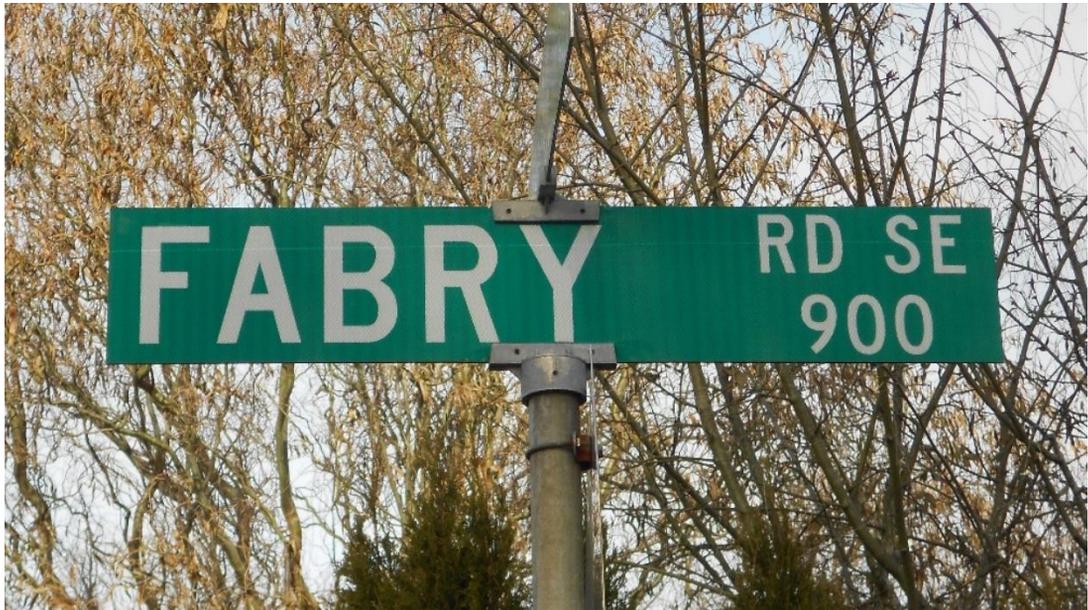


National
FABRY DISEASE
Foundation

The
Fabry Disease
Community Landscape



... a starting point on a road
less traveled

by Jerry Walter, Founder and President, NFDF

As of November 9, 2018

Table of Contents

- Cover – A starting point on a road less traveled
- Page 2 – Table of Contents
- Page 3 – Introduction and the F word (Fabry)
- Page 4 – Awareness information ... Commonly asked questions
- Page 5 – Fabry support organizations
- Page 6 – Where to find information
- Page 7 – The virtual community ... face book
- Page 8 – Fabry disease inheritance
- Page 9 – How many people have Fabry disease?
- Page 10 – The Fabry population (one possible scenario)
- Page 11 – Emergency information ... What should you carry?
- Page 12 – More about the National Fabry Disease Foundation
- Page 13 – How does the NFDF contribute to research?
- Page 14 – Fabry disease testing
- Page 15 to 18 – Explanation of Fabry mutations
- Page 19 – Fabry Disease Treatment Options
- Page 20 – Other topics to be addressed

Please send comments to Jerry Walter at jerry.walter@fabrydisease.org

To receive updates of this document subscribe to our newsletter service.

Comments and suggestions are welcome!

Introduction



There is a great deal of published literature about Fabry disease and there are many resources available to support individuals with Fabry disease and their families. Still, finding the answers you are looking for and finding the resources you need are not always easy. With this document, we are trying to make your journey a little easier. This document does not focus on disease education itself but rather on common questions that arise as well as helpful information and resources.

If you have suggestions for this document, please let us know by sending an email to Jerry Walter at jerry.walter@fabrydisease.org.

Some resources we tell you about may include inaccuracies because the facts have changed since a document was written or because the author(s) has/(have) not kept up with current research. We'll address a few of these issues such as the outdated information about females with Fabry disease in many older publications.

Let's start by talking about the "F" word itself. You have probably wondered which of the names you hear is the most appropriate name.



In 1898 Dr. William Anderson from England and Dr. Johann Fabry from Germany independently described what is now most commonly referred to as Fabry disease among its many other lesser used names.

One would think Fabry disease would always be called Anderson-Fabry disease to consistently give both physicians credit. To the contrary, the most common name used in literature is simply Fabry disease. The other somewhat common names, Anderson-Fabry disease and Fabry's disease are used in literature much less.

We searched PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) to access the U.S. National Library of Medicine's database of world-wide journal articles for Fabry disease. There are well over 4,000 articles about Fabry disease available as of this date (September 2018). Looking at the article titles alone at that time, an overwhelming majority of the articles published over the last 10 years use the name "Fabry" rather than "Anderson-Fabry" or "Fabry's".

So, with this trend among physicians and researchers, the NFDf consistently uses the name **Fabry disease** (singular). Why swim upstream and add to the confusion?

Fabry Disease Awareness Information

Commonly Asked Questions

Do we have an awareness month, day or year?

We celebrate **Fabry Disease Awareness Month** in the U.S. and in a few other countries in **April**. In the U.S. the National Fabry Disease Foundation and the Fabry Support & Information Group (FSIG) work with Fabry community members in each state to obtain as many official state governors' proclamations as possible. We recognize Fabry disease awareness in April in every state but not every state has an official program or some State governors will only grant a week or a day.



Every first Saturday in April we celebrate International Fabry Women's Day, started by the Fabry Support and Information Group Netherlands.

Do we have a color for ribbons and other awareness materials?

Based on community input the NFDF, FSIG and the Canadian Fabry Association (CFA) use dark blue as our awareness color. On the PMS color chart it is PMS 541 shown to the right.



Do we have a ribbon?

The Fabry community's ribbon is a product of many Fabry community members and the support organizations working together. We use the ribbon design in electronic media and to make awareness products such as car magnets, bumper stickers, lapel pins, ribbon, pins, etc.



Do we have a T-shirt?

In 2013 an NFDF volunteer designed the "I define me" T-shirt for our annual Fabry Family Conference. We adopted it as our hallmark T-shirt. The NFDF provides the T-shirt at our annual national conference and by mail.

Do we have wristbands? The NFDF (royal blue), FSIG (light blue) and the CFA all have awareness wristbands and FSIG has a medical alert wristband (red).

Fabry Medical Alert Cards are available. The FSIG has a wallet alert card and the NFDF has a wallet USB drive alert card for Fabry community members upon request.

NFDF T-shirts, wristbands, USB alert cards, and other products are available by sending an email jerry.walter@fabrydisease.org.

Fabry Support Organizations

There are two primary patient support organizations in the United States that are dedicated solely to Fabry disease. Both organizations are registered IRS 501(c)(3) non-profit charitable organizations.



National
FABRY DISEASE
Foundation

Our organization the **National Fabry Disease Foundation (NFDF)**, founded in 2005, is currently led by Jerry Walter.

Website: www.fabrydisease.org Email: info@fabrydisease.org Phone: 800-651-9131. See the NFDF's program handout in the Featured Resources Section of our website.



The **Fabry Support & Information Group (FSIG)** was founded in 1996 and is currently led by Jack Johnson.

Website: www.fabry.org Email: info@fabry.org Phone: (660) 463-1355

The two complimentary U.S. organizations have common broad goals to support the Fabry community and between us we have a very diverse set of valuable programs and services to support people with Fabry disease and their families.

canadian **fabry** association
l'association canadienne de **fabry**

In Canada, the Fabry community is supported by the **Canadian Fabry Association (CFA)** currently led by Julia Alton. Website: www.fabrycanada.com



In Australia, the Fabry community is supported by **Fabry Australia** currently led by Megan Fookes.

Website: <https://www.fabry.com.au/>



In the United Kingdom, the Fabry community is supported by **The MPS Society UK** currently led by Bob Stevens.

Website: www.mpsociety.org.uk



Many other countries have similar Fabry disease support organizations. To find other country organizations, visit the members section of www.fabrynetwork.org.

Patient Services Incorporated (PSI) at www.patientservicesinc.org and **The Assistance Fund (TAF)** at <https://tafcares.org/> are non-profit organizations in the U.S. who provide financial assistance including insurance premium assistance and other financial support related to Fabry disease healthcare needs.



Where to find information

You can find the National Institutes of Health's (NIH's) description of Fabry disease at <https://www.ninds.nih.gov/Disorders/All-Disorders/Fabry-Disease-Information-Page>. This is one of many resources describing Fabry disease.

You can find thousands of peer-reviewed articles about Fabry disease at PubMed - NCBI, PubMed Central (only full-text articles), Europe PubMed Central, PubMed Central Canada, and possibly other countries' library sites by typing "Fabry disease" in each sites' search field? <http://www.ncbi.nlm.nih.gov/pubmed>.

You can find out about Fabry disease research/clinical trials at the U.S. clinical trials registry site at www.clinicaltrials.gov and many other clinical trial registry sites in other countries? Clinical trials in www.clinicaltrials.gov also include information about the non-U.S. clinical trial sites for those trials listed. You can search "Fabry disease" then narrow your search by checking the open studies box.

At GeneReviews (<http://www.ncbi.nlm.nih.gov/books/NBK1116/>) you can find expert-authored, peer-reviewed disease descriptions ("chapters") presented in a standardized format and focused on clinically relevant and medically actionable information on the diagnosis, management, and genetic counseling of patients and families with specific inherited conditions.

You can find information about Fabry disease in the Genetics Home Reference at <http://ghr.nlm.nih.gov/condition/fabry-disease?>

Pharmaceuticals companies involved in Fabry disease have various forms of Fabry disease literature/educational materials available upon request on their websites.

You can subscribe to Google Alerts for Fabry disease news. However, you will also receive many alerts about pharmaceutical company news along with other Fabry community news.

A WORD OF CAUTION: When searching the internet for Fabry disease information you will find information that is inaccurate or not up-to-date. The best sources of information for disease education are peer-reviewed journal articles and patient reported outcomes survey reports reporting on large numbers of participants.

The virtual community (face book)

There are many social media sites available to the Fabry disease community. The difference between face book Pages and Groups: Pages allow organizations, businesses, etc to communicate broadly with people who “like” them. According to face book, Pages may only be created and managed by organization representatives. Groups provide a space for people to communicate about shared interests. Groups can be created by anyone. We would recommend using existing sites rather than creating new ones.

The **National Fabry Disease Foundation** has a face book **Page** with over 2,900 “Likes” at www.facebook.com/FabryDisease. We encourage everyone to “Like” and follow our page. Much of the information we provide to you is posted here first before our newsletter or website.

Pages mostly offer information shared by the organization or entity. **Groups** have more active discussions and provide a great deal of information and mutual support. It is great to be able to interact with people who are so geographically dispersed that you may never meet in person. Local, regional and national meetings also allow opportunities to meet.

The other most popular/most used Pages and Groups that we know about are below.

Fabry’s Disease Info and Support (Not to be confused with Fabry Support & Information Group) at <https://www.facebook.com/groups/Fabry.Disease.Info.and.Support/>. Closed group for privacy reasons. You may request membership.

Fabry Support & Information Group at <https://www.facebook.com/Fabry.org/>. This is the largest of the sites other than our page.

Fabry Support Group at <https://www.facebook.com/groups/fabrysupport/>. Members can add others to this group. It is a secret group for privacy reasons.

Fighting Fabry Disease at <https://www.facebook.com/fightingfabry/>.

Not Defined by Fabry at <https://www.facebook.com/groups/1508471869386119/>.

Canadian Fabry Association at <https://www.facebook.com/groups/27694413535/>.

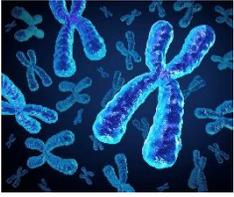
Fabry Australia at <https://www.facebook.com/groups/FabryAustralia/>.

Fabry’s Disease. UK and Beyond at <https://www.facebook.com/groups/379212685584848/>.

Morbus Fabry Interessengemeinschaft (Germany) at <https://www.facebook.com/morbusfabry.interessengemeinschaft>

Please keep in mind that each of us with Fabry disease is an expert about our own disease but what may be true for one person may not be true for another. If you read information about symptoms, medications, management, etc. please ask your physician before taking the advice of a fellow patient or family member. Please verify information before you share something you’ve heard from someone else or read on face book as it may not be accurate for everyone.

Inheritance



The Fabry disease gene (GLA) is on the X-chromosome. Therefore Fabry disease is inherited in an X-linked manner. The X and Y chromosomes, two of the 23 pairs of chromosomes in the body, among many other functions, determine the sex of an individual. Females have two X chromosomes. Males have one X chromosome and one Y chromosome.

Fabry affected males pass their X chromosome to all of their daughters. In this way, all daughters of affected males will have the gene for Fabry disease. This is assuming paternity is not of concern.

Affected males do not pass the Fabry disease gene to any of their sons. Sons receive their father's Y chromosome and cannot inherit FD from their father.

Every time a female with the Fabry gene has a child, there is a 50% chance that she will pass her affected X chromosome to the child, and a 50% chance that she will pass her normal X chromosome to the child. This means there is a 50% chance that every daughter and every son born to a female with the Fabry gene will inherit the affected X chromosome and have the Fabry gene.

As recently as 2001 it was believed that Fabry disease was a typical X-linked recessive disease in which females were carriers only and could not have symptoms. However, researchers and treating physicians have learned that females without Fabry disease symptoms are the exception not the rule.

Many females have symptoms as severe as males with classic Fabry disease, while others may be seemingly asymptomatic, only experience mild symptoms, or exhibit any degree of symptoms in between. A high percentage of females carrying the Fabry disease gene are affected and have many significant symptoms. One study reports 69% of females have symptoms and signs of Fabry disease.

It is generally preferred to refer to a female with the Fabry disease gene but who doesn't have symptoms as an asymptomatic female rather than a "carrier". In medicine, the term "carrier" is usually reserved for a female who is a carrier but CANNOT have symptoms such as with an X-linked recessive disease.

When a gene mutation spontaneously occurs in a family for the first time rather than by inheritance, it is called a de novo mutation.

How many people have Fabry disease?

If you are an individual with Fabry disease or a family member, knowing how many people have Fabry disease is probably not that useful but it's interesting. To researchers, policy makers, drug suppliers, investors, businesses that provide support to care, etc. the number is probably much more useful.

The numbers reported are usually discussed in at least three ways: Incidence, prevalence and the number of people affected.

Incidence (rate of appearance): the number of new cases in a given period of time (day, month, year). Fabry disease newborn screening is a good example. The 2013 six-month, full-state population screening in Missouri revealed a Fabry gene mutation detection rate of a staggering one in 2,913 newborns. Ongoing research indicates many of these detected gene mutations may not cause Fabry disease symptoms but there will still likely be many more people with classic and non-classic Fabry disease than historical estimates indicate.

Prevalence: the proportion of cases at a specific point in time. It is usually expressed as a fraction, a percentage or a number per 10,000 or 100,000 people, etc., such as the commonly used U.S. estimate for Fabry disease described in the National Institutes of Health Genetics Home Reference which states "Fabry disease affects an estimated 1 in 40,000 to 60,000 males." This enables one to calculate an estimate of how many people have Fabry disease at any point in time. But the math is not easy for all categories of people with Fabry (males with a classic mutation, females with a classic mutation, males with a non-classic mutation, females with a non-classic mutation, people with a non-disease causing mutation).

Why are the numbers usually quoted in terms of males? What about females, they are affected also?

The statistics are often quoted in terms of males because with an X-linked inheritance pattern the estimated numbers of males with Fabry disease are easier to determine.

The bottom line: The number of people that have Fabry disease is a very difficult number to calculate. No one really knows how many people are affected but we'll provide some possible numbers and further explanations on the following page.

Fabry Population (one possible scenario)

To follow up on the previous explanation of how many people have Fabry disease, here is an estimate of the U.S. population using the prevalence of 1 in 40,000 to 60,000 (average 1 in 50,000) males cited by the National Institutes of Health.

The estimated U.S. population in 2016 is about 323 million people. The percentage of males and females per year is usually about 50% each.

Estimated males with classic Fabry disease: Half of 323,000,000 people equals 161,500,000 males. Therefore, males with FD equals $161,500,000/50,000$ for a total of 3,230 males in the U.S.

Genetic math states twice as many females inherit an X-linked gene as males which equals about 6,460 females with the Fabry gene in the U.S.

A 2008 study of 1077 females in the Fabry Registry indicated 69.4% females had symptoms and signs of Fabry disease. This yields an estimate of about 4,483 affected females and a total estimated U.S. Fabry population (males and females) of **7,713** based on the current prevalence rate. Only about 4,000 to 5,000 people are known in the U.S. so far.

