Understanding Fabry disease—a serious, progressive disorder with complex pathology

Fabry disease is an X-linked lysosomal storage disorder.1 Caused by a deficiency of α-galactosidase A (α-Gal A), Fabry disease can have a devastating impact on people’s lives.1 Although the disease presents differently in each individual who has it, it can prove to be a significant burden regardless of presentation.1

Individuals with Fabry disease may experience a wide variety of symptoms, including the following:

- Acroparaesthesia1
- Acute pain (“Fabry crises”)1
- Hypohidrosis1
- Corneal verticillata1
- Angiokeratomas1
- Gastrointestinal problems, such as abdominal pain and bloating, diarrhoea, and early satiety1–3
- Renal disease, typically requiring dialysis or transplantation1
- Cardiac disease, such as left ventricular hypertrophy, valvular disease, and rhythm disturbances1
- Cerebrovascular symptoms, including dizziness, vertigo, transient ischaemic attacks, and stroke1

People with Fabry disease are generally categorised into 2 groups: those with classic, severe disease and those with milder, later-onset disease.1 Heterozygous females can experience a variable presentation, ranging from asymptomatic or mild symptoms to symptoms that are just as severe as those experienced by male patients.1
When Fabry disease is diagnosed, it comes with a long list of possible symptoms and how they can progress. But each individual experiences the disease in his or her own way, making Fabry something that is uniquely experienced.¹

Because phenotype is not a consistently accurate reflection of genotype in Fabry, gene sequencing can be an important diagnostic tool.²⁴⁻⁶ Gene sequencing can enhance our understanding of each patient’s unique disease.⁵⁻⁸

Genotype alone does not determine disease progression in Fabry disease—the etiology is complex, and there is a high variability in the manifestation and progression of disease.¹ People with Fabry disease may experience severe symptoms, or seemingly none at all, with a variety of clinical presentations in between.⁸ But even when disease presentation is asymptomatic or mild, disease substrate can accumulate, contributing to long-term damage of organs and tissues.¹⁻⁸

Identification of the genetic mutation specific to an individual with Fabry can provide insight into the unique nature of his or her disease.¹⁻⁸ If there is suspicion of Fabry disease, gene sequencing is recommended.²⁴⁻⁸

Untreated individuals with Fabry disease may experience a shorter lifespan compared with the general population.¹ Lifespans for people with Fabry disease may be shortened to approximately 50 years for men and 70 for women—a 20- and 10-year reduction, respectively.² Cardiovascular disease is the most common cause of death for both men and women.¹⁰

Our understanding of Fabry disease continues to grow. We are only just beginning to understand the intricacies of this disorder, but what we do know is that early diagnosis is critical to better outcomes.¹
Fabry disease: a progressive, multisystemic, multiorgan disorder

Fabry disease is characterised by multiple organ pathology. Although Fabry disease presents in many different ways—including asymptptomatically—its progressive nature is consistent irrespective of its presentation.11

If Fabry disease is not diagnosed in its early stages, irreversible organ damage may develop—although further damage can be managed with a multidisciplinary treatment approach.1,2

Organ damage in Fabry disease is caused by the accumulation of globotriaosylceramide (GL-3) and plasma globotriaosylsphingosine (lyso-Gb3) in the cells, leading to dysfunction in affected cells.2,12

These deposits can potentially affect multiple cell types, including:
- Endothelial cells: vascular and neurovascular
- Cardiomyocytes
- Smooth muscle cells
- Neurons within the central and peripheral nervous systems
- Eccrine sweat glands
- Epithelial cells: cornea, lens, airway
- Perithelial cells: small intestine, colon, and rectum
- Ganglion cells

Damage to organ systems can cause a wide spectrum of symptoms4

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<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>PATHOPHYSIOLOGIC PRESENTATION</th>
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<tbody>
<tr>
<td>RENAL</td>
<td>Glomerular sclerosis, tubular atrophy, interstitial fibrosis</td>
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<tr>
<td>CARDIAC</td>
<td>Left ventricular hypertrophy, heart failure, stenosis, atherosclerotic plaques, coronary vasospasm, thrombotic and thromboembolic complications</td>
</tr>
<tr>
<td>NEUROLOGIC</td>
<td>Ischaemic injury and metabolic failure</td>
</tr>
<tr>
<td>DERMATOLOGIC</td>
<td>Weakening of capillary walls and vascular ectasia, narrowing of small blood vessels around sweat glands</td>
</tr>
<tr>
<td>OPHTHALMOLOGIC</td>
<td>Streaks in cornea, vasculopathy of conjunctival and retinal vessels, central retinal artery occlusion, reduced tear production</td>
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<tr>
<td>PULMONARY</td>
<td>Airway narrowing, capillary blockage</td>
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<tr>
<td>GASTROINTESTINAL</td>
<td>Narrowing of mesenteric small blood vessels</td>
</tr>
<tr>
<td>EAR, NOSE, THROAT</td>
<td>Narrowing or occlusion of cochlear vessels, ischaemic auditory neuropathy</td>
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A unique disease presentation necessitates a unique management strategy

Fabry disease presents with a high degree of phenotypic heterogeneity—phenotypic presentation can differ even within families affected by Fabry.4 When treating a disorder with the potential to be highly disruptive, it is important to attune any management strategy to the diverse pathologies and the variable severity seen in Fabry disease and to tailor management strategies specifically for each patient.

With lifestyle-oriented management programmes, patients can be encouraged to take an active role in their disease management. Personalised programmes can empower patients to feel that they are in control of their disease and to live their lives as they wish—with choice.13
Genetic mutations play a critical role in Fabry disease

Fabry is an X-linked disease caused by mutations in the GLA gene, which encodes the α-Gal A enzyme. These mutations can cause α-Gal A, which breaks down GL-3 and plasma lyso-Gb, in healthy individuals, to be either absent or deficient. When α-Gal A is absent or deficient, GL-3 and lyso-Gb accumulate, leading to damage of cells within affected parts of the individual’s body and causing the various pathologies seen in Fabry disease.

To date, more than 800 mutations of the GLA gene have been found to cause Fabry disease. A variety of mutation types can give rise to Fabry disease, such as missense mutations, splicing mutations, small deletions and insertions, and large deletions. Many genetic mutations are specific to individual families affected by Fabry disease, whereas some are more widespread.

Gene sequencing is the only valid tool to diagnose Fabry disease in heterozygous females because in these women, enzyme activity can appear normal. Additionally, in families affected by Fabry, targeted mutational analysis can be used to diagnose at-risk individuals who may not yet exhibit the phenotypic characteristics of the disease.

Approximately 60% of mutations known to cause Fabry disease are missense mutations. Missense mutations—caused by the replacement of one amino acid by another—can result in severe disease, as they can cause structural changes that significantly affect the function and stability of the GLA gene.

Other types of mutations known to cause Fabry disease include splicing mutations, small deletions and insertions, and large deletions.

Males with Fabry disease cannot transmit Fabry 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.
Confirming a patient’s genetic mutation may help you to better understand his or her disease⁵⁻⁸

Manifestations of Fabry disease can differ significantly from individual to individual. Evidence suggests that certain genotypes can result in classic or later onset phenotypes. Furthermore, select genotypes have been described as renal or cardiac subtypes (or variants) of disease. In one study, the functional effects of different mutations were studied. Each patient presented in a unique way.⁰

<table>
<thead>
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<th>AGE AT DIAGNOSIS</th>
<th>GENOTYPE</th>
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<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 oedema. George has also presented with cardiac involvement.</td>
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</tbody>
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*Not the patient’s actual name.

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

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<tr>
<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>
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<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. He experienced acroparaesthesia, hypohidrosis, and discomfort. He was previously diagnosed with coeliac disease.</td>
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*Not the patient’s actual name.

Fabry is a unique disease, uniquely experienced. With more than 800 known mutations, there is no single genotypic cause of Fabry disease.⁵

Regardless of phenotype, Fabry disease is always progressive, even for individuals with mild symptoms.²

Gene sequencing can inform diagnosis and lead to a more personalised approach to disease management.²,⁵⁻⁸,²³
References:


