Fabry Disease: A Unique Disease — Uniquely Experienced
Fabry disease is a progressive, multisystemic, X-linked lysosomal disorder affecting both males and females, caused by mutations or variants in the galactosidase alpha (GLA) gene.\textsuperscript{1,2}

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

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

**LEADING CAUSES OF DEATH IN FABRY DISEASE\textsuperscript{3}**

| Cardiovascular disease (53.6% and 50.0% of male and female deaths, respectively) | Cerebrovascular complications (12.5% of males) | Renal disease (10.7% of males) |

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

**Understanding the complexities of Fabry disease and its symptoms**

**What causes Fabry disease?**

| Fabry disease is caused by mutations, or variants, in the GLA gene.\textsuperscript{1,2} | These mutations can cause absent or deficient α-galactosidase A (α-Gal A).\textsuperscript{1,2} | When α-Gal A is absent or deficient, globotriaosylceramide (GL-3), plasma globotriaosylsphingosine (lyso-Gb\textsubscript{3}), and other disease substrates accumulate.\textsuperscript{1,2} | This leads to cell damage within affected parts of the individual’s body and causes the various pathologies seen in Fabry disease.\textsuperscript{1,2} |

**Fabry disease symptoms are diverse and multisystemic**

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

- Cerebrovascular symptoms, including dizziness or vertigo, transient ischaemic attacks, and stroke\textsuperscript{1}
- Cornea verticillata (whorls in the cornea)\textsuperscript{1,3}
- Renal disease, typically requiring dialysis or transplantation after prolonged disease\textsuperscript{1}
- Cardiac disease, such as left ventricular hypertrophy, valvular disease, and rhythm disturbances\textsuperscript{1}
- Gastrointestinal symptoms, such as abdominal pain, bloating, diarrhoea, constipation, and early satiety\textsuperscript{2,3}
- Angiokeratomas (reddish-purple, non-blanching maculopapular lesions)\textsuperscript{3}
- Acroparaesthesia (abnormal tingling or burning sensation in the extremities)\textsuperscript{3}
- Acute pain (“Fabry crises” often in hands and feet, accompanied by fever that may last hours to days)\textsuperscript{3}
- Hypohidrosis (too little sweat, affecting regulation of body temperature)\textsuperscript{3}
To date, there are more than 1000 mutations of the GLA gene. A variety of mutations in the GLA gene can give rise to Fabry disease, such as:

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

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

Why GLA gene mutations matter in Fabry disease

Understanding the X-linked inheritance pattern of Fabry disease

The orange X indicates an affected X chromosome.

- An individual with a gene mutation that causes Fabry disease
- An individual without a gene mutation that causes Fabry disease

INHERITANCE THROUGH AN AFFECTED MOTHER

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

INHERITANCE THROUGH AN AFFECTED FATHER

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

Males with Fabry disease cannot transmit Fabry disease to their sons, but will always transmit the disease to their daughters.

Females with Fabry disease have a 50% chance of transmitting the disease to their sons and daughters.
Each Fabry disease mutation can present in a unique way

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

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

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

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<td>BILL* 18</td>
<td>W226X</td>
<td>Bill was diagnosed with Fabry disease after being evaluated due to severe growth retardation, skeletal dysplasia, and delayed puberty.†</td>
</tr>
<tr>
<td>MARC* 11</td>
<td>W226X</td>
<td>Marc was diagnosed with Fabry disease after being referred for evaluation due to a family history of Fabry disease. He experienced acroparaesthesia, hypohidrosis, and discomfort. He was previously diagnosed with celiac disease.</td>
</tr>
</tbody>
</table>

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

Regardless of phenotype and level of disease severity, Fabry disease is always progressive.3
Women with Fabry disease experience more than just physical symptoms

Heterozygous women are not just carriers

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

Common symptoms in women with Fabry disease

- Cornea verticillata
- Left ventricular hypertrophy
- Arrhythmia
- Severe abdominal cramping
- Diarrhoea
- CNS involvement (transient ischaemic attacks, stroke, white matter lesions)
- Hearing loss
- Renal hyperfiltration
- Decreased eGFR
- Albuminuria/proteinuria
- Angiokeratomas
- Neuropathic pain

Depression and QoL

Depression is often an underdiagnosed, under-reported problem in Fabry disease and reduces QoL. In general, 46% of patients have depression.3 In another study, about one-third of women living with Fabry disease admitted to feelings of depression, anxiety, fatigue, and frustration.15

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

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

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

Fabry disease is “often seen, rarely diagnosed”\(^{16}\)

It is estimated that patients visit an average of 10 different specialists before a Fabry disease diagnosis is confirmed, leading to a delay of ~15 years from symptom onset to diagnosis.\(^{17,18}\)

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

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

- Initiating treatment early before irreversible organ damage occurs\(^1\)
- Carefully monitoring multiple organ systems\(^2,25\)
- Individualising management (ie, specific genetic mutation/variant, symptoms, and presentation of disease)\(^3,25\)
- Stabilising disease progression in various organ systems\(^26,27\)

Clinical vigilance and regular monitoring are vital

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

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

Gene testing can inform Fabry disease diagnosis and management

Genotype alone does not determine disease progression in Fabry disease—the etiology is complex, and there is great variability in the manifestation and progression of disease.\(^{17,19}\) Even when disease presentation is asymptomatic or mild, the accumulation of disease substrates (including GL-3 and lyso-Gb\(_3\)) can contribute to long-term damage of organs and tissues.\(^{3,20}\) If there is suspicion of Fabry disease, gene testing is generally recommended to confirm diagnosis.\(^3,21\)

Gene testing can be an important diagnostic tool to enhance our understanding of each patient’s unique disease and lead to a more personalised approach to disease management.\(^23,24\)

DIAGNOSIS IN MALES VS FEMALES IS DIFFERENT

In males, an absence or low levels of α-Gal A activity in blood cells or dried blood spots is sufficient to make the diagnosis.\(^27\)

However, GLA gene sequencing is required for women, as α-Gal A activity can appear normal.\(^17,22\)

For families affected by Fabry disease, targeted mutational analysis can be used to diagnose at-risk individuals who may not yet exhibit the phenotypic characteristics of the disease.\(^22\)

Help patients feel in control of their disease

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

Gene testing can be an important diagnostic tool to enhance our understanding of each patient’s unique disease and lead to a more personalised approach to disease management.\(^23,24\)
Fabry disease is a progressive, multisystemic, X-linked lysosomal disorder caused by mutations, or variants, in the GLA gene, which encodes the α-Gal A enzyme.\(^2\) Accumulation of disease substrates (including GL-3 and lyso-Gb\(_3\)) can contribute to long-term damage of organs and tissues.\(^3,6\)

Patients visit an average of 10 different specialists before a Fabry disease diagnosis is confirmed.\(^17\)

 REGARDLESS OF PHENOTYPE AND LEVEL OF DISEASE SEVERITY, FABRY DISEASE IS ALWAYS PROGRESSIVE\(^2\)

Regardless of phenotype and level of disease severity, Fabry disease is always progressive.\(^2\) In males, an absence or low levels of α-Gal A activity in blood cells or dried blood spots is sufficient to make the diagnosis. However, GLA gene sequencing is required for women.\(^17,22\)

Patients with Fabry disease have a delay of ~15 years from symptom onset to diagnosis.\(^18\)

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

References: