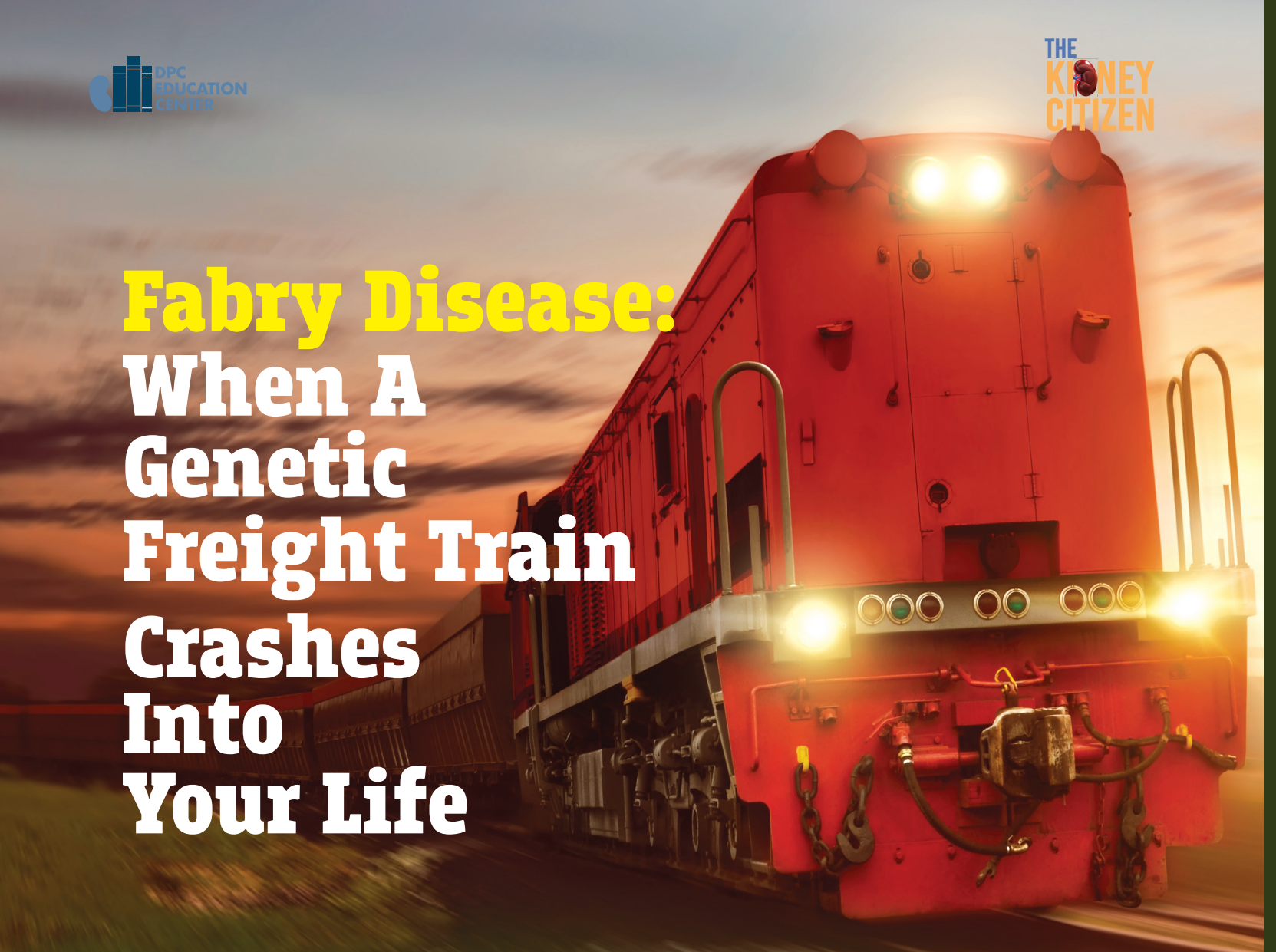

Fabry Disease: When A Genetic Freight Train Crashes Into Your Life

By **Dawn Laney**, M.S., C.G.C.

