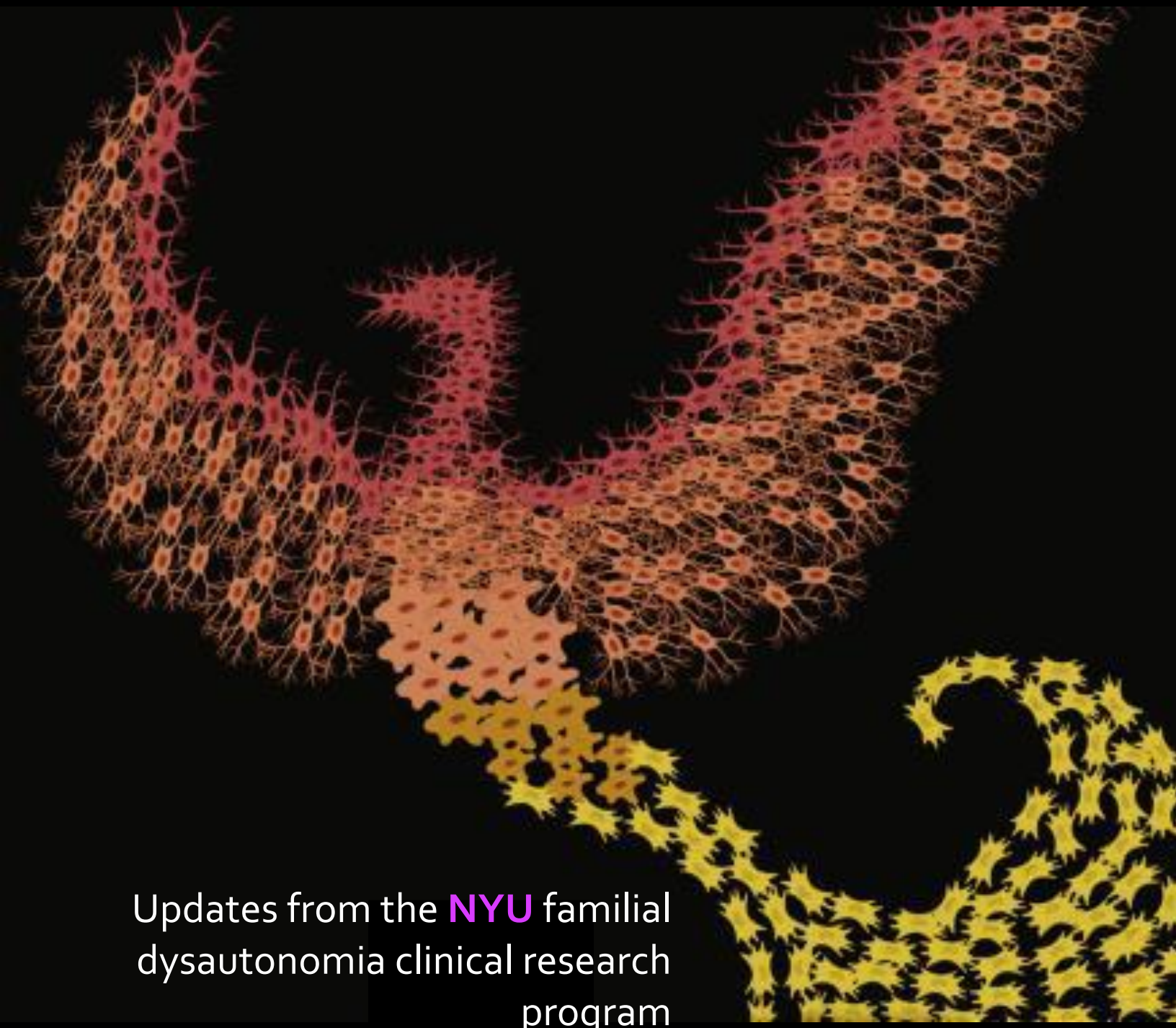
2022 -2023
YEAR IN REVIEW



Updates from the **NYU** familial dysautonomia clinical research program

Our dedicated translational research program for familial dysautonomia (FD) prioritizes creating new knowledge about this rare genetic disease to help develop better treatments

CONTENTS

A MESSAGE FROM OUR DIRECTOR

The first time I met a patient with FD had a profound effect on me. Sixteen years ago, I sat with the family, hearing about their lives, and I made it my mission to help. The gene had been discovered, parents could have healthy children, but FD was still one of the most devastating things I had seen in all my decades as a practicing neurologist. I was ready for the challenge. There were so many unknowns, but at the same time, so much opportunity.

I wanted to fundamentally change our approach. In the early days, we had to argue that the blood pressure instability was also a problem of sensation. People were skeptical, but most scientists agreed with us. This changed our thinking about FD. I spent the next years focused on building our clinical therapeutic program. Since then, we have authored 50+ scientific publications on FD, presented at 70+ conferences, and been awarded 10+ grants.

I remember vividly my first FD Day. Seeing the families together was a powerful moment, and one that instilled a real sense of urgency in me. From then on, we sharpened our focus and re-engineered our team around our highest priorities. We developed alternative treatments for crisis, assembled a multidisciplinary medical network, and identified the risks of complications in FD. Some incredibly talented people have worked very hard on FD over the years. As our program has evolved and matured, I am grateful to have seen our knowledge grow in ways that have benefitted patients. I wanted to create an atmosphere of curiosity and exploring ideas, and to provide reliable information back to our families – which remains at the heart of our program.

The vision and the strategy are clear. How can we better understand the disease to make a positive impact on people's lives? The Center runs a portfolio of research projects that are prioritized according to the likelihood that they will help find a cure, save a life, or make someone feel better. The diversity of the projects is what makes the program special. We approach FD from all angles: cells, molecules, animal models, and people. It's truly translational in nature and one of a kind. This last year was a big year for translational research in FD, with results from the work on stem cells, gut microbes and metabolomics making the headlines.

Together with our families, we have helped many young scientists along their career paths. We have enabled fellows, residents, post-docs, administrative staff, nurses, and medical students to come and learn about FD. Each family that shared their story during one of those visits has helped us build awareness about the disease among the medical community and teach the foundations of neurology through observation.

Some of our wins over the last year include publishing our work in *Nature* – not once, but twice, being awarded a new Blueprint grant from the NIH, and delivering care with more precision to prolong survival in FD. People with FD now live well into their adulthood. Still, a cure remains elusive and there is much work left to do. Our aging population faces new problems and their needs have shifted.

I cannot predict the next 16 years, but I can tell you that our FD Program at NYU has always been a pioneer. The Center has existed for the last 50 years. We are proud of the accomplishments the team has made to change the lives of people with FD. This commitment was made possible thanks to the unwavering support of the Familial Dysautonomia Foundation Inc. in our mission.

Horacio Kaufmann, MD, FAAN
Director of the Dysautonomia Center

NIH grants FD a second shot at developing small molecule splicing enhancers

A Blueprint for FD

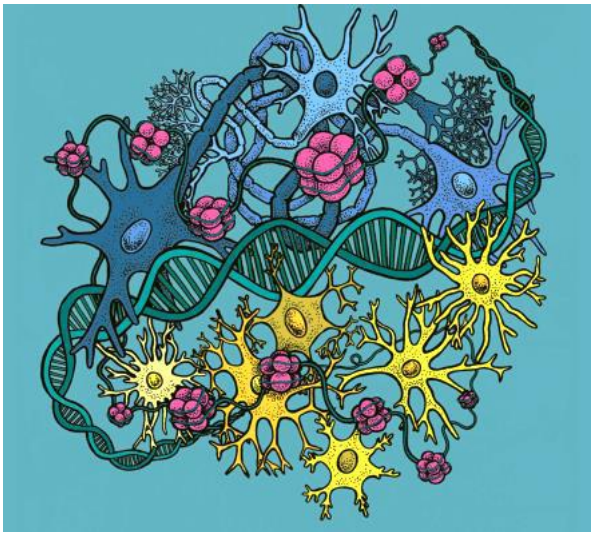
The development of a new drug has a slow return, is costly, and the odds are slim. In the U.S., the "average" drug takes 10 to 15 years of development, around $2.6 billion dollars of investment, and even then, only 10% will make it to approval. Most drugs fall by the wayside either because the side effects are too serious, the drug doesn't have the intended effect, or there is little commercial interest. The task is even harder for rare diseases, which are inherently riskier. As a result, countless brilliant therapeutic ideas, remain on the cutting room floor, unable to advance further.

Small molecules vs. Biologicals

Drug therapies fall into two main categories: small molecules and biologicals. Most existing drugs are small molecules, which have a low molecular weight and are capable of mimicking or blocking a biochemical process to treat a disease. Most blockbuster drugs that have changed human survival from diseases are indeed small molecules (e.g., aspirin, statins, penicillin). They typically have simple chemical structures, are more stable, require less complicated manufacturing processes, can be taken orally, and behave more predictably once inside the body.

In recent years, biologicals have gained a footing in modern medicine. Biologicals are a broader category of medicines that are grown inside other living cells, purified, and used to target a disease-causing mechanism (e.g., vaccines, antibodies or viruses carrying corrected DNA pieces). They are considerably more expensive to develop, more fragile, and require a more complex route of administration (like a spinal tap or infusion). In recent years, small molecules have fallen out of favor when it comes to treating human diseases, with increasing efforts put into developing biologicals - the "New Kids on the Block".

Dr. Susan Slaughenhaupt knows this conundrum all too well. Having screened the library of small molecules available, she saw the plant cytokinin (kinetin) rescue FD cells and later proved to save FD mice. Kinetin, a compound used in the tobacco farming industry as well as in skin care, isn't exactly a drug. It's a naturally occurring small molecule, with a biological effect, that falls somewhere in the murky region of a "nutraceutical". A small pilot study showed that when taken by mouth, kinetin appears to be fixing the FD splicing defect, but sometimes produces horrendous nausea. While promising, it was not an ideal candidate.



Disease modifying therapies for FD aim to protect the nerve cells from dying to preserve sight and walking abilities from declining with age.

Finding a way forward

The story of kinetin was selected for the NIH's Blueprint Program in 2015, a prestigious platform that helps academic scientists develop drug candidates. Several medicinal chemists got to work on tinkering with the structure of kinetin to make it more potent and less likely to produce off-target effects. Several years later, the new drug-like candidate (affectionately known as "super kinetin") graduated from the NIH's Blueprint program, an achievement in itself, and was picked up by a pharmaceutical company (PTC Therapeutics) for further optimization. But it wasn't smooth sailing. A lot of work was done, and super kinetin became even more powerful. As it was near to entering the clinic for testing, the program ground to an abrupt halt. "Super kinetin" was destined to sit on the shelf, stalled.

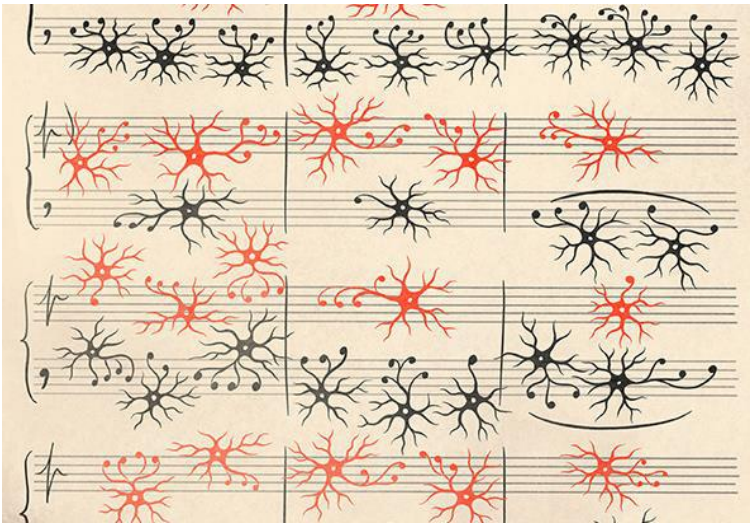
Normally, this would be the end of any potential drug. Dr. Slaughenhaupt refused to stop and enlisted her trusted colleague Dr. Elisabetta Morini. The two had worked together for almost a decade. Spurred by the unmet needs of the FD community and sheer determination, they weighed their options and went back to the NIH's Blueprint program to ask for help. Once a compound is optimized, there is still more that needs to be done to make sure it is ready to go into the human body. Drs. Slaugenhaupt and Morini wrote a second grant. Their strategy put the idea of a kinetin-derived small molecule (splicing modulator) back on the table.

> "NIH's Blueprint program allows us to work with experts to create the ideal candidate drug for FD with the best chance of success"– Dr. Elisabetta Morini

The fact that FD has been through to the Blueprint program, not once but twice, is a testimony to the strength of the idea. The path to developing new drugs is always more difficult when there is no precedent. Currently, there is no therapy that can halt or delay the deterioration in eyesight and gait that robs people with FD of their independence. Small molecule splicing modulators aren't yet approved, despite the years of data suggesting it is worth a shot. A new 5-year Blueprint grant from the NIH, will again shepherd kinetin through the "valley of death" as it is known in drug development. Scientists will go back to working with the compound to maximize its potency and safety. A big part of the grants funding will be spent on toxicology studies, which will ensure at the end we have a molecule that hits its target, does its job, and doesn't produce unwanted side effects.

