



Understanding Fabry Disease

Fabry Disease Fact Sheet

Fabry Disease (FD) is a rare hereditary genetic condition. It is one of a number of disorders known as lysosomal storage diseases. There is currently no cure for people who have FD but this fact sheet explores the disease presentation and clinical management.

This fact sheet is produced by Fabry Australia. It is based upon experiences of those affected by FD, their families and their doctors.

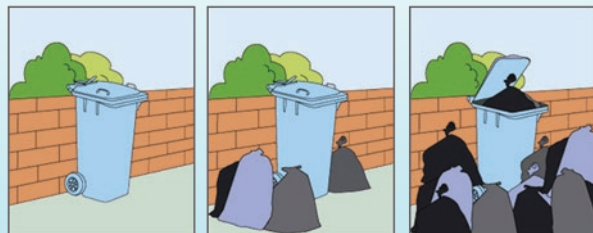
What causes Fabry Disease?

In the course of 'normal' life, there is a continuous recycling process which consists of building new materials and breaking down old ones ready for disposal. Some of these processes occur in a special part of the body's cells, called the lysosome. This process requires a series of biochemical tools called enzymes. Enzymes can only reach the lysosomes after a special signal has been attached to them.

Adults and children with FD are missing, or deficient in, an enzyme called alpha-galactosidase A, (Alpha A) which is essential in the breakdown of waste products in the lysosomes of many different types of cells within the body.

The main waste product is ceramide trihexoside (CTH), also known as globotriaosylceramide, Gb3 or G13. When these waste products build up within the cells of the body they start to cause progressive damage. Babies may show little sign of the disease but as more and more cells become damaged by an accumulation of these waste products, symptoms start to display themselves.

A good analogy is removing household rubbish. If this job was ineffective or non-existent the household rubbish would take over its surroundings. This build up over time is what causes problems. See diagram below.



How common is Fabry Disease?

FD is a rare disease. The symptoms are often mistaken for other illnesses. It affects many organs making accurate diagnosis very difficult. It affects males, females, adults and children.

The prevalence is estimated to be 1:117,000 among males. The condition affects people worldwide across all ethnic groups. The population-specific rates are unknown.

The prevalence may be underestimated as many males with organ-specific variants (i.e. cardiac variant) may not be diagnosed as having FD, although their heart disease may be recognised and treated. It is currently estimated that FD affects approximately 5,000–10,000 people worldwide.

Can females have Fabry Disease?

Yes! Many females with FD still call themselves 'carriers' however this term is inaccurate. The presentation of signs and symptoms among females with FD is highly variable, some live a long life with few symptoms, others have as many symptoms and complications as a male with FD.



Diagnosis of Fabry Disease

FD encompasses a wide spectrum of clinical symptoms which may or may not appear in all individuals with this disease. This together with its rarity often delays diagnosis. Many individuals may experience some of the symptoms that are listed here in the fact sheet before they receive an actual diagnosis of FD.

Overview of Symptoms

FD often presents itself during early childhood as pain and maybe overlooked by a GP and misdiagnosed as growing pains. Signs and symptoms vary from case to case even within the same family. However, not all cases of FD are noticed and or experienced at such a young age.

Symptoms include:

- Burning sensations (or pain) in hands/feet
- Headaches
- Vertigo / dizziness
- Fatigue
- Small raised dark-red dots on the body (called angiokeratomas)
- Sweating too little (condition called hyperhidrosis)
- Intolerance to heat
- Fever
- Abdominal pain
- Vomiting & diarrhoea
- Tinnitus (ringing sound in the ears)
- Impaired hearing (sometimes hearing loss)
- Alterations in the eye, leading to clouding that can occur in the cornea (known as 'Opacity of the Cornea')
- Depression (patient studies indicate that pain does vary and can cause depression, fatigue and feelings of social isolation)

Over time, patients typically develop more serious symptoms that affect the kidneys, heart and brain.



Are there tests for Fabry Disease?

Yes. A genetic test can be used to confirm diagnosis of Fabry Disease. In many cases a diagnosis of FD only occurs after another family member is found to have the disease. Therefore, it is important to advise members of your immediate and extended family. Both amniocentesis and chorionic villus sampling can be used to diagnose FD in early pregnancy.

How do I test for Fabry Disease?

A blood test to check levels of the enzyme (Alpha-galactosidase A) will determine if FD is present, as there are lower levels than normal in FD affected individuals.

DNA analysis determines whether a female is affected by finding the specific change or mutation in the Fabry gene. When this is known, any female relatives can be reliably tested.



What should I do now?

If you or someone in your family has been diagnosed with FD it is very possible that other members of your family are at risk of having inherited this condition.

If you suspect this is the case, it is very important to see your GP and have a referral written to see the Fabry Clinic in your State (see State Fabry Clinics listed in the back of this brochure). You can take this Fact Sheet with you, as it is likely your GP will not have heard of FD. It is vitally important that other family members are encouraged to consider undergoing testing once a diagnosis of FD has been confirmed within the family. This will ensure that informed decisions can be made over treatment options and family planning choices.

Genetic Counselling

People diagnosed with FD should consider asking for genetic counselling before having children. The counsellor should be able to provide non-directive advice on the risk to close relatives, pattern of inheritance, family planning, genetic screening and other issues. The State Fabry Clinics can advise patients where to obtain Genetic Counselling.

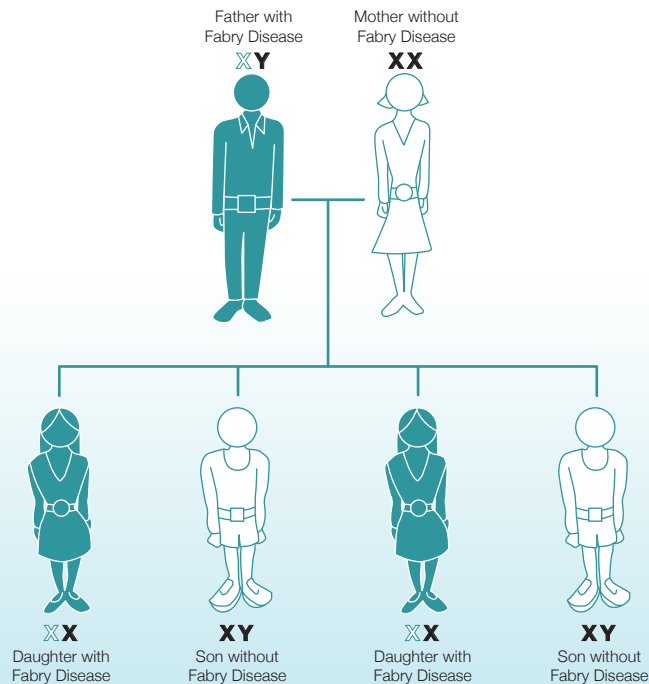
How is Fabry Disease inherited

We all inherit genes from our parents. These genes are contained on 46 chromosomes arranged in 23 pairs. One of these pairs determines whether an individual is male or female.

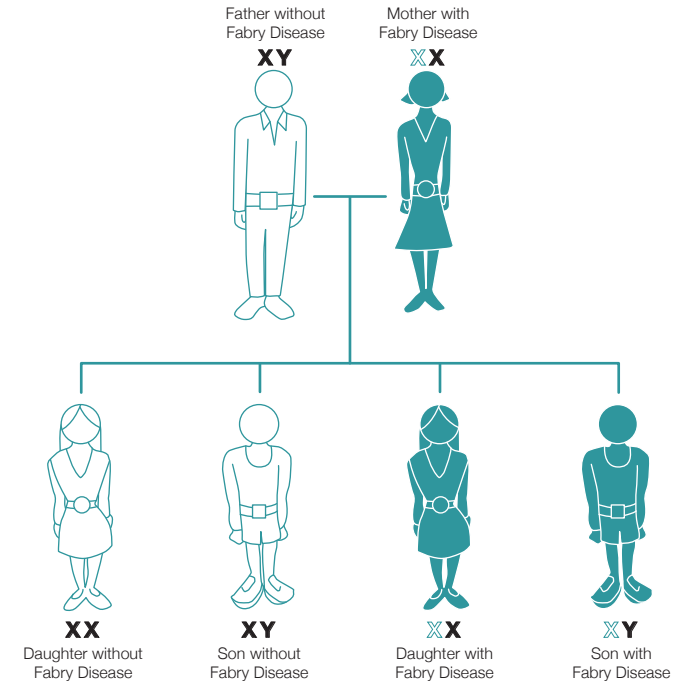
$\text{Y} + \text{X} = \text{XY}$
Man's Y-chromosome + Woman's X-chromosome = A baby boy
Males have a 'Y' and 'X' chromosome

$\text{X} + \text{X} = \text{XX}$
Man's X-chromosome + Woman's X-chromosome = A baby girl
Females have two 'X' chromosomes.

In FD, the defective gene is located on the 'X' chromosome.
The disease is therefore following an X-inheritance pattern.



An affected male (see diagram above) will have sons who are healthy and not have FD but all his daughters will have FD.



In affected females (see diagram above) there is a 50% chance that a daughter will have FD and a 50% chance a son will have FD.



Clinical Presentation of Fabry Disease

FD encompasses a wide range of clinical symptoms which may not appear in all affected individuals. The symptoms usually worsen with age. **NB: Not ALL individuals with FD will experience all these symptoms outlined in this Fact Sheet.**

Pain

Pain is the most common symptom of FD and is often the symptom that most people with FD first experience. Pain often goes undiagnosed as being a symptom of FD during childhood, and is usually labelled as 'growing pains'. Fabry pain is caused by the accumulation of waste products in the nerve cells. The pain can be a constant background pain or short term severe pain, and can be triggered by change in temperature, episodes of stress or physical activity. Short term severe pain is often known as a 'Fabry Crisis', lasting from a few minutes to several days, and is often described as an intense burning which starts at the extremities (fingers and toes) and spreads throughout the body. No matter what type of pain, it is often debilitating and may affect everyday activities.

Kidney Function

The accumulation of waste products in kidney cells and in the wall of blood vessels supplying the kidney, can impair kidney function over time. This may lead to reduced kidney function by early adulthood, and will be indicated by raised protein levels in the urine.

Heart

Accumulation of waste products within the cells of the heart or the walls of the coronary arteries may cause individuals with FD to develop heart problems. Some initial symptoms include; shortness of breath, irregular or fast heartbeat, enlarged heart, chest pain (angina) and increased risk of heart attack or heart failure.

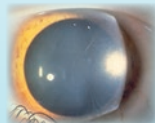
Treatment of heart conditions associated with FD may include medication and/or the fitting of a pacemaker. For more severe conditions heart bypass surgery and transplantation may lead to some improvement.

Stroke

Individuals with FD may develop a stroke. This may be a minor stroke followed by a full recovery (Transient Ischaemic Attacks or TIA's), but more severe strokes can occur. Medication to thin the blood may be prescribed by a doctor.

Eyes

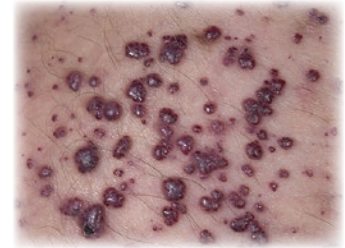
The surface layer of the eye (cornea) may appear abnormal when examined by an optician or an eye specialist (ophthalmologist) with special equipment. This starburst, or whorling appearance, which is



called cornea verticillata, does not affect vision but may increase with time. It occurs in approximately three-quarters of patients and can be a reliable indicator of FD.

Skin

Angiokeratomas are the most visible recognisable clinical feature of FD. These dark red or purple skin lesions (ranging in size from pinpoint to several millimetres in diameter) do not blanch with pressure and are usually distributed on the buttocks, groin, umbilicus, and upper thighs (bathing trunk distribution). This rash-like skin condition is not painful. It can also appear on other parts of the body such as the lips, tongue, hands and toes. They generally start to appear in adolescence or young adulthood.



Reduced Sweating (Hyperhidrosis)

Many people with FD sweat less than people without the disease. They may either perspire very little (hyperhidrosis) or not at all (anhidrosis). This can cause overheating, frequent fevers, and sensitivity to weather extremes. Some patients may have increased sweating (Hyperhidrosis), which is more common in females. Impaired sweating is generally caused by damage to the nerves and sweat glands.

Nervous System

Individuals with FD may suffer from headaches, vertigo and a ringing sound in the ears (Tinnitus). Some patients may experience a degree of hearing loss, and this can either progress over time or be quite sudden.