The year was 2003, and I was preparing to step into an exam room and see a very ill, 30-year old man on hemodialysis. At this point, I was an experienced genetic counselor, but had worked mostly with pregnant women, newborns, and parents. I was not yet aware that walking into this room was a life-altering moment, one that would change the focus of my career and introduce me to the amazing patients, families, and stakeholders of one frustrating, sneaky, life-limiting genetic condition: Fabry disease.

Fabry disease is an inherited, progressive disease that is caused by genetic changes or mutations in the GLA gene that lead to reduced levels of the enzyme alpha-galactosidase A (AGA) in the body. Without enough AGA enzyme, specific molecules in the body that should be broken down instead build up in such a way that the blood vessels all over the body become narrowed. There are two main forms of Fabry disease: a severe "classic" form which impacts health beginning in childhood and a "non-classic" form that leads to early kidney and heart disease but does not start in childhood.

Classic Fabry is like a freight train. The condition starts out slowly, making you wonder if the Fabry train is actually moving. In childhood, kids have stomach pain, overheat easily, and have invisible burning pain in their hands and feet particularly during fevers. They may have a few reddish-purple freckles in their belly button or in the "bathing trunk" region around the groin. Additionally, they may have a non-vision affecting "corneal whorl" that their eye doctor saw on a routine eye exam with the slit lamp. Other than genetic testing for Fabry disease, there is not an easy test that the pediatrician can do to explain the health issues, so kids are often told they are too anxious, having growing pains, or faking illness.

In their teens and twenties, the Fabry freight train picks up speed: the burning pain in the hands and feet is constant, pain crises are more frequent, stomach issues worsen, daily fatigue limits activities more noticeably, and the reddish-purple freckles in their belly button spread. In addition to

those issues, the first measurable medical hints appear: protein in the urine (proteinuria) and a slow heartbeat (bradycardia). In early adulthood, the Fabry freight train begins to come off the rails, roaring down the tracks and leading to kidney failure, serious heart issues including an enlarged heart and arrhythmias, severe and chronic fatigue, depression, anxiety, vertigo, hearing loss, neuropathy and pain in the hands and feet, fluid retention (edema), and eventually, strokes. All of these health issues create a laundry list of life-limiting problems that have patients moving from doctor to doctor seeking answers.

Back at the clinic, when I walked into that room in 2003, I met that exhausted, very ill man who was happy that he had been diagnosed with Fabry disease during a genetics consult by Emory physician, Dr. Paul Fenoff when he was in the hospital. Yes, you read that right, **THRILLED** to be diagnosed with this rushing freight train of a disease. Why? There were three reasons: First, he had an answer to all the pain and miserable health issues he had experienced. It was payback and "I told you so" to all the people who had told him it was all in his head and that his kidney and heart disease was from the drugs he took to dull the Fabry related pain. Second, there was an FDA approved treatment for Fabry disease, and although it was too late to save his kidneys, it hopefully could help stall the progression of Fabry disease in his body and help him have a better quality of life. Third, it explained the "family curse", and maybe all that he had gone through would keep his kids, his mother, his brother, and his cousins from having to suffer without an answer for their medical issues. The earlier they began treatment, the more effective the therapy would be in slowing down the Fabry train.

The patient already knew about the therapy that had been approved by the FDA in April 2003 from his discussions with Dr. Fernhoff at his initial consult, but there were some key facts for us to review. Fabrazyme (agalsidase beta), manufactured by Sanofi-Genzyme, is an enzyme replacement therapy (ERT) designed to replace the enzyme that is lacking in people with Fabry disease. It is given through IV infusion every two weeks. Of course, that is not the only thing used to help treat the symptoms of Fabry disease. Patients with Fabry may also take medications to treat their neuropathic pain, decrease protein in their urine, reduce stroke risk, and address their anxiety and depression. Individuals with abnormal heart rhythms may also be treated with implanted pacemakers or implantable cardioverter defibrillators. For those with end stage renal disease, dialysis (hemodialysis and peritoneal dialysis) and kidney transplant are options. Of course, before kidney transplant, particularly from a family member, it is critically important to know that the donor does not **ALSO** have Fabry

WHAT SHOULD YOU DO IF THIS SOUNDS LIKE YOU?

Did anything about the Fabry disease story sound like you, a family member, or the person getting dialysis next to you? We have included with this article an easy checklist that can help you think about Fabry disease. Take a second to run down the list.

1. Discuss with your healthcare provider your interest in getting tested for Fabry disease. Your doctor may be unfamiliar with Fabry disease, and that is ok. The best place for them to start researching Fabry disease is at GeneReviews.org.
2. Ask your eye doctor if you have corneal whorls. Not everyone with Fabry has them, but if you do it is an important clue.
3. Reach out to the Fabry Support and Information Group or the National Fabry Disease Foundation for help finding a Fabry expert in your area.
1. Talk to a genetic counselor. Find one in your area at: http://www.aboutgeneticcounselors.com/.

DO SOME RESEARCH USING THE RESOURCES LISTED BELOW.

Resources:

2. Fabry Support and Information Group: http://www.fabry.org/
3. National Fabry Disease Foundation: https://www.fabrydisease.org/
4. Fabry information on ThinkGenetic.com: http://www.thinkgenetic.com
5. Emory Fabry resources: http://genetics.emory.edu/patient-care/lysosomal-storage-disease-center/resources.html
6. GeneReviews Summary on Fabry disease: https://www.ncbi.nlm.nih.gov/books/NBK1292/
7. AAKP free family testing project: http://genetics.emory.edu/patient-care/lysosomal-storage-disease-center/lab-testing.html
8. Fabry disease summary sheet at my46.org https://www.my46.org/trait-document?trait=Fabry%20disease&parent=Genetic%20Syndromes&type=profile
9. Fabry community- https://www.fabrycommunity.com/en/Patients/Education/Overview.aspx Studies in Fabry disease
10. Search for Fabry disease on Clinicaltrials.gov https://clinicaltrials.gov/

disease.

That one follow-up clinic visit in 2003 and the dizzying array of follow-up and treatment needs hooked me. I left that visit with as many questions whizzing through my head as the intake coordinators ask you at check-in when you visit the hospital. How can we help more people living with Fabry disease get diagnosed earlier? How many family members can realistically be expected to have Fabry disease after the first person is diagnosed? Does Fabry disease affect men differently than women? What other therapies could help people with Fabry disease live a better life? What could one genetic counselor do to help in this community?

Some of those answers became incredibly clear over the next few years. Fabry runs through families in an X-linked pattern. That means that every woman with Fabry disease has a 50% chance of passing Fabry disease to each of her children. It also means that every man with Fabry disease will pass the gene change causing Fabry disease to **ALL** of his daughters and none of his sons. On average when you find one person affected by Fabry disease, **FIVE** more of their family members will also be affected. In 2003, we had just fully realized that Fabry disease affects both men and women. Today, we know that some women with Fabry disease can be just as severely affected as men and most will have at least one life-impacting symptom of Fabry disease. This means that every woman with Fabry disease needs individualized care, monitoring, and treatment.

Getting tested for Fabry disease takes one simple blood test. For men, testing usually starts with a measurement of alpha galactosidase A enzyme levels in blood followed by DNA testing designed to "spellcheck" the gene and look for mistakes that could cause Fabry disease. For women, the alpha galactosidase A enzyme test will miss many women affected by the disease, and so the DNA test looking at the GLA gene must be done to confirm Fabry disease. Once the gene change is known in a family, then other family members can be tested for the GLA mutation in the family. In fact, there is a program that provides testing for free, and can be done using a saliva or blood sample.

Additionally, now there are studies investigating everything from the impact of Fabry disease on babies diagnosed through newborn screening to gene therapy treatments. In 2017, there are at least four therapeutic approaches being tested through clinical trials, each trying to effectively treat Fabry disease. Once these clinical trials are completed, the FDA will review the evidence and decide which ones will be approved for use in the United States.

As you can see there are plenty of questions that can keep Fabry experts very busy. I have learned that one genetic counselor can help solve a few mysteries of Fabry disease through listening to key things that most impact the people and family members living with the condition and designing ways to systematically study those questions.