Now consider the 2013 Missouri newborn screening result with a 1 in 2,913 detection rate applied to the entire U.S. population of 323 million people. $323,000,000/2,913$ is about 110,882 people with a Fabry gene mutation. Even if only 25% of those detected have a mutation that causes symptoms, the estimated population would be about **27,720** people with classic and non-classic Fabry disease in the U.S. alone.

Please do not quote these numbers as proven population numbers but they represent a very real possibility and may still be very conservative numbers.

Many in the Missouri study will likely have a non-classic form of disease (which could still cause significant symptoms especially heart and kidney problems) or a non-disease causing form of the Fabry mutation. More to come!

Bottom line: We suggest there are thousands of people unknowingly living with classic and non-classic Fabry disease in the U.S. and around the world.



Emergency Information



In an emergency patients should report they have Fabry disease. Emergency medical personnel should be made aware that people with Fabry disease may experience cardiovascular, cerebrovascular and renal disease at a younger age which may include heart disease, abnormal ECGs, Left Ventricular Hypertrophy, arrhythmias, heart failure, TIAs/stroke, proteinuria and other symptoms of kidney dysfunction. Emergency medical personnel may want to check kidney function as it can be low in Fabry patients and this may affect which type of initial testing is obtained and also alert care providers about prescribing any medications potentially toxic to the kidneys.

Items to always have with you

1. Primary and secondary emergency contact information
2. Who can make medical decisions in the event you cannot communicate them yourself and the location of your living will, medical power of attorney, DNR order, etc.
3. Contact information for your primary Fabry physician, primary care physician if different, and key specialists such your cardiologist, nephrologist, neurologist, and others as needed
4. Insurance cards
5. A list of allergies (medications, food and environmental allergies)
6. A list of prescription medications, over the counter medications and supplements
7. Things that have not worked in the past such as meds for pain or severe lymphedema
8. A copy of your most recent ECG especially if you have an abnormal ECG
9. Existing conditions/chronic illnesses: (Fabry disease, Chronic Kidney Disease, etc.)
10. Existing Fabry symptoms like angiokeratomas, lymphedema, or other visible manifestations
11. Any major illnesses/events with dates: such as heart attack, stroke, kidney failure and others major illnesses bacterial meningitis, Guillain-Barre, rheumatoid arthritis, etc
12. Past hospitalizations with dates
13. Past surgeries with dates
14. Vaccinations: Flu, tetanus, pneumonia, TB screen, Prevnar 13, etc.
15. Physical limitations: corrected vision prescription/eyeglasses, hearing loss information/hearing aids, impaired mobility information

Thank you for contributions to this page from these experienced Fabry disease physicians: Dr. Rob Hopkin (Geneticist), Dr. William Wilcox (Geneticist), Dr. John Jefferies (Cardiologist), Dr. Andrew Lundquist (Nephrologist), Dr. Katherine Sims (Neurologist), and Dr. David Warnock (Nephrologist).

Please request a **“My Health Handbook Kit”** to keep all your information by emailing Jerry at jerry.walter@fabrydisease.org. See the NFDf program handout.

More about the National Fabry Disease Foundation

Established by Jerry Walter, Founder and President, in June 2005 as a U.S. Internal Revenue Service (IRS) 501(c)(3) non-profit charitable organization.

Vision: No longer will any individual's quality of life be diminished, nor will their lives be shortened because of Fabry disease.

Mission: To help ensure all individuals with Fabry disease are identified, diagnosed and treated in time to avoid a diminished quality of life or life threatening consequences, to provide assistance to individuals with Fabry disease and their families, to provide Fabry disease education and awareness, to promote continued data-gathering and research to improve treatment opportunities and to find a cure.

Slogans the NFDF uses:

Giving more life to our children's years and more year's to our children's lives!
(This slogan is adapted from the Belgium Fabry disease support organization.)

Fighting Fabry Disease ... Living Better Longer (on our wristband)

Fighting Fabry disease for better and longer lives

Trademarked Programs:

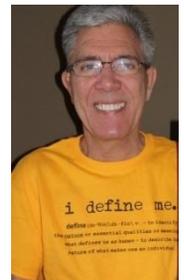
Work up a sweat for someone who can't™

Break a sweat for those who can't™

Hallmark programs:

- We have a **R.A.R.E.** opportunity to **Recognize And Rescue Everyone** with Fabry disease.
- The Eyes Have It campaign (working with eye doctors)
- The Connecting the Dots campaign (working with dermatologists)
- The Fabry Legion – the Fabry community's Army fighting Fabry disease

Our T-shirt theme: The "I define me." T-shirt was first designed and distributed in 2013. T-shirt front: "I define me." T-shirt back: "Fighting Fabry Disease ... Living Better Longer"



Please request our Program Handout for information about our many programs and services, a "My Health Handbook" kit, and an educational symptoms calendar.

Please share information widely about our programs, services and materials.

Website: www.fabrydisease.org | Email: info@fabrydisease.org

U.S. Toll Free: 800-651-9131 or non-toll-free phone: 919-732-2799

How does the National Fabry Disease Foundation contribute to research?

The NFDF occasionally provides funding for small research projects but with limited resources we usually contribute to research in other important ways.

At the NFDF annual conference and occasionally throughout the year we facilitate participation in research being conducted by the medical community. The NFDF has made a significant contribution to the successful completion of many published research articles.

Patient Reported Outcomes Surveys (PROS) – Learning from the pros

Beginning in 2014 the NFDF began administering periodic surveys to the Fabry community. This program provides a great deal of useful information for the following purposes.

- To learn about symptom trends among people with Fabry disease to help identify future research needs
- To provide individuals with questions about Fabry disease to ask their physicians based on the symptom trends of others
- To understand the Fabry community's needs to enable us to revise and expand the NFDF's programs and services as needed
- To understand the collective voice of the Fabry community so the NFDF may represent the community according to your opinions on important issues. We do not want the medical community making critical decisions on important issues without knowing what our community thinks.

In June 2018, the NFDF resumed distributing surveys in the contest format that was very successful in 2014. **Having the greatest number of survey participants possible helps to ensure the survey findings are a good representation of the overall Fabry community.**

PLEASE PARTICIPATE IN NFDF SURVEYS WHEN THEY ARE ANNOUNCED.

Fabry Disease Testing

The test to diagnose Fabry disease is called the GLA gene test. There are two primary methods for testing the GLA gene. Blood samples can be used for DNA sequencing and enzyme analysis. Saliva cannot be used for enzyme analysis, only for DNA sequencing.

In males, an enzyme analysis (enzyme assay) is diagnostic for Fabry disease which means it can be used to confirm whether a male has Fabry disease or not.

In females, an enzyme assay is not diagnostic because females with a Fabry gene mutation may have normal enzyme levels. DNA analysis of the GLA gene must be performed for females.

Various labs test for Fabry disease such as LabCorp, those listed below, and others.

We are aware of three free Fabry testing programs: Mount Sinai School of Medicine (MSSM) in New York City, EGL Genetics via Emory University Medical Center (free with a known family member), and the PerkinElmer Genomics Lantern Project.

Here is a link to Emory's free testing program via EGL Genetics for:

<http://genetics.emory.edu/patient-care/lysosomal-storage-disease-center/lab-testing.html>. Does not perform Lyso-GL3.

For information about MSSM's testing program contact Ms. Loskove at yonina.loskove@mssm.edu or 212-241-7518. Does not perform Lyso-GL3.

For PerkinElmer see <https://www.perkinelmergenomics.com/lanternproject/>. If enzyme levels are low for males or if DNA sequencing is positive for females, free Lyso-GL-3 testing is also completed.

Other labs that perform GLA enzyme analysis, DNA sequencing, and lyso-GL3 for a fee:

Duke University Medical Center (<https://clinlabs.duke.edu/biochemical-genetics-laboratory>) and the Mayo clinic (https://www.mayomedicallaboratories.com/it-mmfiles/Fabry_Disease_Testing_Algorithm.pdf)

Fabry Mutation Repository: PLEASE SEND YOUR MUTATION to jerry.walter@fabrydisease.org. Please send the alphanumeric identifier beginning with a "p." and/or beginning with a "c." We maintain a list of family mutations so we can alert individuals with Fabry of any information published about your mutation or any studies about your family mutation available for you to participate in if you desire.

WE DO NOT SHARE YOUR INFORMATION WITH ANYONE. WE ONLY CONTACT YOU ABOUT OPPORTUNITIES.

Fabry Disease Gene Mutations

(an explanation for lay-people)

DNA is called the “blueprint” for how our bodies function. A gene is a specific sequence of DNA that contains a set of instructions. For example, the Fabry gene is called GLA. The GLA gene is a set of instructions that tells the body how to make the lysosomal enzyme α -galactosidase A (or α -gal A). Genes are made of DNA and DNA is made from nucleotides.

A genetic mutation occurs when a DNA gene is damaged or changed in such a way as to alter the instructions carried by that gene.

Production of enzymes to perform specific functions in the body is similar in some respects to baking a cake. There is a recipe (DNA instructions/nucleotides), baking ingredients (amino acids assembled together), and the finished cake (the resulting enzyme). When ingredients are omitted, extra ingredients are added, or ingredients are substituted, the result may or may not be an edible cake (or enzymes that functions properly).

Some changes in the production of an enzyme don't affect the enzyme's ability to perform its intended function. These are called benign mutations (also called non-disease causing or non-pathogenic mutations). Other changes result in enzymes that do not function properly and cause disease symptoms. These are called disease-causing or pathogenic mutations.

Fabry disease is caused by changes (mutations) in the GLA gene that provides instructions to produce the lysosomal enzyme α -galactosidase A (α -gal A). When α -gal A is damaged or there is an insufficient quantity, the result is lipid accumulation in cells and a cascade of subsequent symptoms.

Fabry gene mutations are usually passed from parents to children but may also occur spontaneously (called de novo mutations) that occur new in a family for the first time.

All members of an immediate and extended family have the same mutation(s), although theoretically, a family member could have another (second) spontaneous mutation not found in parents or siblings that may be passed to his/her children. This would be extremely rare and may never happen. There have been a few cases reported of some families having two inherited Fabry disease mutations simultaneously.

Fabry Disease Gene Mutations (continued)

(an explanation for lay-people)

In medical literature, the most common types of Fabry gene mutations described include missense, nonsense, deletion, and insertion mutations. Missense mutations are the most common Fabry mutations reported but all types occur frequently. A mutation's alphanumeric designation describes the type and location of the error in the GLA gene.

Mutations can be described by their amino acid (protein or "p.") change in a short form and a long form, and by their DNA nucleotide change ("c.") such p.**N215S** (short form), p.**Asn215Ser** (long form), and **c.644A>G** respectively that all describe the same mutation.

A missense mutation is caused by a single nucleotide change that results in the wrong amino acids being used to build the enzyme.

A deletion mutation occurs when one or more nucleotides are inadvertently deleted. The missing sections can be large or small. The designation will include "del" such as 1188delC.

An insertion mutation occurs when an extra nucleotide(s) is inserted into the DNA. The extra sections can be large or small. The designation will include "ins".

A nonsense mutation is one where the GLA gene production is prematurely halted so that no functioning enzyme is produced. It is also called a "null" mutation. The designation is similar to a missense mutation but will have a "Ter" at the end in the long form such as p.Arg220**Ter** (**Termination**) or an "X" or "*" at the end in the short form p.R220X or p.R220*. They will also have a corresponding nucleotide change such as c.658C>T in this example.

Much work is being done to identify a correlation between mutations (genotypes) and the physical characteristics (the phenotype or symptoms) a person exhibits. This work results in the characterization of classic and non-classic disease (disease-causing or pathogenic) mutations and benign (non-disease-causing or nonpathogenic) mutations.

Some mutations are designated as causing "classic disease". Males with classic disease experience most, if not all, the common symptoms of Fabry disease. Levels of α -gal A enzymes are usually at or near zero.

Fabry Disease Gene Mutations (continued)

(an explanation for lay-people)

Other mutations are designated as causing “non-classic disease”. In general, (with possible exceptions) people with non-classic disease have some α -gal A enzyme but lower than normal levels. Typically, they are not expected to have symptoms at a young age but may still have serious cardiac or renal disease similar to those with classic disease as they get into their 30s, 40s and 50s. There is a great deal yet to be learned about non-classic disease and its effects.

For some mutations a genotype-phenotype correlation has not yet been established. While many mutations have been designated to always cause classic or non-classic disease, some mutations have been reported as benign, classic/severe and non-classic in different people with the same mutation. Disease manifestations are even more difficult to predict for these mutations.

The definition of classic and non-classic disease is not always clear based on enzyme levels alone. The classifications seem to be based on an evaluation of enzyme levels, symptoms, and a Fabry disease biomarker called LysoGL3, rather than just levels of enzyme.

Especially with the rise in newborn screening programs, an unexpectedly high incidence of non-classic Fabry disease and various mutations likely to be benign have been discovered. Non-classic disease forms are also called later-onset or variant forms. People with non-classic disease have more enzyme than people with classic disease (none or nearly none) but still have lower levels of enzyme than normal.

Having provided the explanations above, the most important considerations are the specific symptoms that each individual experiences. People should work closely with their physicians to monitor, manage and treat their disease as appropriate!

In addition to the explanations provided above, skewed X-chromosome inactivation in females also plays a role in determining disease manifestations. Because females with Fabry disease have two X chromosomes, either the Fabry affected X chromosome OR the unaffected X chromosome will be turned on in every cell in a female’s body. This results in a mosaic distribution of disease. Females may range from seemingly asymptomatic to having the full range of symptoms seen in males with classic disease.

Fabry Disease Gene Mutations (continued)

(an explanation for lay-people)

Between classic and non-classic disease enzyme levels and female skewed X chromosome inactivation, there are essentially four categories of people with Fabry disease.

1. Males with a classic disease mutation – are expected to have most, if not all, the common symptoms of Fabry disease.
2. Females with a classic disease mutation – have variable symptoms because of a mosaic distribution of affected cells and from skewed X-chromosome inactivation. Females may range from being seemingly asymptomatic to having all the symptoms possible in a male with classic disease.
3. Males with a non-classic disease mutation – have higher levels of enzyme than with classic disease mutations. They usually do not have early symptoms but are at risk for severe heart and kidney manifestations consistent with males who have classic disease.
4. Females with a non-classic disease mutation – have higher levels of enzyme than with classic disease mutations and potentially more (or less) effective enzyme based on skewed X-chromosome inactivation.

The bottom line doesn't really change. Symptoms are difficult to predict and should be managed as evidence of disease is revealed.

Do not consider anything you have read here as the absolute truth nor as medical advice. Verify everything with your physician before taking any actions about your healthcare.

Written by Jerry Walter

Fabry Disease Treatment Options

The future of individuals with Fabry disease looks brighter as research continues. Not only does the Fabry community in many countries have three approved treatments available and the U.S. has two treatments available, many clinical trial investigations for additional treatment solutions are underway.

Approved Treatment Solutions

- Sanofi Genzyme's Enzyme Replacement Therapy (Fabrazyme) available in many countries including the U.S.
- Amicus Therapeutics' Oral Chaperone Therapy (Galafold) available in many countries including the U.S.
- Shire's Enzyme Replacement Therapy (Replagal) available in many countries but not in the U.S.

Investigational Therapies - Potential Treatment Solutions

- Protalix Biotherapeutics' proposed Enzyme Replacement Therapy
 - Sanofi Genzyme's proposed Substrate Reduction Therapy
 - Idorsia's proposed Substrate Reduction Therapy
 - Sangamo Therapeutics' proposed Gene Therapy
 - Avrobio's proposed Gene Therapy
- ... and possibly other potential solutions

Participation in clinical trials is very important to everyone with Fabry disease. Past clinical trials got us to where we are today.

Please consider participating in a clinical trial if there is one that is right for you! See www.clinicaltrials.gov.

Other Topics to be included in the next version:

Which physicians treat Fabry disease?

We appreciate your suggestions on how to improve this document. Email suggestions to Jerry Walter at jerry.walter@fabrydisease.org

From the perspective of a new person finding out they have Fabry, what else should be addressed in this document?

Keep in touch to stay informed. We are always adding and improving our programs.

Please subscribe to our e-newsletter from the orange newsletter icon below the top right of corner of our website homepage at www.fabrydisease.org

Please register at the register/login link at the top of our website.

Please like and follow our face book page at www.facebook.com/FabryDisease

Please participate in our Patient Reported Outcomes Survey (PROs) program. PROs means you, people with Fabry disease!

Please take our periodic surveys to help provide information about our disease and our community.

Thank you for your support and participation!

Sincerely, Jerry Walter