>
<td>FABRY DISEASE</td>
</tr>
</tbody>
</table>
**Gene structure.** GLA spans approximately 13 kb of gDNA and contains seven exons; the cDNA is 1290 bases and encodes a polypeptide of 429 amino acids including a 31-amino acid signal peptide. For a detailed summary of gene and protein information, see Table A, Gene.

**Benign variants.** The variant p.Asp313Tyr, a common exon 6 variant with decreased activity in vitro and reduced activity at neutral pH resulting in low plasma alpha-galactosidase A (α-Gal A) activity, has been identified in 0.45% of normal individuals (n = 800 alleles). Expression of p.Asp313Tyr in COS-7 cells resulted in approximately 60% of wild type enzymatic activity and showed normal lysosomal localization [Froissart et al 2003, Yasuda et al 2003]. Thus, p.Asp313Tyr is a variant that does not cause Fabry disease.

**Pathogenic variants.** More than 800 GLA pathogenic variants have been identified, and most are family specific, occurring only in single pedigrees. Affected males with frameshift and nonsense variants typically present with classic Fabry disease; males with missense pathogenic variants can present with either classic or atypical phenotypes [Pan et al 2016]. GLA pathogenic variants that result in residual α-gal A activity of about 20% have been identified in individuals with atypical variants of Fabry disease. The clinical manifestations of atypical cases are not specific to Fabry disease (e.g., stroke, cardiomyopathy); therefore, the pathogenicity of some variants is unclear [Lukas et al 2016]. A number of variants including p.Ile91Thr, p.Arg112His, p.Phe113Leu, p.Asn215Ser, p.Met296Ile, p.Arg301Gln, and p.Gly328Arg are recurrent and associated with late-onset cardiac disease [Patel et al 2015]. Most individuals with the IVS4+919G>A pathogenic variant were not diagnosed until newborn screening identified this variant in their grandsons [Liu et al 2015]. The pathogenicity of some GLA variants is disputed. The p.Arg118Cys variant has been recurrently described in large Fabry disease screening studies of high-risk individuals; however, this variant does not always segregate with Fabry disease in a Mendelian fashion, and could be a modulator of cerebrovascular disease risk [Ferreira et al 2015]. The p.Ala143Thr variant has been associated with renal failure, stroke, and left ventricular hypertrophy which could potentially be the result of selection bias, as most individuals were detected in screening studies [Terryn et al 2013].
Table 3. Selected GLA Variants

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>c.937G&gt;T</td>
<td>p.Asp313Tyr</td>
<td></td>
</tr>
<tr>
<td>Uncertain</td>
<td>c.352C&gt;T</td>
<td>p.Arg118Cys</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.427G&gt;A</td>
<td>p.Ala143Thr</td>
<td></td>
</tr>
<tr>
<td>Pathogenic</td>
<td>c.272T&gt;C</td>
<td>p.Ile91Thr</td>
<td>NM_000169.2</td>
</tr>
<tr>
<td></td>
<td>c.335G&gt;A</td>
<td>p.Arg112His&lt;sup&gt;1&lt;/sup&gt;</td>
<td>NP_000160.1</td>
</tr>
<tr>
<td></td>
<td>c.337T&gt;C</td>
<td>p.Phe113Leu</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.427G&gt;C</td>
<td>p.Ala143Pro</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.640-801G&gt;A (IVS4+919G&gt;A; c.639+919G&gt;A)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.644A&gt;G</td>
<td>p.Asn215Ser</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.888G&gt;A</td>
<td>p.Met296Ile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.902G&gt;A</td>
<td>p.Arg301Gln&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.982G&gt;A</td>
<td>p.Gly328Arg&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

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.

<sup>1</sup> See Genotype-Phenotype Correlations.

**Normal gene product.** Alpha-galactosidase A (α-Gal A) is a lysosomal exoglycohydrolase. The mature α-Gal A enzyme polypeptide is 398 amino acids and contains three functional N-glycosylation sites. The active enzyme is a homodimer of approximately 101 kd.

**Abnormal gene product.** GLA pathogenic variants result in mRNA instability and/or severely truncated α-Gal A or an enzyme with markedly decreased activity.

**References**

**Published Guidelines / Consensus Statements**


**Literature Cited**


**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)
Derralyynn A Hughes, MA, DPhil, FRCP, FRCPath (2008-present)
Atul Mehta, MA, MD, FRCP, FRCPath (2008-present)

**Revision History**

- 5 January 2017 (sw) Comprehensive update posted live
- 17 October 2013 (me) Comprehensive update posted live
- 10 March 2011 (me) Comprehensive update posted live
• 26 February 2008 (me) Comprehensive update posted live
• 27 August 2004 (me) Comprehensive update posted live
• 2 January 2004 (rd) Revision: Management - ERT
• 5 August 2002 (me) Review posted live
• 17 September 2001 (rd) Original submission

License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (http://www.genereviews.org/) and copyright © 1993-2021 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the GeneReviews® Copyright Notice and Usage Disclaimer. No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the GeneReviews® Copyright Notice and Usage Disclaimer.

For questions regarding permissions or whether a specified use is allowed, contact: admasst@uw.edu.