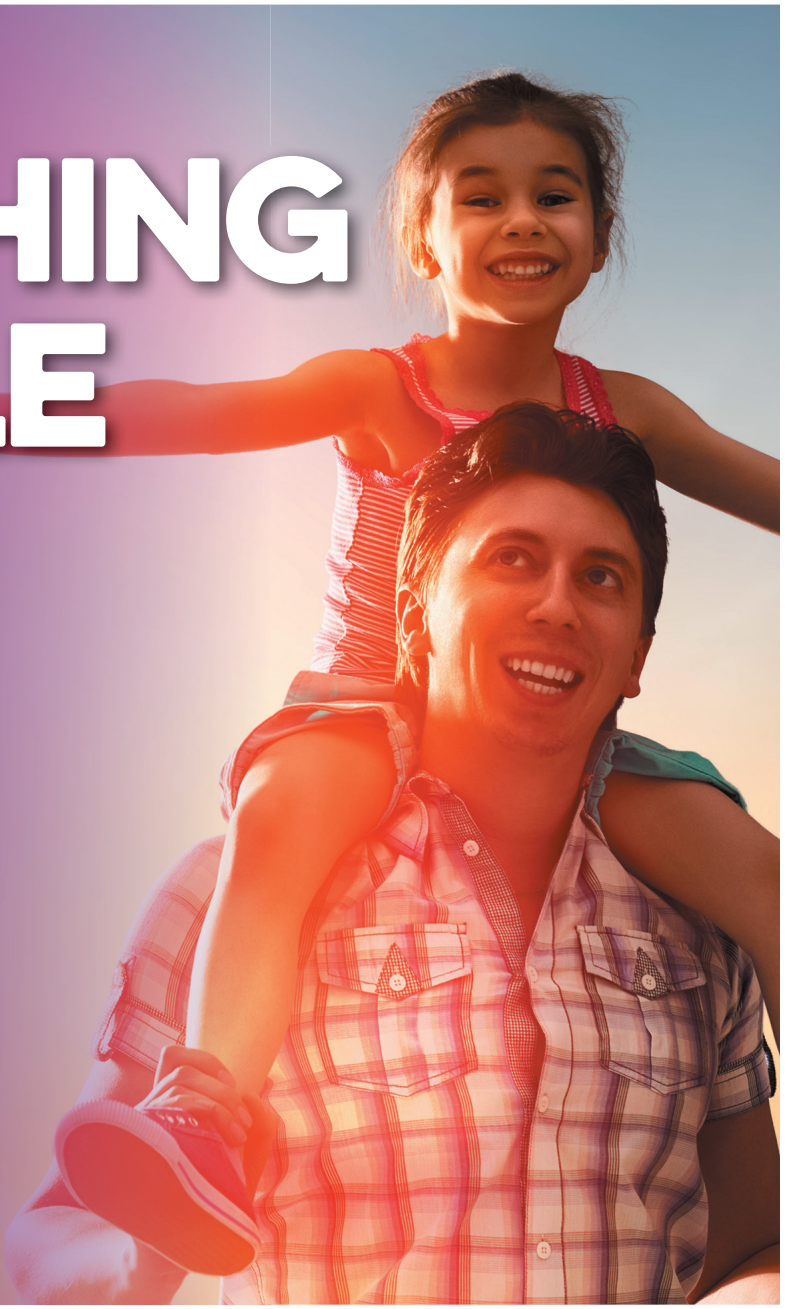
SOMETHING TO SMILE ABOUT

The Journey Toward a Cure with Rare Disease Foundation NFED



by **Lauren Chunn**

Family Foundations Play a Key Role in Accelerating Cures for Rare Disease

Using internet resources to research symptoms can quickly lead down a path to paranoia. A simple ache becomes a harbinger of a deadly disease in record time. It's best to leave such work to the professionals. However, professionals must be aware of the disease to provide a proper diagnosis. In the case of many rare diseases (see Inset 1), this is simply not the case.

Shire Diagnostics found that 60% of patients with rare diseases and their caregivers had to provide healthcare professionals with information on their disease. Additionally, 60% of these rare disease patients were given conflicting information on the treatment options for their disease.[2]

When the healthcare professionals you rely on don't have sufficient knowledge of your disease, where do you turn? For many rare disease patients and families, there is only one answer – they have to become their own experts in their rare disease. These patients and their families must take on new roles – researcher, care coordinator, and advocate.[2] Often, these roles become a full-time job; one they, as non-medical professionals, were never trained to do. Out of this need, foundations like NFED are born.

The National Foundation for Ectodermal Dysplasias (NFED)

NFED was founded in 1981 in Mascoutah, Illinois by Mary Kaye Richter and 12 other families who had children affected by a rare disease known as ectodermal dysplasia (ED). Ectodermal dysplasias include more than 100 different disorders that affect the outermost layer of tissue of the embryo, known as the ectoderm, that makes up the skin, sweat glands, teeth, hair, nails, and other structures.[3] Some symptoms


Mary Fete and Becky Abbott

of ED include teeth abnormalities (including missing teeth or hypodontia), sparse hair, inability to sweat (hypohidrosis), and various skin and/or nail abnormalities. The disease is thought to have a cumulative prevalence of 1 out of every 1,429 individuals, although the prevalence of individual subtypes is far smaller.[4]

NFED plays a huge role in supporting families facing the everyday challenges of living with or caring for someone with a rare disease. Foundations like NFED and the families that compose them are playing an ever-increasing role in furthering research on rare diseases (see NFED's Mission in **inset 2**). NFED now supports over 8,600 families and has funded over $3.6 million in research at 40+ centers around the world.

Mary Fete (*pictured above with Becky Abbott*), executive director of NFED, understands the immense value of accessing the most up-to-date genomic research on the genes and variants related to ectodermal dysplasias (see **Figure 1**). Her dream is "to create a database for clinicians, researchers, and families that connects the phenotype, genotype, and molecular and protein pathways and provides a catalyst for research."

A diagnostic and therapeutic odyssey burdened by financial challenges

Despite great work from foundations like NFED, the rare disease community faces medical challenges primarily in acquiring accurate diagnoses; access to treatments; and availability of, and access to, information. A case in point: it takes, on average, 7.6 years for a rare disease patient in the US to receive an accurate diagnosis. This typically requires visits to 8 physicians and 2 to 3 initial misdiagnoses.[2] A look through the financial consequences of having a rare disease in figure 2 shows that this "rare disease odyssey" comes at a high cost – not just money, but time, opportunity, and emotional distress.

One of the largest concerns of advocates for a rare disease is whether patients will have access to a disease-specific therapy if and when it is developed. This is due to the long process of drug development, and, when a treatment is finally available, compounded by the comparatively high cost of rare disease drugs (aka orphan drugs). The median cost of orphan drugs was about $147,000 per patient per year in 2017, compared to $30,708 for non-orphan drugs.[5] Insurance coverage is also more likely to be restricted for rare diseases.[6]

Due to their underdeveloped dentition, many individuals born with Ectodermal Dysplasias, especially smaller children, need to adjust their diets to include softer and easier to chew foods. Children often have a difficult time chewing and swallowing many types of foods suitable for their age, and this often limits which types of foods they can consume, due to issues with choking and digestion.

For NFED, insurance coverage and access to treatment are some of the primary challenges that patients and their families face. With hypodontia (or absence of adult teeth) and other dental abnormalities being a unifying symptom across the subtypes of ectodermal dysplasia, many patients require extensive dental work that can cost upwards of $100k. Due to these procedures being considered "cosmetic" in nature, they often do not qualify for insurance coverage; many of these patients can go years or even a lifetime with no treatment. Mary Fete stresses that these treatments are *medically* necessary and that these patients' inability to access them is nothing short of heartbreaking.

In response to these challenges, NFED has worked extensively on a new bill called the "Ensuring Lasting Smiles Act", which would require private health insurance plans to provide coverage for dental procedures needed to treat congenital anomalies, such as those caused by ectodermal dysplasia.[7]

But before facing the challenge of accessing a therapy, patients must first be properly diagnosed and a therapy developed based on that data. This process is heavily burdened by yet another challenge: access to information.

Inset 1

In the United States, a rare disease is defined as one that affects fewer than 200,000 people. It is estimated that 25-30 million Americans have one or more of approximately 7,000 rare diseases. This amounts to nearly 1 in 10 individuals in the United States, or 350 million worldwide. Thus, while it may be uncommon to have a specific rare disease, having a rare disease in general is not quite so rare.[1]

Inset 2

NFED's Mission: "We work with families to help them understand treatment options, to increase their access to care and to find financial assistance for that care….and perhaps our greatest success comes from providing individuals and families affected by ectodermal dysplasia with a place to turn for reliable information, support and hope. We publish high-quality information to empower families with knowledge that their doctors often cannot give. We stand with open arms to welcome the family who has just been diagnosed, to answer their questions, and to allay their fears."

Too much information, too little access

This problem of access to information is a major issue. According to an NPR article:

> *"Families who have a child with an illness that's likely genetically based, but never before described in the scientific literature, are lost in an information desert. They can be isolated by research protocols that keep scientific findings quiet until they are published, and by health privacy laws that prevent, for example, a genetics lab from connecting two families who have the same mutation."* [8]

This challenge is precisely why these patients and families have turned to social media and other resources for identifying similar patients, aggregating information for research, and identifying scientists who are willing to study their disease. In the same report, Dr. Christian

Inset 3

"You talk to people every day that struggle to find ways to pay for this and subsequently they end up going a lifetime without teeth. Can you imagine growing up without teeth? It's something we take for granted...thinking about chewing, speech, smiling, something that gives us good self-esteem, it's just heartbreaking… That is the number one call we get in the office"

Mary Kaye Richter

Schaaf states that there are "two major inadequacies in genetic medicine — the absence of support for families whose kids are ill but don't yet have a diagnosis, and the lack of a clearinghouse where families and researchers can find one another."[8]

The rare disease community seeks greater collaboration between physicians, more support for families, and more research to expand the current body of knowledge about their disease.[2] With the advocacy work undertaken by patients, their families, and foundations, diagnosing and treating rare diseases is becoming increasingly collaborative. Research for many rare diseases, however, is still severely limited.

Expanding the body of knowledge on a disease requires access to all of the currently published medical and genetic literature on the disease. Unfortunately, finding this information can be like looking for a needle in a haystack. In 2018, there were 33,100 active, scholarly, peer-reviewed, English-language journals (and another 9,400 non-English language journals) publishing a collective 3 million articles a year.[9] Any rare disease makes up an extremely minute portion of this mass of literature, and the task of identifying what is relevant can be plagued by inconsistencies in naming diseases and/or variants, misdiagnoses, or a search tool's inability to find and match the wanted information accurately.

Once some information thought to be relevant is identified, accessing it can present yet another challenge. Only a third of the published literature is freely available, while the rest sit behind a paywall.[9] Access to information is the primary barrier to productive research. For patients and their families, that barrier can seem impenetrable.

Dr. Mark Kiel

Giving back

One former patient who is aiming to lower this barrier is Dr. Mark Kiel (*above*), Chief Scientific Officer of Genomenon, Inc., which provides a comprehensive source for genomic evidence. He and his twin brother had hypodontia, or missing adult teeth, in their youth. His mother relentlessly searched for a diagnosis and advocated for her sons when the doctors didn't deem such a search to be necessary. Eventually, a geneticist was able to diagnose Mark and his brother with ectodermal dysplasia, which led to a connection with NFED.

In the early 1990s, NFED provided Mark and his brother with support and financial assistance in treating their hypodontia. With their help, Mark and his brother both received full dental implants at no cost, a treatment that wasn't covered by insurance (see inset 3). To date, NFED has provided more than $1.5 million in treatment assistance to patients like Mark.

Living with a rare condition as a child focused Mark's attention on genetics, and his decision to pursue a medical degree and PhD was a result of his desire to make an impact for rare diseases. Thirty years later, Mark was in a position to give back to the foundation that changed his life through Genomenon, the company he had founded as a result of his childhood experience. In the fall of 2019, he reached out to Mary Fete, to see if he could make their "dream database" a reality.

Genomenon partners with NFED to make the ectodermal dysplasia genomic landscape open for all

NFED has many hopes for what this "dream database" would offer to their patients and families, but the main goals are that it will serve as a tool for families who have trouble accessing information needed for a diagnosis or for better understanding the disease, clinicians who may not be familiar with ectodermal dysplasias and how to diagnose them, and researchers trying to put together the pieces of the genetic puzzle that underlies ectodermal dysplasias.

Genomenon's *Mastermind Genomic Search Engine* is a powerful tool for understanding the genomic drivers behind every rare disease. Because of their rarity, published information is sparse and difficult to find; an unfocused

Inset 4

The personal toll of Ectodermal Dysplasia

Julie Kiel discovered that her twin sons Mark and Kris were missing their adult teeth when they were around age 6. Their family dentist's reaction was, "Oh, well." That answer wasn't enough for Julie, and it sparked the beginning of a diagnostic odyssey for the Kiel's that lasted 7 years. In that time, the brothers' hypodontia led to many very challenging issues. They had difficulty speaking, foods were restricted due to the fragile nature of their over-extended baby teeth, and self-consciousness led to an aversion to smiling. The constant fear of losing these teeth or of having the temporary dental veneers break off was, in Mark's words, "like a waking nightmare" until NFED helped the Kiels receive treatment at age 15.

PRIMARY CAUSATIVE GENES FOR ECTODERMAL DYSPLASIA		*EDA*	*EDAR*
EDARADD	*TP63*	*IKBKG*	*PORCN*
WNT10A	*CDH3*	*PKP1*	*NECTIN1*
KRT81	*KRT83*	*KRT85*	*KRT86*

Figure 1: Primary Causative Genes for Ectodermal Dysplasia[16]

search tool returns results fraught with false matches and irrelevant information, and often misses extremely valuable excerpts. On the other hand, Mastermind is expertly tuned to find and annotate genetic and medical information comprehensively, no matter how few mentions there may be. Recently, we put Mastermind to the test and developed a genomic landscape for a rare neurodegenerative disease known as beta-propeller protein-associated neurodegeneration (or BPAN), which is now freely available.[10] This landscape consisted of 94 unique genetic variants in the disease's causative gene – *WDR45* – with detailed phenotypic and therapeutic information to aid in both diagnosis and drug discovery. The foundation we partnered with – BPAN Warriors – has already begun conversations with researchers with this comprehensive database in hand.

To Mark, offering such a database to NFED seemed like an obvious next step; it was a very personal piece of a wider goal – to make a lasting impact on rare disease. It is a goal that all of us at Genomenon share.

Soon after Mark reached out to Mary Fete at NFED, the curation team at Genomenon set to work developing a genetic landscape for the primary causative genes associated with ectodermal dysplasia. In a few weeks' time, we gathered an astonishing 2,908 variants, 821 of which were determined to be pathogenic or likely pathogenic according to the standards set by the American College of Medical Genetics (ACMG). In order to further aid diagnosis, we also carefully annotated the phenotype of the patients, recording 112 unique clinical symptoms, and collected published photos to help clinicians better understand the physical features associated with ectodermal dysplasia. Additionally, we annotated functional studies in detail, recording the effects of particular variants on protein function as well as how those effects were discovered.

Speaking about their future goals and the potential of this database, Mary Fete states:

> *"This database is going to help us understand ectodermal dysplasias better, find correlations between the genes and pathways, and help us find new discoveries... it will also entice researchers to be more involved in ectodermal dysplasia research"*

Similarly, Becky Abbott (see photo with Mary Fete), Manager, Treatment and Research for NFED and parent of child with XLHED, states:

> *"There are so many medical professionals who have never heard of ectodermal dysplasia, and this database can help them understand what ED is...any additional information that we can provide will help our families get a quicker diagnosis"*

Our team at Genomenon has been so inspired by NFED that the comprehensive genomic landscape for ectodermal dysplasia will be made freely available to anyone, whether a patient, family member, researcher, or pharmaceutical company. The availability of this data will ultimately aid in earlier and more accurate diagnosis, as well as in the development of better treatment options.

We will continue to work with great organizations like BPAN Warriors and NFED in our quest to have every rare disease patient accurately diagnosed and properly treated.

To contact NFED, visit nfed.org or call 618-566-2020. JoPM

FINANCIAL CONSEQUENCES OF RARE DISEASE	US	UK
Had to use savings to pay for medical expenses	53%	31%
Incurred direct medical expenses not covered by insurance/national health	55%	18%
Borrowed money from family and/or friends to pay for expenses	37%	21%
Sought help from charity or public assistance	34%	18%
Negatively impacted credit score	32%	10%
Used retirement funds to pay for expenses	23%	10%

Figure 2: Financial Consequences of Rare Disease Diagnosis[2]

Lauren Chunn is a data analyst and bioinformatician for Genomenon, where she works on increasing the speed and accuracy of variant interpretation. She holds a bachelor's of science degree in cell and molecular biology and philosophy from Grand Valley State University, where her focus was on bioethics, culminating with an internship in clinical ethics at Spectrum Health Hospitals and a research project concerning whether the genome should be considered private property. She is also a passionate advocate for rare disease awareness.

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