National
FABRY DISEASE
Foundation

Answers to Fabry disease Frequently Asked Questions (FAQs)

Answers to 50 FAQs and related information in this document were made into a playing card deck that can be obtained by contacting the National Fabry Disease Foundation (NFDF) at info@fabrydisease.org.

In the information provided in these FAQs, we changed the **British spelling** of words to the **American spelling** of words for consistency. You may notice some information refers only to males. Many studies are completed for males with classic Fabry disease (FD) first to obtain a better grasp of FD manifestations before studying the greater variability of females and people with the later-onset disease who have varied residual α-Gal A enzyme levels. Jerry Walter
Red Joker

The information provided in this **educational playing card deck** consists primarily of excerpts from published medical literature. In many cases, it has been revised for brevity and clarity for the layperson while maintaining the intent of the information. Related medical definitions are included. Always speak to your doctor to verify any of this information. Jerry Walter
King of Diamonds

1. **Fabry disease** is caused by absent or deficient Alpha galactosidase A (α-Gal A) enzyme activity resulting in the buildup of fatty substances (glycosphingolipids), primarily globotriaosylceramide (GL-3/Gb3) and its derivative globotriaosylsphingosine (lyso GL-3/Gb3) in body fluids and a variety of tissues including the kidney, heart, and central and peripheral nervous systems.
https://pubmed.ncbi.nlm.nih.gov/35926321
Queen of Diamonds

2. Fabry disease (FD) is an **X-chromosome-linked inherited** lysosomal storage disorder (LSD) that leads to progressive organ damage and reduced life expectancy. FD can affect males and females and is classified into classic or later-onset forms with different sets of physical traits called phenotypes.
https://pubmed.ncbi.nlm.nih.gov/35926321
Jack of Diamonds

3. Fabry disease is the **most common of the lysosomal storage disorders** (LSDs), a group of over 70 diseases characterized by lysosomal dysfunction. Lysosomes are structures that act as recycling centers in cells that use digestive enzymes to process worn-out cell components and recycle usable parts. https://pubmed.ncbi.nlm.nih.gov/20301469, https://www.nature.com/articles/s41572-018-0025-4
Ten of Diamonds

4. **Other names and synonyms** used for Fabry disease (the most commonly used name) include Fabry's disease, Anderson-Fabry disease, Alpha-galactosidase A deficiency, Angiokeratoma corporis diffusum, Ceramide trihexosidosis, Ruiter-Pompen-Wyers syndrome, Sweeley-Klionsky disease.
https://pubmed.ncbi.nlm.nih.gov/21092187
Nine of Diamonds

5. **Fabry disease (FD) has two main form**s, "classic" and "later-onset." Classic FD typically manifests during childhood, progressing eventually to life-threatening renal, cardiac, and/or neurological complications, with reduced quality of life and life expectancy. Later-onset FD frequently only involves cardiac manifestations as severe as with classic disease.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9304128
Eight of Diamonds

6. **Classic Fabry disease manifestations** may include neuropathic pain and pain crises, angiokeratomas, cornea whorls, reduced sweating and overheating, fatigue, gastrointestinal upset, hearing loss, lung disease, chronic kidney disease leading to kidney failure, transient ischemic attacks, strokes, left ventricular hypertrophy and arrhythmias eventually progressing to heart failure, and often premature death. https://pubmed.ncbi.nlm.nih.gov/29530533
Seven of Diamonds

7. **Later-onset Fabry disease (FD) is** seen in individuals with residual α-Gal A activity. Individuals with later-onset FD do not "usually" experience early clinical features. Manifestations in key organs may occur later in life and may be limited to cardiac involvement, which can be severe.
https://pubmed.ncbi.nlm.nih.gov/35926321
Six of Diamonds

8. Fabry disease (FD) has an **X-chromosome-linked inheritance pattern**. With only one X chromosome, males with FD pass their affected *GLA* gene to all their daughters and none of their sons. Females have two X chromosomes with *GLA* genes. Each child of a female with FD has a 50% chance of inheriting their mother's affected *GLA* gene (a variant) or unaffected *GLA* gene.
https://pubmed.ncbi.nlm.nih.gov/21092187
Five of Diamonds

9. The ***GLA* gene provides instructions for making the enzyme alpha-galactosidase A** (α-Gal A) needed for the body to function properly. The enzyme α-Gal A is active in lysosomes. Fabry disease is caused by *GLA* genes that do not function properly. The *GLA* gene is located on the long arm of the X-chromosome in position Xq22. https://medlineplus.gov/genetics/gene/gla/
Four of Diamonds

10. Changes in the normal sequence of the *GLA* gene are called ***GLA* gene variants** (or mutations). *GLA* gene variants can be pathogenic and cause Fabry disease, or they can be non-pathogenic (benign) and not cause Fabry disease. The *GLA* gene on the X-chromosome is present in all people (females have two), but only pathogenic *GLA* gene variants cause Fabry disease.
https://medlineplus.gov/genetics/gene/gla/
Three of Diamonds

11. The term **Genotype refers to an individual's unique sequence of DNA** inherited in a specific gene (e.g. *GLA* gene variant for Fabry disease). Phenotype is the visible/detectable expression of the genotype (e.g. Fabry disease manifestations). A person's **phenotype** results from the interaction between their genotype and their environment. https://www.garvan.org.au/news-resources/genomics-explained/genotype-phenotype
Two of Diamonds

12. **Most disease-causing (pathogenic) *GLA* gene variants are private**, occurring in a single or a few families. Intra-familial phenotype variability (IFPV) complicates the study of genotype-phenotype (gene variants and the set of physical traits) correlation [IFPV means: symptoms may vary greatly even among members of the same family who always have the same *GLA* gene variant.]
https://pubmed.ncbi.nlm.nih.gov/32606714/
Ace of Diamonds

13. A **de novo *GLA* gene variant** is the spontaneous change in the *GLA* gene that is present for the first time in a family member. Fabry disease (FD) is typically inherited from a parent but it can start as a de novo pathogenic *GLA* gene variant in a family without a history of FD.
https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/de-novo-mutation
King of Clubs

14. Currently, there are **more than 1,000 known *GLA* gene variants/mutations** according to the Human Gene Mutation Database. Many have been identified through newborn screening protocols which are more susceptible to disclosing non-pathogenic (benign) variants or variants of uncertain significance (VUS). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9304128
Queen of Clubs

15. **The Human Genome Variation Society** (HGVS) advised replacing the term "mutation" with the term "variant". *GLA* gene variants are categorized as benign, likely benign, a variant of uncertain significance (VUS), likely pathogenic, or pathogenic).
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8234732/
Jack of Clubs

16. There is a **definitive lab test for Fabry disease**. Whole blood or blood spot testing can be used for *GLA* gene DNA sequencing (molecular/ genetic testing) or *GLA* gene enzyme analysis (biochemical testing). Saliva can only be used for DNA sequencing, not enzyme analysis. Testing with whole blood or blood spots also allows for lyso GL-3/Gb3 testing. https://pubmed.ncbi.nlm.nih.gov/32606714/
Ten of Clubs

17. **In males, undetectable or <3%** of the expected **α-Gal A enzyme activity** can lead to a diagnosis of classic FD. Residual α-Gal A activity of 3% or more but still low plus Fabry-specific symptoms (neuropathic pain, angiokeratoma, cornea verticillata) are used to determine later-onset FD. The expected value (mean normal) varies due to different lab protocols.
https://pubmed.ncbi.nlm.nih.gov/35926321 ,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4241201/
Nine of Clubs

18. **Females have two X-chromosomes** (XX) and males have one (XY). The term heterozygous for Fabry disease indicates the presence of two different versions of the gene on a female's two X-chromosomes, one affected (disease-causing) *GLA* gene (a variant) and one unaffected (non-disease-causing) *GLA* gene. With a few possible rare exceptions, all females with FD are heterozygotes.
https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/heterozygous-genotype/
Eight of Clubs

19. **Females are not just carriers** like some X-linked disorders. Contrary to the historical misconception that females are marginally affected given the X-linked inheritance, many females develop early symptoms and, later on, vital organ involvement (~ 70%). For FD, the term X-linked "recessive" is misleading and has been discontinued. https://onlinelibrary.wiley.com/doi/10.1002/mgg3.2029 ,
https://pubmed.ncbi.nlm.nih.gov/21092187
Seven of Clubs

