FIN FABRY EXPERT MEETING 2023

April 21-23, 2023

Amsterdam, NL

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Fabry International Network

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The international FIN Fabry Expert Meeting 2023 took place in Amsterdam from 21-23 April 2023. During these days, all kinds of Fabry related topics were discussed. Renowned speakers from around the world provided new insights into a number of hot topics included in this article.

Fabry disease (Clinical Geneticist Dr. Robert Hopkin, United States)

Fabry disease is a genetic and rare disease caused by a mutation in the GLA gene, which is located on the X chromosome. As a result, little or no alpha-galactosidase A enzyme is produced in the body. This enzyme is required for the breakdown of globotriaosylceramide (Gb3). However, due to the deficiency of alpha-galactosidase A, this does not happen properly and Gb3 slowly accumulates in the cells in different places in the body. This causes a range of symptoms including pain, gastrointestinal complaints, heart rhythm disturbances, kidney failure and strokes. Because Fabry is a so-called 'storage disease', these complaints only get worse without treatment and can even be life-threatening. It is therefore very important that this accumulation process can be stopped as early as possible. Currently, there are 2 effective treatment therapies available: enzyme replacement therapy and chaperone therapy. Both treatments aim to get enough of the missing enzyme into the body, with the aim of inhibiting the accumulation process and preventing further organ damage. Unfortunately, it is not possible to reverse the damage done. The urgent advice is therefore to diagnose and treat Fabry disease as early as possible.

Fabry fog (Psychologist Dr. Nadia Ali, United States)

A common problem in Fabry disease concerns mental health complaints. For a long time, research into Fabry focused mainly on physical complaints and only recently attention has been paid to the influence of the disease on mental health. For example, it is known that depression is more common in people with Fabry. Other complaints also mentioned by patients include forgetfulness, concentration problems and impaired cognition, also referred to as 'Fabry fog'. The number of people who suffer from this varies considerably in the studies: between 0 and 30%. The cause of Fabry fog remains quite unclear for the time being. Is it the disease itself that has a direct effect on the brain or is it the challenges and difficulties people with Fabry experience that have mental consequences? In addition, one can also wonder to what extent the mental decline is caused by Fabry instead of the normal aging process that everyone goes through. The same kind of cognitive problems that are seen with Fabry fog also occur with aging. Research in this area often contradicts each other. What is certain is that taking good care of yourself has a positive influence on your mental health.

- Taking good care of yourself may look like this
- Decorate your workplace with pictures of things that make you happy
- Put on headphones when you are working and listen to some music
- Use your lunch breaks to have lunch with your colleagues, take a walk or read a book
- Treat yourself to a massage
- Regularly meet up with a close friend
- Go do something fun, e.g. a game, gardening, painting, etc.

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The role of biomarkers (Paediatrician Prof. dr. François Eyskens, Belgium)
The diagnosis of Fabry can be made in several ways. Since it is a hereditary condition, Fabry in the family history is a clear cause for further research. Although a genetic test can provide clarity, not all mutations that cause Fabry are known yet. That is why we also look at the presence of certain substances, called biomarkers, that can indicate that someone has Fabry. Someone with Fabry generally has little alpha-galactosidase A in the blood and a lot of globotriaosylceramide (Gb3), although this does not apply to all patients. In women, for example, the amount of Gb3 does not say much, so it is necessary to also look at other substances. Lyso-Gb3 is a substance that is very similar to Gb3 and is a more reliable measure for diagnosing Fabry than Gb3 alone. Ideally, testing should be done on as many biomarkers as possible to get the best possible picture. It is also important that these values are checked regularly so that the course of the disease can be tracked. Because Fabry is a rare disease and relatively little long-term research has been done on it, doctors are often unaware of the various options for making the diagnosis. A clear protocol for diagnosis and monitoring is therefore important.

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Arrhythmias in Fabry disease (Cardiologist Dr. Ashwin Roy, United Kingdom)
In Fabry disease, an accumulation of sphingolipids (a type of fat cell) causes thickening of the heart, also known as hypertrophy. At a later stage, inflammation (inflammation) can also occur and scar tissue forms on the heart muscle. In addition, the conduction system of the heart - which is important for controlling the heart rhythm - can be affected. These factors put people with Fabry at high risk for cardiac arrhythmias, heart attacks, and strokes. A change in heart rhythm may be an indication that heart function is deteriorating. In that case, an intervention is sometimes necessary, such as the placement of a pacemaker, to reduce the risk of heart failure. It is therefore important to monitor whether changes occur in the heart in people with Fabry who have cardiac hypertrophy. These types of abnormalities can be detected with MRI scans or ultrasound. This is just a snapshot, and usually does not reflect all information. Nowadays it is possible to implant a heart rhythm monitor. This small device is inserted just under the skin and can constantly monitor the heart rhythm for 3 years. This appears to be very effective and makes it easier for cardiologists to make a risk assessment.

The GLA gene; Fabry and women (Medical Geneticist Prof. dr. Dominique Germain, France)
For a long time it was assumed that women were only carriers of the mutation in the GLA gene and that they suffered little or no symptoms from Fabry. This idea arose from the fact that women have 2 X chromosomes. If 1 chromosome has the faulty gene, the other X chromosome could compensate for it. However, this image is incorrect, because women often do have symptoms. However, the severity of this varies greatly. Here's how: early in embryonic development, it is determined for each group of cells which of the two X chromosomes will be active. This process is random, so most women will have roughly an equal distribution of cells with the wrong gene and cells with the correct gene. In these women, the symptoms usually start a little later than in men, but treatment is necessary. However, there are also women who have mainly unaffected cells and women who have mainly affected cells. The latter group is most affected by the symptoms and may even develop a course of disease such as that commonly seen in men. It is possible to study the proportion of cells that cannot make alpha-galactosidase A. In this way, a good estimate can be made of how the disease will develop later. If many cells are affected and therefore there is little enzyme in the body, it is important to start treatment as early as possible.

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Gene therapy (Haematologist Prof. dr. Derralynn Hughes, United Kingdom)
Although treatment for Fabry disease is now available in most countries, there are still a number of challenges in this area. Not every treatment is successful, for example due to the development of antibodies in enzyme replacement therapy. Besides, people are still getting diagnosed too late and the damage in the organs that is often already there cannot be reversed. Under the motto of 'prevention is better than cure', people are looking for a treatment in which it is no longer necessary to regularly receive a drug. For example, gene therapy offers the possibility of replacing the 'wrong' GLA gene with a 'good' version of it. If this is successful, the body produces enough enzymes on its own and there is no more accumulation of Gb3. This technique is already used in other diseases, such as various forms of cancer. In fact, people who have been vaccinated with the Pfizer or Moderna corona vaccine have already had some form of gene therapy! Although there are still many questions surrounding gene therapy in Fabry disease - such as how exactly the faulty GLA gene should be replaced - it appears to be a promising treatment technique that will hopefully become available in the future.

Discussion on Fabry variant D313Y (Fabry patient Berthold Wilden, Germany)
In Fabry disease, there are several types of mutations that can cause too little enzyme to be produced. However, it is not (yet) officially known whether some mutations are actually 'responsible' for Fabry disease. In some cases it is therefore difficult to get acknowledgment that Fabry is indeed involved.

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Kidney Disease News (Nephrologist Dr. Alberto Ortiz, Spain)
Many people with Fabry suffer from decreased kidney function; in men, a kidney transplant is often required. The primary function of the kidneys is to keep the dissolved substances in the blood constant through filtering. This filtering takes place mainly in special cells in the kidneys, the podocytes. With age, one gradually loses these structures and kidney function deteriorates. In Fabry patients, this decline occurs much faster. This is because the podocytes in Fabry patients are packed with glycolipids, causing more podocytes to be lost. Recently, there are certain medicines (the so-called SGLT2 inhibitors) that are used for different types of kidney problems. These means, as it were, ensure that the kidneys have to work less hard. It is believed that this may also limit the process of podocyte loss in order to maintain renal function. For that reason, SGLT2 inhibitors are also prescribed to people with Fabry. This may help delay or even prevent a kidney transplant.

Nutrition (Naturopath Dr. Seema Kanwal, Canada)
Gastrointestinal complaints are the order of the day for about half of the Fabry patients. It is not exactly clear why these complaints are common, but it is thought that the problems mainly arise in the small intestine. This often results in complaints such as diarrhoea, constipation, abdominal pain, nausea and vomiting. These complaints often persist even when treated with enzyme replacement therapy or chaperone therapy. Correct nutrition can often help to reduce these kinds of complaints, although it differs per person what works and what does not. First of all, it is important to find out whether there is an allergy or sensitivity to certain ingredients of food such as gluten or lactose. It is also possible that there is a shortage of certain nutrients such as choline. This is mainly in animal products, but also in certain types of vegetables and nuts. Pro- and prebiotics can also help balance the right bacteria in the gut (microbiome), which benefits digestion. In addition, it is recommended – especially women – to eat well only a few times a day and not to eat anything for 12 hours after dinner. In this way, the digestive system can, as it were, get a 'reset'.
Tips for gastrointestinal complaints at Fabry

- Choline-rich foods
- Eggs (whole egg)
- Meat
- Poultry
- Fish, shellfish, shrimp
- Cruciferous vegetables (Brussels sprouts, broccoli, cauliflower, but this can backfire for some people (containing vinegar can help)
- Walnuts, hazelnuts, almonds
- Probiotics
  - Kimchi
  - Kefir
  - Kombucha
  - Sauerkraut
- Yoghurt
  - Prebiotics
- Jicama (yam bean)
- Green from the dandelion
- Garlic
- Chicory root
- Jerusalem artichoke
- Quit dairy
- Other sources of calcium such as salmon, sardines, almonds (sometimes soaked in water before eating), bok choy, broccoli, spinach, sweet potato

Fabry Australia (Fabry patient Dianne Wallyn, Australia)
Curious about how to tell children about Fabry? In Australia, a special booklet has been published to help children – who have Fabry themselves or have a relative with the disease – understand what it is like to live with Fabry. Look at https://youtu.be/6dMsoiXqqdk for the story of Faber the dragon.

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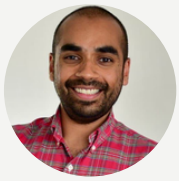
Meet the experts!



Dr Ashwin Roy is a Cardiology registrar from **Birmingham, UK** undertaking a PhD investigating arrhythmia in Fabry Disease. He is involved in a multi-centre clinical trial assessing the use of implantable loop recorders in Fabry Disease. He is also undertaking laboratory based work using iPSC-derived cardiomyocytes with the N215S GLA mutation. His particular interest is imaging markers of arrhythmia.

Dr Nadia Ali is Director of Psychological Resources for the Emory Genetic Clinical Trials Center in **Atlanta, USA** where she participates in clinical drug trials for genetic conditions, as well as conducting her own clinical research into neurocognitive and psychological manifestations of lysosomal storage diseases and other metabolic disorders. She is co-author of the book, "Transitions: Managing Your Own Healthcare: What Every Teen with an LSD Needs to Know."

Dr. Ali also serves as Co-Assistant Director of the Emory Genetic Counseling Master's degree training program, where she trains future genetic counselors in the counseling skills necessary for compassionate, effective patient care. Dr. Ali earned her doctorate in Clinical Psychology from the University of South Florida and completed both an internship in Neuropsychology and a post-doctoral fellowship in Health Psychology.

Prof Dominique P. Germain is Professor of Medical Genetics at the University of Versailles (UVSQ), and head of the Division of Medical Genetics at the Raymond Poincaré Hospital (AP-HP) in **Garches, France.** He is also Director of the French Referral Center for Fabry disease in Garches, France. In 2016, Prof Germain was appointed Director of a European Referral Centre for rare disorders (MetabERN: rare metabolic diseases) at the Hôpitaux Universitaires Paris Ile de France Ouest.

In 2017, he also became the Director of a Centre of Expertise for developmental disabilities band rare disabling congenital malformations. He has a strong interest in enzyme replacement therapies, chaperon therapies, the genetics of neuro-muscular diseases, and the use of clinical exome sequencing for deciphering unknown disabling genetic diseases.

Throughout his career, Prof Germain has contributed extensively on the topics of Fabry disease and hereditary diseases of connective tissue. He has written several book chapters and has published over 130 peer-reviewed papers in medical journals.

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Meet the experts!

Dr Seema Kanwal has been a practicing naturopathic doctor in Vancouver since 2006 and is the only Naturopathic doctor trained in **Canada** in the Apo E Gene diet. She has extensive experience with and is passionate about working with individuals who have rare genetic diseases and suffer many stress related conditions as a result such as mental health issues, insomnia, and low energy.

She helps to guide people living with rare diseases to increased mental wellness, energy, vitality and an overall higher standard of life – they often didn't know was possible to experience with their condition.

She has 10 years of experience in sport medicine and treating a wide range of conditions such as cancer, hormonal imbalances for women and men, stress related conditions, pre and post natal care, cardiovascular disease, chronic fatigue, autoimmune, thyroid imbalances, digestive issues (IBS, Chron's, Candida), Alzheimer's (through the APOE Gene), sports related injuries and many more.

Dr Robert J. Hopkin, is an associate professor of clinical pediatrics at Cincinnati Children's Hospital Medical Center within the University of **Cincinnati** College of Medicine. Dr Hopkin graduated from the University of Nevada Medical School. He completed residency and chief residency in pediatrics at the Phoenix Children's Hospital, Maricopa Medical Center Combined Residency Program. His training in medical genetics was completed at Cincinnati Children's Hospital Medical Center.

The majority of Dr. Hopkin's time is spent in caring for patients with genetic disorders. He participates in clinics from Fetal Care to Adult Genetics. He is also actively involved in education of health care providers regarding the application of genetics for patient care. Dr Hopkin has participated in a number of clinical trials and is a member of American College of Medical Genetics Committee on Therapeutics.

He has participated in natural history studies on Fabry disease, Pompe disease, velocardiofacial syndrome, Pierre Robin sequence, neurofibromatosis type I, and several other genetic conditions. The unifying principle in his research interests is application of scientific knowledge to improve outcomes for patients afflicted with genetic disorders.

Annelies Sweeb is 61 years old and Fabry affected. She is the President of FSIGN and mother of two daughters. Erica van de Mheen is 66 years old, Fabry affected, she is the Vice President for FSIGN and mother of two daughters. Both are living in The Netherlands.

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Meet the experts!

Prof. Derralynn Hughes is Professor of Experimental Haematology at the University College **London**, Clinical Director of Research and Innovation at the Royal Free London NHS Foundation Trust, and Co-Clinical Director of the NCL cancer Alliance. She is also chair of the European Working Group on Gaucher Disease.

She has clinical responsibilities in the area of Haematology and Lysosomal Storage Disorders and is chair of the anaemia clinical practice group. She directs the research programme in the LSD unit where interests include understanding the pathophysiology of phenotypic heterogeneity in Fabry Disease and bone related pathology in Gaucher disease and malignancy.

Prof Hughes is Principal Investigator of a number of clinical trials examining the efficacy of Enzyme, Chaperone and gene therapies and other new agents in the treatment of Gaucher, Fabry, Pompe and MPS disorders. A particular interest relates to the clinical and biological effects of bone disease and malignancy in Gaucher disease. She is an author of over 150 papers in the area of macrophage biology and lysosomal Storage Disorders.