Perhaps the greatest challenge has always been convincing others this is worthwhile. Undoubtedly, had Drs. Slaughenhaupt and Morini given up, a potential therapy for FD would have remained in limbo. The T > C genetic transition found in the FD gene creates perseverance, that's for sure. Patients never give up, no matter how sick they are in the hospital; they fight back, they get up, they walk out, sometimes beyond all expectations. That same determination appears to have rubbed off on the scientist team working on FD. The door has been reopened, and we are ready for round two of the NIH's Blueprint program.

TRAINING IN FD



The NYU FD Program helps shape the next generation of clinical scientists

Scientists aren't born overnight. It starts with curiosity, then takes years of training to equip a scientist with the tools they need to tackle complex healthcare problems. The FD Program at NYU has an extraordinary track record helping young scientists further their careers and has produced several leaders in the field. FD is an ideal training ground for the most inquisitive minds who want to take on a serious disease that currently has no cure.. There are days when it feels like there are more questions than answers and the disease is unpredictable. Patients can be feeling well, then quickly spiral downhill. There are also chronic problems to deal with in the lungs, eyes, bones, kidneys, and gut that require a specialist to consult. Although guidelines exist, there is no rulebook for treating FD, "but there is evidenced-based medicine and that's what we do every day,"explained Dr. Kaufmann.

> "By meeting patients with FD, young scientists are introduced to the fields of autonomic diseases, peripheral neuropathy, and neurogenetics. They get hooked!" – Dr. Alejandra Gonzalez-Duarte

Evidenced-based medicine has become somewhat of a buzzword in recent years, along with personalized or precision medicine. All these terms really mean that we can look at large datasets of people with a disease and use a person's individual health records or traits to tailor a healthcare plan that is unique to them. It uses data to guide decisions, rather than an empirical "one size fits all" approach, which can be prone to error. It requires considering each person, weighing the options, and thinking through how best to approach the underlying problem. The Center invites young scientists to come see how this is done and engrained in our philosophy.

A launching pad

The very essence of a training program is to deepen expertise so that people can skillfully practice. It means that people move on afterwards and continue to climb their career ladders, taking with them their expertise. The Center has

Training in FD has helped shape the careers of several research scientists.

trainedpre-med students, post-docs, neurologists, program managers, and nurses. In 2009, it became an accredited site to run a UCNS-approved fellowship in autonomic disorders, creating a curriculum, goals, and milestones. The Familial Dysautonomia Foundation, Inc. has supported the fellowship program for neurologists to spend 1 to 2 years dedicated to FD since its inception. A total of 7 fellows have since graduated. Some went on open their own practices, hold key positions in industry, or became academic scientists.

Being part of a teaching hospital is the fabric of NYU. It is the philosophy at the very heart of our program, and one that also promotes a diverse group of learners from all backgrounds. Over the years, the Familial Dysautonomia Foundation, Inc. has supported students from local high schools, nurses looking to diversify their training, early career scientists, front desk staff, and visiting professors. Because people with FD are in the hospital a lot, with a variety of problems, along the way, they are likely to encounter residents in training. These are young physicians that have chosen to specialize in one area. Because FD affects so many body systems, patients that are hospitalized can meet with a resident gastroenterologist, radiologist, pulmonologist, or neurologist at various levels of their training. This builds awareness within the medical community about the disease. Some residents, like Dr. Chethan Ramprasad, become curious about FD and carry out their own research projects (**page 18**).

Nearly all our former front desk assistants have gone on to medical school, dentistry school, or in pursuit of a master's degree or PhD. These are smart young people who on average spend 2 years at the Center. They learn by fielding the phones how to channel information and later get the opportunity to help with research, which for many becomes a career path. It is up to each person to set their own goals and career trajectory. Most recently, we collaborated with the NYU Rory Meyers College of Nursing to support our specialist nurse practitioner Dr. Zenith Khan in completing her doctorate degree (**page 9**).

Sharing time

In the US, the average medical visit takes 10 to 15 minutes. The Center's staff spend on average 3 hours with each patient, often with trainees in tow. Visiting physicians are often surprised by the thoroughness of each annual evaluation and the "whole team" approach, with everyone weighing in on the discussion recapping the head-to-toe work-up. They learn through observing and hearing the stories of the families. It's a perfect introduction to the field of neurogenetics. Some trainees spend time in our clinic, seeing several other autonomic diseases, so they can hone their skills, learn to ask the right questions, and use data to change clinical practice. There is no substitute for learning through experience, which is a core part of the program.

None of this would be possible without the family's openness in telling their stories. It's the very basis of taking clinical history. This is where the information is gathered. Where you listen, ask relevant questions, and direct the interview so you can extract the key points. Often it is the first time a trainee hears what life is like without pain sensation, without muscle feedback, strategies to manage erratic blood pressure, or how to approach sleep-disordered breathing. A person's training may take decades, years, or months, depending on their own goals. Most trainees are expected to "fly the nest" once they have developed the skills they need and continue to grow. While it can be sad when a staff member moves on, we know they are going on to take positions where they will continue to make a difference. FD remains imprinted in all of them. But once in a while, a former trainee will return. Dr. Alejandra Gonzalez-Duarte was the first graduate of the autonomic disorders fellowship program at NYU. Last year, she came back to the Center to become the new Co-Director and now holds the Seaman Family Professorship for FD. Out of all the candidates in the world, she was by far the best equipped to take on the role. Her initial time at the Center spurred a life-long commitment to autonomic disorders. Continuing the legacy, she is now the Director of the Center's Visiting Scholar Program, which brings physicians from all over the world

into the FD clinic (**page 10**). Their experience is a two-way street and frequently a visiting scholar's particular expertise helps us understand FD better.

STAFF NEWS

Dr. Zenith Khan, DNP.

Shortly after joining the Center, nurse practitioner Zenith Khan embarked on her goal of obtaining a doctorate in nursing. She was accepted into NYU's Doctorate of Nursing Program (DNP). Zenith applied her experience in FD to implement a quality control project to ensure that survivors of head and neck cancer, who also experience erratic blood pressures, can receive the care they need. She implemented a screening questionnaire, which gathered the relevant information to direct their clinic work-up. Her thesis defense committee were impressed with her patient centric approach, which led to improved patient experiences. We are excited to see where this takes her next.

Lee-Ann Lugg, BS.

Lee-Ann is the glue that holds literally everything together at the Center. She is our program manager, administrative lead, and organizer. She has been with the Center for over 10-years. In 2022, Lee-Ann was accepted into NYU's Master of Public Health Program to continue her education. She will focus on longitudinal data analysis and learn the analytic tools necessary to make sense of the data. Lee-Ann has spent many years at the Center seeing how this methodical approach to data collection can deepen our understanding and translate into better quality clinical care. She will remain at the Center while she pursues her degree on a part time basis.

NEW FACES

Matthew Hertzberg. Social Work Intern

Matthew joined our Center in August 2022 with one mission: to understand the journey that the FD community faces each day. To achieve this, he began meeting patients weekly, to talk about their goals and expectations. Recently, he began directing a support group for family members of our FD patients (**page 11**). Matt is completing his Master of Social Work degree at Fordham University. We are incredibly grateful to have a dedicated social worker on our FD team.

Mike Yates. Project Assistant

Mike joined our Center in November 2022, taking over the task of running the busy front desk. This job is not easy. Mike is on the front line when it comes to taking calls from patients and family members. He has learned to prioritize emergencies and direct patients to the necessary resources as well as coordinating the schedule for patients to have their appointments and tests. Mike's dedication to the program ensures that patients' needs are met.

VISITING SCHOLARS PROGRAM

In 2023 we had a very successful year for the **Visiting Scholar Program**. This Program supports clinician scientists who wish to visit the Center, spend time with our patients, and learn our research methods. The Visiting Scholar Program is led by Dr. Alejandra Gonzalez-Duarte, who remains committed to raising awareness of FD among physicians throughout the world.

For one to six months, 7 doctors from all over the world took part in the Center's Visiting Scholars Program to learn about familial dysautonomia. They followed the team members' every move from Monday through Friday. They took part in daily clinical rounds, observed annual visits, and rounded on hospitalized patients. We hope that we ignited the spark for them to start looking for potential FD patients across the world.