20. **X-chromosome inactivation (XCI)** patterns in females are assumed to influence various disease manifestations. XCI is unique to each organ so XCI in the blood may not reflect XCI in specific organs. The first study cited below found no correlation between the XCI patterns and females' symptoms.
https://onlinelibrary.wiley.com/doi/10.1002/mgg3.2029 ,
https://pubmed.ncbi.nlm.nih.gov/18037317/
Six of Clubs

21. **In females, a-galactosidase A activity may be within the normal range**. Diagnostic confirmation should be made by genetic analysis (DNA sequencing) of the *GLA* gene. Enzyme analysis is not appropriate for female diagnosis. The disease spectrum in females varies more than in classic males, ranging from asymptomatic to severely affected. https://pubmed.ncbi.nlm.nih.gov/21092187
Five of Clubs

22. **Lyso GL-3/Gb3** has been established as a diagnostic biomarker (biologic indicator) in individuals with classic FD. Lyso GL-3/Gb3 levels appear to decrease in response to enzyme replacement therapy, suggesting it is a useful indicator for diagnosis and for monitoring response to therapy. It may be less useful in females due to lower baseline lyso GL-3/Gb3. https://pubmed.ncbi.nlm.nih.gov/35926321
Four of Clubs

23. Fabry disease (FD) was **traditionally considered an adult disease**, but it is now recognized that disease processes and symptoms start in infancy or early childhood. Early manifestations of classic FD in children include neuropathic pain, reduced or absent sweating, corneal whorls (cornea verticillata), angiokeratoma, and gastrointestinal discomfort. https://pubmed.ncbi.nlm.nih.gov/30941742
Three of Clubs

24. The first **clinical symptoms interfering with well-being** and performance arise in childhood, typically between the ages of 3 and 10 years, and generally a few years later in girls than in boys. With age, progressive damage to vital organ systems develops in both genders, potentially leading to organ failure. https://pubmed.ncbi.nlm.nih.gov/21092187
Two of Clubs

25. **Peripheral nervous system manifestations** caused by FD include neuropathic pain (formerly called "acroparesthesia"), pain crises, atypical localized chronic or episodic pain, tinnitus, hearing loss, headache, dizziness, vertigo, heat/cold intolerance, unexplained fevers, impaired sweat function, and rarely, vascular dementia. https://pubmed.ncbi.nlm.nih.gov/29530533 , https://pubmed.ncbi.nlm.nih.gov/21092187 , https://pubmed.ncbi.nlm.nih.gov/32797665/
Ace of Clubs

26. **Avoiding circumstances that can trigger acute neuropathic pain attacks**, e.g. significant physical exertion and temperature changes, may be beneficial. Neuropathic pain associated with FD can be managed with analgesics, but nonsteroidal anti-inflammatory drugs are generally ineffective and can potentially harm kidney function, while narcotic analgesics should be avoided, although this is debated. https://pubmed.ncbi.nlm.nih.gov/21092187
King of Hearts

27. **Angiokeratomas** are the most visible early clinical feature of Fabry disease. They are non-blanching red to blue-black skin lesions (spots) from 1 to 5 mm in diameter found individually or in clusters and typically found on the buttocks, groin, umbilicus, upper thighs, and trunk, but also sometimes on mucosal areas, such as the mouth.
https://pubmed.ncbi.nlm.nih.gov/21092187, https://pubmed.ncbi.nlm.nih.gov/22452439/
Queen of Hearts

28. **Anhidrosis** (absent sweating) or **hypohidrosis** (decreased ability to sweat) is a significant problem for people with Fabry disease and can cause heat and exercise intolerance. Excessive sweating (hyperhidrosis) is rarely seen. https://pubmed.ncbi.nlm.nih.gov/21092187 , https://pubmed.ncbi.nlm.nih.gov/16939546/
Jack of Hearts

29. **Gastrointestinal** (GI) symptoms caused by Fabry disease are similar to irritable bowel syndrome or inflammatory bowel disease such as intermittent diarrhea and constipation, nausea, vomiting, abdominal pain and/or bloating, early satiety (feeling full quickly when eating), and difficulty gaining weight, especially in childhood. https://pubmed.ncbi.nlm.nih.gov/35090382/ , https://pubmed.ncbi.nlm.nih.gov/29530533
Ten of Hearts