The Bowel

Individuals with FD may experience discomfort or pain after eating, due to the accumulation of waste products within the cells of the intestine, or the blood vessels and nerves supplying the intestine. Other possible symptoms include; vomiting, nausea and diarrhoea. These symptoms can be reduced by eating small meals regularly, adjusting the diet, and seeking medication prescribed by a doctor. Some Fabry patients experience weight loss and become quite thin.

Depression / Psycho-social aspect

Living with difficult physical symptoms is only one of the challenges people with FD may face. They may experience feelings of fear, depression, isolation or guilt about passing the disease along. Family members may be affected as well. FSGA is a helpful place to start, as there will be someone in a similar situation, with similar concerns and fears. Mutual support is very beneficial as Fabry patients often understand a great deal about FD, and can offer a lot through sharing experiences and connecting with others in the 'same boat'.

Development of Fabry Disease

There are differences between FD in childhood, adolescence and adulthood. It also important to remember that not all individuals with FD will experience all the symptoms outlined here in this Fact Sheet and some adults with the disease will experience some of the symptoms associated with the disease in childhood and vice versa.

Children

Pain and angiokeratomas, characteristic abnormalities of the eye, gastrointestinal symptoms (such as alternating between bouts of diarrhoea and constipation), tummy pains and hearing problems are usually the only symptoms of FD in childhood. The pain is often attributed to common 'growing pains'. After diagnosis, it is important that children are given support in understanding their disease and any limitations it may present, but are also encouraged to remain positive, and to participate in normal activities with their family and peers.



Adolescents

During adolescence, many of the skin problems experienced during childhood may worsen. This is often the time when bowel pain develops. The first stage of impaired functioning of the kidney and heart can also occur at this time.

Adults

FD is slowly progressive. Symptoms result from damage to the kidneys, heart and central nervous system. Kidney problems in males with FD usually become much more severe during early adulthood. The heart becomes affected after the age of about 40 years and the risk of strokes increase.

Atypical Variants

Recent research indicates that some patients with FD present with features only involving a single organ system, specifically cardiac and renal. These arise as a result of mis-sense mutations when a patient has sufficient residual enzyme activity to prevent symptoms in childhood and early adult life. However, the existence of atypical variants is still the subject of medical debate. Patients that have been diagnosed with an atypical variant may actually have changes in other organs. Such patients may have mutations associated with residual enzyme activity which could, in turn, be associated with a less severe presentation of the disease.

Living with Fabry Disease

FD can be a debilitating condition, associated with many problems and shortened life expectancy. With the development of Enzyme Replacement Therapy (ERT) however, many Fabry affected individuals and families are able to live fulfilled lives. Alleviation of symptoms often enables adults with FD to participate in day to day family life, sustain relationships and seek employment. Children affected by the disease can enjoy social and physical activities with their peers.



Many adults who have FD understand it is an inherited genetic condition and that this affects more than just themselves. Many have prematurely experienced the loss of a parent or loved one through the disease. In a significant number of cases, FD has gone undiagnosed or misdiagnosed for a long period of time. Many affected individuals are somewhat relieved when they receive a diagnosis, as they find the cause of the unusual childhood symptoms of pain, burning hands and feet, bowel issues, tiredness and inability to sweat.

For many Fabry patients, accessing funded treatment which alleviates symptoms, has greatly enhanced quality of life. This enables them to contribute and participate as full functioning individuals in society, and can have a positive effect on relationships and the family. It also allows the family to not be so restricted by the debilitating symptoms and emotional burden of living with this rare and complicated disease.

Thoughts from Fabry patients

'What a relief to know all the pain and suffering from a relatively miserable childhood was not actually something in my head but actually as a result of FD!'

'I am so glad I contacted Fabry Australia. They were a Godsend and a huge emotional and practical support to me and my family. Thank you Fabry Australia!'

'A tip to others who receive a positive diagnosis is to learn as much as you can about this complex condition and try not to panic.'

'When I was diagnosed with FD, I felt somewhat guilty that I had given this to my children. It took a while for me to accept I have this condition and so do my loved ones. But we are learning together.'

'Everyone copes differently. It is important not to let the negative comments influence you. Keeping positive is essential.'



My Dad's Story by Megan Fookes OAM



In 1994 a man (David Davie), was diagnosed with FD at the age of 48. After researching and finding very little information about such a rare fatal condition, his wife, Margaret, wrote to the *Australian Women's Weekly* with an article featuring her husband and his new predicament. As a result, many other people who had been diagnosed with this fate came in contact with them and the group was formed.