Tizana De Santis

Instituto Clinico Humanitas
MILAN, ITALY

Claudio López

Hospital Virgen de las Nieves
GRANADA, SPAIN

Lilia Correa

Hospital del Mar
BARCELONA, SPAIN

Carmen de Rojas

Hospital Virgen de la Victoria
MALAGA, SPAIN

María Eugenia Briseño

Instituto Nacional de Neurología y Neurocirugía Manuel Velazco Suárez
MEXICO CITY, MEXICO

Karla Cárdenas Soto

Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán
MEXICO CITY, MEXICO

María Trinidad Herrero

Universidad de Murcia
MURCIA, SPAIN

NEW THERAPY PROGRAM

Bringing talk therapy to parents

The role of a caregiver is one few can predict. When it comes to a genetic disease like FD, that role usually falls on the parents. Families watch as their healthy children graduate, leave home, get jobs, and have their own families. Many FD patients won't meet these milestones. A growing number of parents are now older and face their own health challenges, while still coping with the complex medical challenges of FD. Others are just starting out on their journey with FD.

Parents who passed on the faulty gene to their children have no symptoms, but they do not have an easy life. FD affects the entire family dynamic. They deal with uncertainty, medical visits, gastrostomy feedings, connecting BiPAP machines, monitoring oxygen, and watching for an impending crisis. For parents, their connection begins with a single T > C base pair change in the DNA code, but ultimately goes deeper. Their shared experiences are unique. Only they know what it is to handle the day-to-day stresses of FD and the resilience this takes. Half a century ago, soon after the discovery of FD, the parents of affected children came together to form what is now the Familial Dysautonomia Foundation, Inc. This strength in numbers approach has proven very advantageous.

But sometimes even the strongest people need help. Five years ago, with the support of the Schwartzberg family and the Montreal Chapter for FD, we set up a therapy program for FD patients with a dedicated therapist. The program provided a forum for patients to share their struggles with others that faced similar problems. We now want to expand that program to parents. We have a responsibility to care for the whole family, which is why we recognized the need to build a community program where parents can advocate for their needs. The parent therapy group is led by our clinical social work intern Matthew Hertzberg (**page 9**). The sessions are a space to talk, to share challenges, fears, and frustrations; and to celebrate having courage when facing uncertainty and strategies that work. The guided therapy sessions allow the families to direct the conversation flow. Our hope is that by sharing their experiences, we can support the parent community. Please contact the Center if you are a parent or extended family member caring for a patient and interested in participating.

FD gene linked to missing healthy microbes from the gut

The inner ecosystem of FD

For patients with FD, maintaining a healthy body weight is often a struggle. Their metabolic rates are higher, their body mass indices run lower, and they have little fat content. When a call comes into the Center that a patient is losing weight, staff take this seriously. In a short space of time, patients can become undernourished. Low body weight has several serious consequences. It can make it harder to fight off infections and increases the risk of mortality. Dr. Frances Lefcort, head of the Scientific Advisory Board for the FD Foundation is no stranger to this problem. Her cousin was born with the disease, and she has dedicated a large part of her career to solving some of the biggest mysteries of FD with elegant experiments. She enlisted the help of Montana State University's top microbiome expert Dr. Seth Walk to help understand the GI symptoms of FD better.

There are trillions of microbes in our gut that live in harmony within our bodies. They live with the millions of nerve cells that innervate the gut and connect via various routes to the brain. This connection is known as the brain-gut axis, which allows a two-way channel of communication between the gastrointestinal tract and the central nervous system. Microbiome dysregulation is implemented in several neurological diseases. Pilot data showed that the gut microbes were different in patients with FD compared to their unaffected relatives. The Montana State team received a grant from the National Institute of Diabetes and Digestive and Kidney Diseases to embark on the largest study of the microbiome in patients with FD to date.

Collecting samples

Together with the Center, they recruited patients with FD and enrolled them in their study. The team also recruited relatives within the same household to give a sample. Prior to their annual evaluations, families were sent stool collection kits. Most patients were very happy to see their parents also participating in the study. Soon, we had over 100 samples, which were shipped to Montana for analysis.

Analyzing microbiome data is no small feat. The data arrives in streams of raw sequences containing fragments of the genetic information from the bacterial species present. It requires processing the data through a pipeline so that we can pinpoint exactly which species of bacteria are present or absent (taxa) and their relative abundances (alpha and beta diversity).

Findings

FD has its own microbial signature, and there were clear differences in the microbes present in cases and controls. Patients had only a subset of species that were found in their relatives, with on average 45 fewer taxa. They then performed cluster analysis, which showed patients were missing many of the "healthy" microbes that are present in the human body. Their next step was to look at the metabolites in the samples to understand the impact of these missing microbes. They found patients with FD had higher levels of choline, which is a nutrient essential for cellular health and the structural integrity of the cell wall. Choline is metabolized by the liver and produces TMAO, which is a well-known risk factor for cardiovascular and renal disease. Levels of TMAO were also higher in blood.