30. **Ophthalmological** (eye) manifestations include cornea verticillata (also called corneal opacities or whorls), conjunctival and retinal vasculopathy (disease of the blood vessels), cataracts, central retinal artery occlusion (rarely), and reduced tear secretion (dry eye syndrome).
https://pubmed.ncbi.nlm.nih.gov/29530533
Nine of Hearts

31. **Lymphedema**, common in Fabry disease, appears to be related to the accumulation of lipids in the lymph vessels rather than to kidney or heart disease. Lymphedema can occur in all or part of a limb (also below the eyes), and may manifest as pitting edema. Lymphedema may necessitate the use of compression stockings. https://pubmed.ncbi.nlm.nih.gov/29530533 , https://www.ncbi.nlm.nih.gov/books/NBK11605/
Eight of Hearts

32. **Skeletal** manifestations of Fabry Disease (FD) include osteopenia or osteoporosis. In one study of individuals with FD, osteopenia was present in approximately 50% of the cases. Identification and treatment of vitamin D deficiency should be considered. https://pubmed.ncbi.nlm.nih.gov/21092187 https://pubmed.ncbi.nlm.nih.gov/29530533
Seven of Hearts

33. **Anemia:** Data from the Fabry Outcome Survey® and the Fabry Registry® show that mild peripheral blood cytopenias (deficiency in numbers of any of the blood cell elements), particularly **anemia**, are prevalent among individuals with FD. https://pubmed.ncbi.nlm.nih.gov/21092187
Six of Hearts

34. **Depression** is a frequent and under-reported manifestation in people with FD. As many as 46% and 28% of individuals may have depression and severe clinical depression, respectively. Depression can seriously impact quality of life in people with FD. https://pubmed.ncbi.nlm.nih.gov/21092187
Five of Hearts

35. **Early signs of cardiac and cerebrovascular concerns** in FD may occur during adolescence in both genders. Signs of sinus node (steady/ regular heartbeat) issues and conduction system disease (e.g. shortened PR interval, arrhythmias), heart rate variability, inability to increase heart rate adequately with exercise, and mild valve insufficiency are reported. https://pubmed.ncbi.nlm.nih.gov/21092187, https://pubmed.ncbi.nlm.nih.gov/29530533
Four of Hearts

36. **Cardiac manifestations** of FD include left ventricular hypertrophy, fibrosis (thickening and scarring), conduction system defects (arrhythmias), reduced exercise tolerance, syncope (fainting due to a fall in blood pressure), and heart failure (mostly with preserved ejection fraction). Slow heart rate and short PR interval are some of the first signs of cardiac involvement.
https://pubmed.ncbi.nlm.nih.gov/35926321/, https://pubmed.ncbi.nlm.nih.gov/21092187
Three of Hearts

37. **Significant valvular heart disease (VHD)** of the mitral, tricuspid, and aortic valves has been seen in individuals with Fabry disease. Findings typically include narrowed valves (stenosis), leaking valves (regurgitation), or a valve with bulging leaflets (prolapse). https://pubmed.ncbi.nlm.nih.gov/34627970/
Two of Hearts

38. **Chronic kidney disease (CKD)** is a significant and common complication of Fabry disease. Management includes initiation of a Fabry specific treatment, adjunctive therapies (for proteinuria/albuminuria), lifestyle and dietary (restricted sodium intake), and managing other complications of CKD, including cardiovascular risk, hypertension, and CKD-associated mineral bone disorders. https://pubmed.ncbi.nlm.nih.gov/21092187
Ace of Hearts

39. **Albuminuria** and estimated glomerular filtration rate (eGFR) are the current gold-standard indicators for monitoring Fabry disease (FD) nephropathy (kidney function decline). A healthy kidney doesn't let albumin or protein (**proteinuria**) pass from the blood into the urine. The first clinical sign of kidney involvement in FD is albuminuria. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9198369/ , https://pubmed.ncbi.nlm.nih.gov/35926321
King of Spades

40. **Parapelvic cysts** have been linked to Fabry disease and reported as a possible feature of renal involvement. Proteinuria/albuminuria has been considered the most important indication for Fabry nephropathy (decline in kidney function); however, a large proportion of renal impairment occurs without proteinuria/ albuminuria. The presence of parapelvic cysts may offer another indicator of FD. https://karger.com/nef/article-pdf/143/4/274/3169183/000502907.pdf
Queen of Spades