The first Fabry Australia meeting was held on 4th June 1994 at the Murdoch Institute, Royal Children's Hospital, Victoria with over 55 people in attendance. It was an outstanding success and the consensus of the meeting was that a Fabry Support Group be formed. Fabry Australia was officially incorporated from 20th June 1994. It was at this time that the Royal

Melbourne Hospital Nephrology Department agreed to form a central Fabry Clinic at the Royal Melbourne hospital and to do some Genetic Research at this clinic. One of the problems of suffering a rare disease such as Fabry is that any individual doctor is likely to have limited experience in treating the condition.

In setting up the Fabry Clinic many aims were achievable. The years that followed saw the Fabry Australia formulate a Mission Statement: "To provide support for those affected directly or indirectly by FD throughout Australia. Increase recognition, awareness and understanding of FD, its effects and potential solutions".

Fabry Australia is very fortunate to have a lot of support from its members and some quiet 'heroes' like Merle the 'coat hanger queen' who has lost 2 daughters and a

husband from FD. Merle worked extremely hard to hand made craft items such as covered coat-hangers and clothed children's teddy bears with a message attached saying 'all proceeds go to Fabry Research'. Merle's fundraising supported several medical students to research FD, and all produced papers – first on scope and general manifestations of FD in Australian patients, and later on neurological and cardiac manifestations of FD. Today Fabry Research is a high priority and Fabry Australia is looking to further this with its Medical Advisory Board.



Current Treatments for Fabry Disease

There are many valuable symptomatic and protective/preventative treatments recommended for FD. As well as Enzyme Replacement Therapy (ERT) there are many treatments in development.

Enzyme Replacement Therapy (ERT)

Enzyme Replacement Therapy (ERT) for FD is designed to replace the missing or malfunctioning enzyme, Alpha A, in individuals with FD. The enzyme is manufactured from cultures of cells which have been genetically engineered to express the human enzyme. This enzyme is given by intravenous infusion each fortnight to stabilize and reduce FD symptoms.

Treatments are administered in a local hospital or via home infusion, administered by a nurse, and some patients infuse themselves. The first 12 treatments are co-ordinated in the State Fabry Clinic.

The principle underlying this treatment is that the enzyme that is missing or not functional may be partially replaced by infusing this therapeutic form of the enzyme. The enzyme used in treatments contains a particular chemical address on its surface, that allows it to be taken up by cells from the blood and transferred to the lysosome of the cell, where it carries out its work in breaking down the storage material Gb3 (GL3). The aim of the treatment is to help relieve symptoms and to prevent progression of damage to important organs, like the kidney and heart. Criteria have been devised for the initiation of therapy and are based on the responsiveness of various organs to treatment. In Australia, criteria are based around changes in the heart, brain and kidneys or pain and gastro-intestinal symptoms which affect quality of life.

FD tends to have a different course in males than in females and the criteria for initiating therapy is different between genders. Distressing symptoms can start at an early age and treatment is available for children in co-ordination with a paediatrician. Studies have shown that ERT can greatly benefit individuals with FD by reducing pain, stabilize or improve renal function, stabilise or improve cardiac abnormalities and improve quality of life. It is hoped that by treating people with FD as early as possible, it will be feasible to prevent the clinical manifestations of the disease.

How is treatment for Fabry Disease funded?

FD treatments are approved and funded by the Federal Health Department under the Life Saving Drugs Program (LSDP). Treatment is available only to those who qualify and meet criteria for approved therapy. Further information can be found at: www.health.gov.au/lscp. It is important to talk with your State Fabry doctor about treatment options.

How often do I go to the Fabry clinic?

It is important to be seen once a year if not on treatment, and every 6 months whilst on treatment. Any change should be reported to the Fabry doctor as it is a progressive disease and things can change over time. Ask to participate in the FD Registry. Registries are important to further assist FD experts in the clinical management of patients.



Tracking symptoms of Fabry Disease

It is useful to keep a diary of symptoms for you or your child such as pain, gastro symptoms, illness, dizziness, fatigue, fever – see Fabry Australia for a Fabry Diary.