The team then set out to explore why patients with FD had this unique microbiome signature. Their first step was to look at the impact of gastrostomy tube feedings. Our microbiomes are influenced by many factors, but the food we eat has a big effect. The team observed that patients who received mostly gastrostomy feedings had less diversity in their microbiomes.

The next step was to explore this further in a mouse model of FD. Dr. Lefcort has spent years breeding mice genetically engineered to lack the ELP-1 gene. These mice provide a unique insight into the mechanistic basis of FD. Mice with the "mutant" FD gene showed changes in their microbiome from a very early age and continued to lose diversity as they aged. Their microbiome remained dysregulated even after being housed with healthy littermates in the same cage. Remarkably, the FD mice also had high choline levels. This suggests that it is the mutation itself that is driving the loss of microbial density.

Missing microbes from the gut appear to be a result of the low ELP-1 levels. The microbiome signature of FD may hold clues for why some patients are more prone to cardio-renal disease.

Importance for patients

The most important message for families is that the microbial ecosystem of the gut is affected in patients with FD. These changes appear to be due to the gene mutation, occur early in life, and become more divergent over time. The fact that this shift in microbes causes metabolic changes that are associated with poor neuronal health and a higher risk of developing cardio-renal disease are important. Ongoing neurodegeneration and cardiorenal complications are progressive complications of the disease. FD patients are not alone, this reduction in microbes is a feature of other brain diseases, including autism spectrum disorder, where it has been shown that replacing the missing microbes can help mitigate some of the symptoms. This is the first study to show that the ELP-1 gene has an impact on the gut. The findings were published in *Nature Communications*. It raises the possibility that promoting the growth of "good bacteria" might have broader effects on long-term health. The team will explore whether replacing the missing microbes can impact the health status of someone with FD.

Alterations in cell membrane receptors in FD neurons makes them hyperactive

Stem cells in crisis

Today we have the technology to take cells from a living person and reprogram them to go back in time to turn into immature pluripotent stem cells. Stem cells are the raw materials for building other cell types. With a lot of biological coaxing in the laboratory, pluripotent stem cells can be used to create specific cells to explore human diseases. Stem cells can be grown into nerve cells, which allow us to probe their biochemical behaviors, activity levels, and how they interact with neighboring cells.

One of the biggest mysteries of FD is why patients suffer from hypertensive vomiting crises. Other patients with lesions in the neck that have the same erratic blood pressure do not vomit when they are anxious, nor do they release massive amounts of dopamine. Dopamine is a neurotransmitter that is secreted, along with norepinephrine, by the sympathetic nerves. The sympathetic nerves innervating the blood vessels outside the brain orchestrate the "flight or fight" response, which becomes exaggerated in an FD crisis. The team have long wondered why these nerves, which are reduced in number from birth appear to be hyper-excitable. This pattern of hyperactivity does not happen in other conditions.

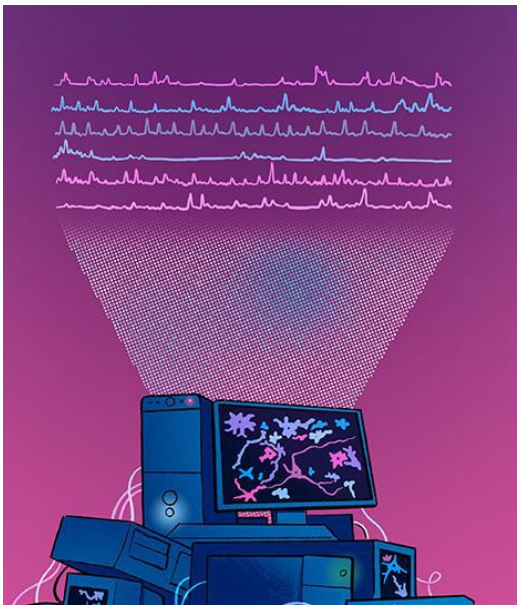
Questioning the unknown

Hyperexcitability of sympathetic neurons was first shown by Dr. Kaufmann. This was confirmed by Professor Vaughan Macefield, who traveled from Australia to place a tiny needle in the legs of FD patients and measure their sympathetic nerve activity. This work showed that instead of being tightly regulated and in sync with the heartbeat, the sympathetic nerves of FD patients were more active at rest and increased their firing rates with even the smallest emotional stress.