41. **Cerebrovascular manifestations** include Transient Ischemic Attack (TIA); ischemic stroke (stroke caused by restricted or reduced blood flow and oxygen) and less frequently, hemorrhagic stroke (stroke accompanied by or produced by hemorrhage), cerebral venous thrombosis (blood clot), and cervical carotid dissection (tear in a carotid artery). https://pubmed.ncbi.nlm.nih.gov/21092187
Jack of Spades

42. **White matter intensities** (lesions) have been associated with cognitive impairment and stroke in individuals with Fabry disease, however, it is important to note that this indicator lacks specificity and can be present in other conditions such as multiple sclerosis.
https://pubmed.ncbi.nlm.nih.gov/35926321
Ten of Spades

43. **Stroke** may be the first serious clinical manifestation of Fabry disease (FD), and is commonly caused by atrial fibrillation. Physicians should be aware of FD as a potential cause of stroke at an early age (20–50 years). In addition, the risk of stroke is 5–30 times higher in individuals with chronic kidney disease (CKD), i.e. FD nephropathy. https://pubmed.ncbi.nlm.nih.gov/35926321
Nine of Spades

44. **A brain MRI** is recommended to be performed at first assessment in males >21 years old and females >30 years old, then at least every 3 years and as clinically indicated (e.g. in the presence of neurological changes that could potentially lead to stroke).
https://pubmed.ncbi.nlm.nih.gov/35926321
Eight of Spades

45. **Pulmonary/Respiratory involvement** in FD may manifest as dyspnea (difficult or labored breathing) with exercise, chronic dry cough and wheezing, and sleep-disordered breathing (e.g. sleep apnea) in both genders). One study found the prevalence of airway obstruction in FD to be 26% in women and 61% in men. https://pubmed.ncbi.nlm.nih.gov/21092187, https://pubmed.ncbi.nlm.nih.gov/35926321
Seven of Spades

46. N**euro-psychological manifestations** of Fabry disease are common and include depression, anxiety, panic attacks, social adaptive function difficulties (personal independence and social responsibility), and rare manifestations to include cognitive decline and dementia.
https://pubmed.ncbi.nlm.nih.gov/29530533
Six of Spades

47. **Neuro-psychological manifestations are potentially related to living with chronic disease**, plus neuropathic pain, and small vessel occlusions, as well as reduced hippocampal volume, multiple infarcts (areas of tissue death due to inadequate blood supply), small vessel occlusions (blockage), and white matter lesions. https://pubmed.ncbi.nlm.nih.gov/21092187
Five of Spades

48. **Fabry disease-specific treatments** currently include enzyme replacement therapies: agalsidase alfa (Replagal®) and agalsidase beta (Fabrazyme®), although Replagal® has not been approved in the U.S., and an oral chaperone therapy, (Galafold® that is approved for the treatment of many but not all individuals with FD. Other treatments are being investigated.
https://pubmed.ncbi.nlm.nih.gov/35926321
Four of Spades

49. The global **prevalence** of FD is uncertain. Newborn screening suggests a higher prevalence, particularly for later-onset variants than historical estimates. Newborn screening studies have been performed in many countries. A few of the many results are: 1 in 1,250, 1 in 4,600 boys*, 1 in 11,854, 1 in 21,973. *The prevalence of later-onset to classic pathogenic variants in this study was 7:1.
https://jmg.bmj.com/content/60/4/391.long
Three of Spades

50. **Routine assessments** can help monitor the onset of new symptoms and disease progression, prompting timely disease management. The Fabry Registry Board of Advisors developed a minimum schedule of assessments for Individuals both under 18 years old and 18 years old and older.
https://tinyurl.com/RecommendedAssessments
Two of Spades

Thank you to the physicians and researchers for their dedicated efforts to improve the understanding of Fabry disease, and thank you to the many individuals with Fabry disease who selflessly participate in clinical trials and studies for the benefit of everyone with Fabry disease. Please send comments and recommendations to jerry.walter@fabrydisease.org. Proudly supporting the Fabry community!
Ace of Spades - Jerry Walter

The National Fabry Disease Foundation (NFDF) is a non-profit charitable organization under section 501(c)(3) of the Internal Revenue Service Code. We rely solely on charitable donations to provide our many education, community support, and assistance programs to the Fabry community. Please give generously and be a shing star for people with Fabry disease using the Donate button in the right column of www.fabrydisease.org.
Black Joker

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