Dr Alberto Ortiz is Chief of Nephrology and Hypertension at the Health Research Institute of the Jiménez Díaz Foundation (IIS-FJD UAM), **Madrid, Spain,** and Professor of Medicine at the Autonomous University of Madrid (UAM). Professor Ortiz's research interests include the pathogenesis and treatment of acute kidney injury, diabetic nephropathy and proteinuric chronic kidney disease, vascular injury in kidney disease, Fabry disease, and systems medicine.

He is Editor-in-Chief of the Clinical Kidney Journal, an editorial board member of the Journal of the American Society of Nephrology, a council member of the European Renal Association (ERA-EDTA), a member of European Uremic Toxins (EUTox) Work Group and European Renal Best Practice (ERBP) Organization, coordinator of the Spanish Renal Research Network (REDINREN), ERA-EDTA Award for Research Excellence 2020, Distinguished Fellow of the ERA-EDTA, and corresponding member of the Spanish Royal National Academy of Medicine.

Dianne Wallyn received the unexpected Fabry diagnosis in 2009 after her sister pursued a diagnosis to heart problems. A Brisbane cardiologist first suggested Fabry disease but was obliged to eliminate all other possibilities before requesting the genetic test. After her sister's positive diagnosis, Dianne was told she had a 50 percent chance of having the disease. Ever the optimist she assumed the best, however several weeks later the call came in to say that she had also tested positive.

Dianne is incredibly grateful for the support she received from Fabry **Australia** in those early days and is pleased to serve on the board to assist others with this disease. She calls the Sunshine Coast home and enjoys a laidback country lifestyle and she shares this with her husband and two very spoilt dogs.

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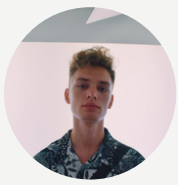
Meet the experts!

Prof François J. M. Eyskens, MD, PhD is the head of the department for the Metabolic Disorders in children (University Hospital of Antwerp, BE). Center of Inherited Metabolic Diseases, Metabolic Lab (PCMA vzw). He did his medical studies at the University of Antwerp. After his training in paediatrics at the Kinderziekenhuis Antwerpen, he became a pediatrician in 1989. His training in metabolic diseases took place in the Wilhelmina Kinderziekenhuis, Utrecht, The Netherlands. From 1987 till now he is involved in the neonatal mass screening program in Antwerp at the Provinciaal Centrum voor Metabole Aandoeningen (PCMA).

In 1997 he obtained his Degree of Doctor in Medical Sciences (PhD) defending his thesis "Neonatal Screening. The Experience in Antwerp". Actually he is working as a chief of clinics in Paediatrics at the University Hospital of Antwerp (UZA) and coordinates the Center of Metabolic Diseases (CEMA) located at the sites of UZA and ZNA.

He is the executive director of the PCMA vzw, the metabolic laboratory, where the analysis of different metabolic compounds is performed. He is an associate professor at the University of Antwerp (Dept of Medicine; Laboratory of Experimental Medicine and Pediatrics). Specific domains of interest and research: creating awareness and screening for inherited metabolic diseases in the neonatal period and in populations at risk ; organic acidurias; lysosomal storage diseases (innovative therapies); learning and cognitive disturbances due to inherited metabolic diseases; psychiatric disturbances as first clinical presentation of inherited metabolic diseases.

Dr Berthold Wilden was diagnosed with Fabry in 2013 and has been a dialysis patient since 2017. He is the President of Morbus Fabry Selbsthilfegruppe (MFSH), i.e. the **German** Fabry Disease Patient Organization, since 2020. However, he is actively working in the group in various positions since 2015. After school, Berthold worked as a chemical lab technician before starting to study chemistry. After his first exams, he switched to biochemistry, where he also earned his PhD. He then worked in the field of clinical and later preclinical research, mainly in quality assurance. Since 2020, Berthold has no longer worked and is now an early retiree.



Wojciech Nadolski is a representative of the Association of Families with Fabry Disease in **Poland**, actively working to improve the situation of patients with Fabry disease. Wojciech has been affected by Fabry since his birth. He is a passionate photographer and traveller.

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Empowering people living with Fabry

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