

Fabry Findings



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In this issue we focus on gastrointestinal (GI) symptoms and their impact on people with Fabry disease

What is Fabry?

Fabry disease is a rare genetic condition which is estimated to affect around one in 100,000 people.¹

In Fabry, an enzyme called α -galactosidase A (α -Gal A) is missing or there is a reduced amount. This means that the body cannot break down a certain type of fat called globotriaosylceramide (GL-3). GL-3 continues to build-up in body cells causing damage to tissues and organs. Gradually, this leads to a range of physical symptoms and complications, which vary from one person to another.¹



Study highlights

In our research news, we look at a study that was designed to investigate the accumulation of GL-3 in the GI tract cells of people with different Fabry mutations who all have GI symptoms.



The **GI tract** is the passage for food to travel all the way from the mouth to the anus and includes all of the organs in the digestive system.



For information on inheritance refer to [Fabry Findings Issue 1](#)



In Fabry disease, globotriaosylceramide (GL-3), a type of fat, builds up in tissues and organs causing damage to the kidneys, heart and central nervous system^{1,2}

Symptoms in Fabry

Day to day symptoms in Fabry are known to vary from one person to another.¹



BRAIN AND NERVES

- Burning in the hands and feet
- Intolerance to heat/cold
- Mini stroke (TIA)/Stroke
- Pain
- Vertigo/feeling dizzy



HEART

- Enlarged heart
- Heart attack
- Heart failure
- Irregular heartbeat



KIDNEYS

- Decreased kidney function
- Kidney failure
- Protein in urine



EYES AND EARS

- Cloudy vision (cataracts)
- Hearing loss (in children)
- Ringing in ears



SKIN

- Small dark red/purple spots located between the belly button and the knees
- Sweating less than normal



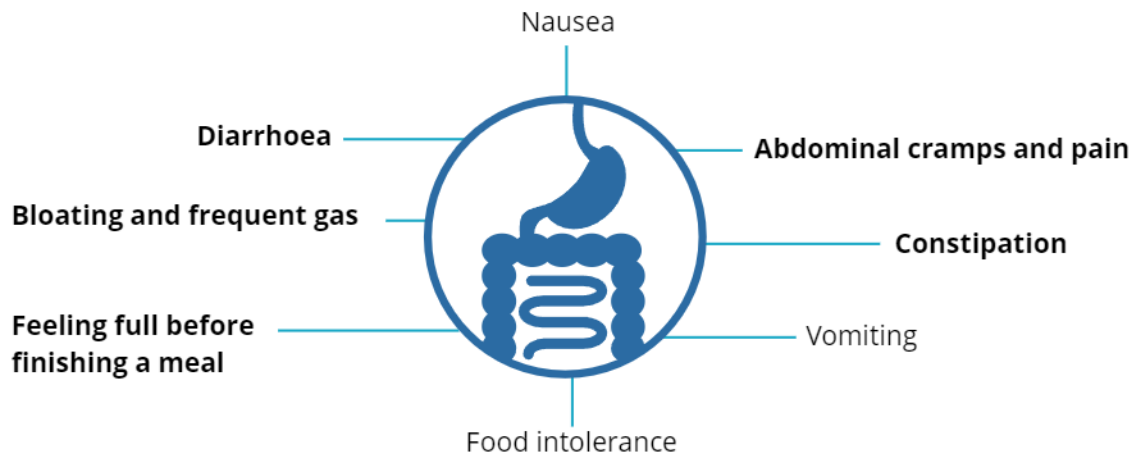
OTHER

- Cough/wheezing
- Shortness of breath
- Tiredness that is not relieved by rest or sleep



GI SYMPTOMS

Approximately 52–66% of Fabry patients report GI symptoms.^{3,4} GI symptoms in Fabry vary from one person to another but often include:^{5,6,7}



Abdominal pain and **diarrhoea** are the most common GI symptoms, affecting around half of the adults with classic Fabry and 60% of children.³



In a study of 25 adult patients, 14 reported **feeling full** before finishing a regular size meal and 12 **feeling bloated**.⁴



Both males and females experience **abdominal pain** with the same frequency, while **diarrhoea** affects more males than females.^{3,4,8}



Constipation is also common and it can be twice as frequent in females than in males.^{3,8}



Overall GI symptoms are experienced by more females than males.³



GI changes

When do symptoms start?



CLASSIC FABRY

Symptoms of classic Fabry become apparent early in childhood and adolescence with GI symptoms being one of the earliest to appear.^{4,9} The average age at which GI symptoms become evident is 5 years in boys and 9.5 years in girls.⁹ GI issues have been reported in children as young as one year old.¹⁰



LATE-ONSET FABRY

Individuals with late-onset Fabry do not show any overall symptoms during childhood or adolescence, usually developing kidney and heart issues between 30 to 70 years of age.¹¹ GI symptoms may also develop in adults but they cannot always be specifically linked to Fabry.⁶

What causes GI symptoms?

GI symptoms are thought to be caused by **two different processes**:⁶



Nerve damage, which affects the messages the brain sends to the GI tract to control movement of food during digestion.



Accumulation of fats in the GI tract cells.

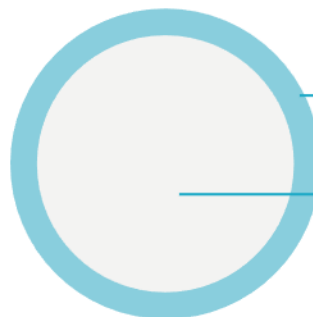
Changes in the gastrointestinal tract

GI changes are complex and there are many factors affecting them.

In people without Fabry disease, the GI tract cells are free from GL-3 accumulation. This means that the normal digestive activities such as:

- breakdown of food
- absorption of nutrients
- removing waste

can continue without disruption.



THE GI TRACT

NO GL-3 BUILD UP IN CELLS



CELLS IN GI TRACT WITH GL-3 BUILD UP

When **GL-3** is not completely broken down it **builds up** within the cells causing progressive damage.

Build-up of GL-3 in the intestine leads to **interruptions in digestive function** and results in many of the different symptoms seen in Fabry disease.^{5,7}



Managing GI symptoms

GI disturbances can have a significant impact on people with Fabry and their quality of life.⁹

Three key approaches can help improve GI symptoms



Early diagnosis



Diet and lifestyle



Treatment

Early diagnosis



A Fabry diagnosis is often delayed and can take an average of 14 years in males and 16 years in females from when symptoms first appear.¹²



If Fabry disease signs and symptoms are recognised promptly, then treatments can start earlier and possibly help delay more serious complications.



Many people with Fabry who experience GI symptoms are incorrectly diagnosed with Crohn's disease, celiac disease, or irritable bowel syndrome (IBS).⁵

Diet and lifestyle

People with Fabry have to manage their diets to help improve GI symptoms. Some changes may include:¹³



Adjusting meal sizes and patterns towards smaller, more frequent meals.



Timing of meals, such as avoiding late night eating.



Eliminating foods from the diet that are not tolerated such as spicy, lactose containing or greasy foods.

Treatment

There is no cure for Fabry disease but current treatments may prevent organ damage and greatly improve the quality of life of patients.



ORAL CHAPERONE THERAPY

Chaperones are small molecules that assist enzymes in becoming functional by helping them take the correct shape and stay stable. Chaperone therapy is only suitable for people with amenable mutations of the α -Gal A enzyme. Treatment has shown meaningful reduction in diarrhoea in patients with Fabry disease and amenable mutations.¹⁴



INTRAVENOUS ENZYME REPLACEMENT THERAPY (ERT)

For people with Fabry, ERT is a long-term therapy whereby the missing or deficient enzyme is given via an intravenous infusion. Recent studies looking at improvements of GI symptoms for patients on ERT have shown a reduction in abdominal pain and diarrhoea in females¹⁵ and a reduction in abdominal pain or diarrhoea from weekly occurrences to only occasionally in males who had been on ERT for 6–7 months.¹⁶



Research news



'Pathologic substrate of gastropathy in Anderson-Fabry disease' was published in *Orphanet Journal of Rare Diseases*.¹⁷

The study



In 2020, researchers in Italy published a study **investigating the causes of GI symptoms** in six unrelated individuals with Fabry.

Fabry is caused by mutations in a gene known as GLA, which affects the production of the α -Gal A enzyme. The type of mutation of the GLA gene was used in this study to describe the form of the disease: classic Fabry, late-onset Fabry and Fabry-affected.