Clinical Trials

For many years, Australian Fabry patients have enrolled in clinical trials. Patients are needed to collect data required by the Australian government, to demonstrate that a medicine is safe and effective. Results from trials can lead to the development of medicines to further improve lives of people suffering from FD. Further information about Clinical Trials go to medicinesaustralia.com.au/issues-information/clinical-trials

About Fabry Australia

Fabry Australia (formerly known as Fabry Support Group Australia) is a not-for-profit Patient Organisation founded and operated by people with a direct connection to a rare inherited disease called Fabry Disease. Fabry Disease is often difficult to diagnose due to its rarity and its many different symptoms. Fabry Australia connects with over 200 children and adults living with FD including their families, carers and professionals throughout Australia. Fabry Australia works in collaboration with a range of stakeholders such as the Fabry State Clinics, Health Professionals, Allied Health, Pharmaceutical Companies and Government Departments in relation to issues surrounding access to appropriate health care, services and treatment of Fabry Disease in Australia.

Fabry Australia offers a range of services and implemented projects to further support its members. Fabry Australia produces an online newsletter, website, educational materials and provides a range of services including advocacy, support to individuals suffering from FD, funding research, coordination of regional Fabry meetings, national Fabry conferences with local and international Fabry experts, providing 'grass-roots' support and meetings and contact through social media. Fabry Australia has received unrestricted educational grants from a number of pharmaceutical companies with an interest in FD. Fabry Australia is a patient lead membership organisation that relies on support and donations received by fundraising from its members and the general public. It is a registered charity with Direct Gift Recipient (DGR) Status thus allowing all donations over \$2 (AUD) to be tax deductible. For further information about the work of Fabry Australia and its services please contact us directly.



Please note this Fact Sheet is not intended to replace medical advice or care.

Australian Fabry Clinics

Adult Clinics

Royal Melbourne Hospital (VIC & TAS)

Dr Kathy Nicholls
Nephrologist
Ph: 03 9342 7143

Royal Adelaide Hospital (SA)

Associate Prof Ian Chapman
Internal Medicine
Ph: 08 8222 4162

Royal Brisbane and Women's Hospital (QLD)

Dr Charles Denaro
Internal Medicine & Aged Care
Ph: 07 3646 7678
or 07 3646 8346

Royal Perth Hospital (WA)

Dr Mark Thomas
Nephrologist
Ph: 08 9224 2550

Westmead Hospital (NSW & ACT)

Dr Michel Tchan
Metabolic Clinic
Department of Genetic Medicine
Ph: 02 9845 9780

Paediatric Clinics

Royal Children's Hospital (VIC)

Dr Heidi Peters
Clinical Metabolic Services
Ph: 03 9345 6251

Women's and Children's Hospital (SA)

Dr Drago Bratkovic
Metabolic Clinic
Ph: 08 8161 6726

Royal Children's Hospital, Brisbane (QLD)

Dr Jim McGill
Metabolic Medicine
Ph: 07 3646 8111

King Edward Memorial Hospital (WA)

Associate Professor Nicholas Pachter
Genetic Services of Western Australia
Ph: 08 6458 1525

The Children's Hospital at Westmead (NSW)

Dr Carolyn Ellaway
Genetic Metabolic Disorders Service
Lysosomal Disorders Multidisciplinary Management Clinic
Ph: 02 9845 3654



Fabry Australia

Fabry Australia is a patient lead non-profit membership patient organisation founded in 1994. Fabry Australia is a registered charity supported by voluntary donations, educational grants, fundraising and is managed by the members themselves.

Our Aims

- Improve contacts, information and support to people affected by FD and their families.
- Bring about more public awareness of FD
- Improve medical services to Fabry patients in Australia.
- Promote and support research into FD.
- Share information on FD, ongoing management and care available treatments/therapies to Fabry patients.
- Build links with families, clinicians, researchers, support groups to strengthen and support local knowledge about FD.
- Co-operate and collaborate with other Fabry related groups and individuals interested in rare diseases to promote common interests.
- Help raise money to support these aims.

Services include:

- Website
- Social Media
- Australian Fabry Expert Meetings
- State Fabry Patient Meetings
- Fabry Australia Newsletters
- Fabry Disease Advocacy
- Educating families and doctors
- Funding Fabry research
- Fabry Educational Materials
- Visiting international Fabry Experts
- Fundraising activities
- Fabry Awareness Month Campaigns
- Fabry Australia Membership Retreats

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