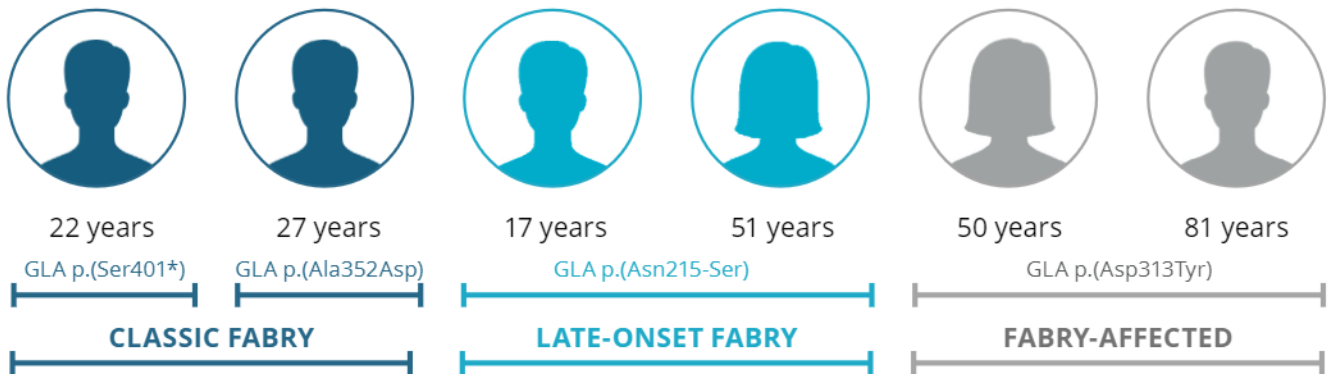
The researchers were aiming to assess if **GL-3 accumulation** was seen in the GI tract cells of people with Fabry and how this could help to determine if all GI symptoms are attributable to Fabry.



GI symptoms are usually attributed to Fabry for all forms of the disease.

Study participants

The study included men and women with classic Fabry (mutations GLA p.(Ser401*) and p.(Ala352Asp)), late-onset Fabry (mutation GLA p.(Asn215-Ser)) and Fabry-affected (mutation GLA p.(Asp313Tyr)) individuals.



Study details



All individuals in the study had experienced **long-lasting GI disturbances** that were poorly controlled with medications commonly used to treat GI symptoms.



The two males with classic Fabry disease had experienced **GI symptoms from infancy**.



Individuals with **classic Fabry** and with **late-onset Fabry** disease were **on ERT treatment**.



Fabry-affected individuals were **not on ERT treatment**.



Gastropathy is the medical term for stomach diseases



'Pathologic substrate of gastropathy in Anderson-Fabry disease' was published in *Orphanet Journal of Rare Diseases*.¹⁷

GI symptoms that were experienced by individuals in the study:

	Constipation	Early satiety	Epigastric pain	Heartburn	Intestinal disturbances	Nausea	Vomiting	Weight loss
 22 years Classic Fabry			✓		✓	✓	✓	
 27 years Classic Fabry			✓		✓	✓	✓	
 17 years Late-onset Fabry			✓				✓	✓
 51 years Late-onset Fabry			✓	✓		✓		
 50 years Fabry-affected	✓	✓	✓			✓	✓	
 81 years Fabry-affected	✓	✓	✓			✓	✓	



Early satiety

is feeling full before the end of a meal.



Epigastric pain is felt in the upper abdomen, the area that is just below the ribs and above the belly button.



The assessment



In the study, researchers assessed the changes in GI cells by using an **endoscope** to look at the lining of the throat, stomach and the first part of the small intestine.



A small sample of the GI tract cells was taken, this is called a **biopsy**. The biopsies were examined under a microscope and the researchers looked for GL-3 accumulation in the cells.



An **endoscope** is a flexible tube with a light and camera at the end that is used to look inside the body.



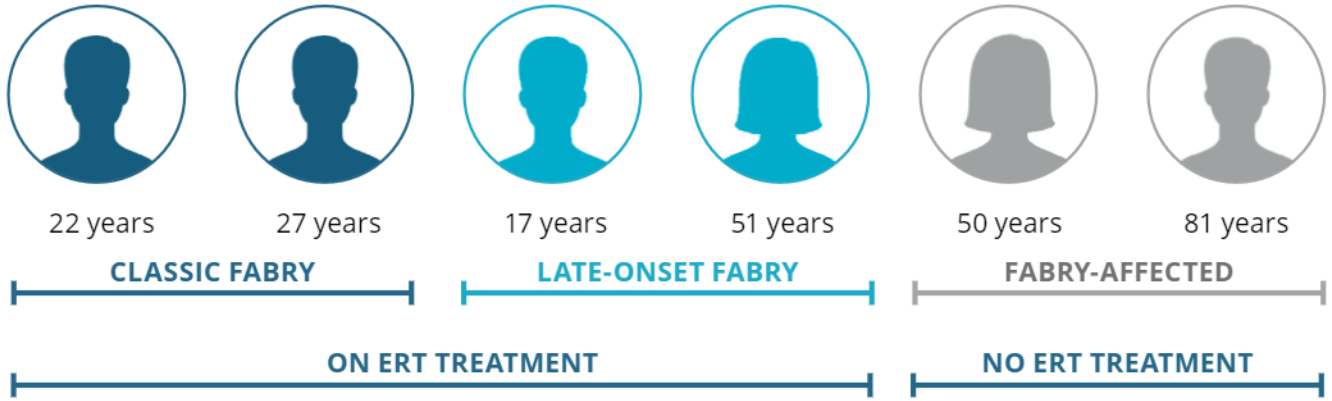
A **biopsy** is a medical procedure that involves taking a small sample of body tissue so it can be examined under a microscope.

The findings



'Pathologic substrate of gastropathy in Anderson-Fabry disease' was published in *Orphanet Journal of Rare Diseases*.¹⁷

Researchers investigated the accumulation of GL-3 in the GI tract cells of six individuals with Fabry.



ALL INDIVIDUALS HAD EXPERIENCED LONG-LASTING GI DISTURBANCES



GI symptoms were present in all six individuals.

FABRY GASTROPATHY



Fabry gastropathy was diagnosed in both individuals with **classic Fabry**.

GASTRO-OESOPHAGEAL REFLUX DISEASE



Gastro-oesophageal reflux disease is caused by acid reflux from the stomach and inflammation of the oesophagus. It was confirmed in both **Fabry-affected** individuals and the **late-onset Fabry female**.

GL3 ACCUMULATION



Biopsies showed GL-3 was **present** in GI tract cells of both individuals with **classic Fabry**.

NO GL3 ACCUMULATION



Biopsies showed GL-3 was **absent** in GI tract cells of **late-onset Fabry** and **Fabry-affected** individuals.

ATTRIBUTED TO FABRY



Fabry gastropathy could be **explained** by GL-3 accumulation in the GI cells of patients with **classic Fabry**.

NOT ATTRIBUTED TO FABRY



GI symptoms in patients with **late-onset Fabry** and **Fabry-affected** individuals could not be directly explained by Fabry as there was no GL-3 accumulation in the cells. These GI symptoms were common in adults and may have developed with **age** or by the presence of **other diseases**.

Findings in brief



'Pathologic substrate of gastropathy in Anderson-Fabry disease' was published in *Orphanet Journal of Rare Diseases*.¹⁷

A study published in 2020 by researchers in Italy investigated changes in GI tract cells of six unrelated individuals to determine if all GI symptoms can be attributed to Fabry.

GI symptoms tend to be attributed to Fabry disease for all forms of Fabry because symptoms of common GI diseases are similar to those of Fabry gastropathy.

The precise diagnosis of Fabry gastropathy can be achieved through biopsies to assess GL-3 accumulation in GI cells.

GL-3 accumulation confirmed the diagnosis of Fabry gastropathy in individuals with classic Fabry.



Generally, diagnosis of Fabry gastropathy is solely based on symptoms. This study has shown that there is potential to determine whether GI symptoms are Fabry-specific by conducting biopsies to assess GL-3 accumulation in GI cells.



The study found patients with classic Fabry had Fabry gastropathy with GL-3 accumulation in the GI cells, hence their symptoms were specific to Fabry.



The study showed no accumulation of GL-3 in the GI cells of late-onset Fabry and Fabry-affected individuals, implying their symptoms were not Fabry-specific. Symptoms were common in adults and could have been linked to other diseases.



Further studies may be able to measure how well ERT treatment is working by comparing levels of GL-3 before and throughout ERT treatment.



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Fabry International Network

[Fabrynetwork.org](https://fabrynetwork.org) 



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