These findings intrigued Dr. Nadja Zeltner, a scientist who had just set up her own laboratory at the University of Georgia. Dr. Zeltner had spent years perfecting her technique so she could grow sympathetic neurons in a dish from cell lines derived from FD patients. She received funding from the NIH to explore the biochemical profiles of these nerves to understand FD better.

An up-close look at the nerves

Dr. Zeltner optimized her technique to create cells that had a similar biochemical profile and discharge pattern as the sympathetic neurons innervating the blood vessels and heart. Her first observation was that it was much harder to grow nerves from FD patient cell lines. Many of the FD stem cells she tried to culture did not differentiate, instead forming irregular shapes or dying – which is consistent with the early-stage developmental loss that is seen in patients. The few nerves that survived the developmental process went on to become hyperactive. Very soon after they were formed, FD nerves behaved differently, discharged at high levels, and maintained their hyperactive state over time. Her next step was to understand how this increased activity impacts the target organs. She grew heart cells and connected them to FD sympathetic neurons. She observed that the heart cells were beating at a faster rate. She then went on to explore the receptors and transporters that regulate neurotransmitter release. Her findings showed that FD nerves had an altered biochemical makeup that primed them to become hyperactive. Under normal circumstances, once a neurotransmitter is released by a nerve, it is quickly re-ingested by the cell and removed from the circulation (a process called reuptake). Prolonged exposure to neurotransmitters can result in toxicity and damage to the underlying organ, which becomes overstimulated. FD nerves were primed to become maladapted, and unable to re-uptake norepinephrine once it was released. This creates an "all gas no breaks" situation. The remaining sympathetic nerves are lying in wait, ready to be activated, and capable of responding in a way that far surpasses a normal healthy neuron. She partnered with Dr. Frances Lefcort to explore this further in mice genetically engineered to lack the ELP-1 gene. Sympathetic nerves grown from these FD mice showed a similar pattern of hyperactivity. Suggesting it was the low levels of ELP-1 protein that were driving their maladapted behavior.

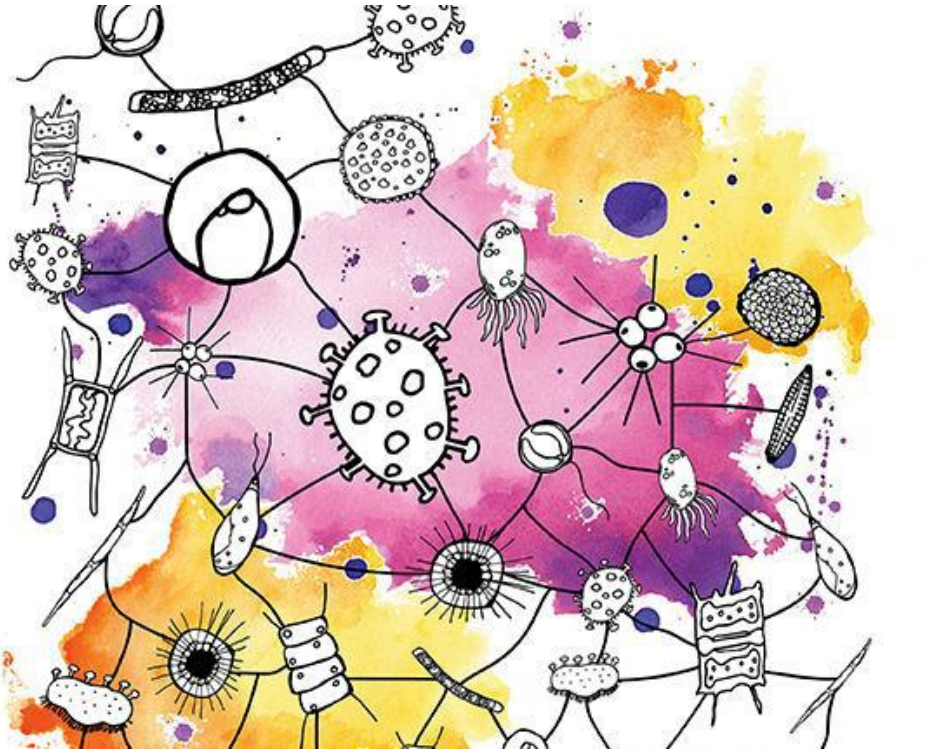


Recording the activity of FD nerve cells grown in the laboratory shows that they have a pattern of hyperexcitability, which could explain why patients suffer from vomiting crises.

Most people would have stopped here, but Dr. Zeltner turned her thoughts to what could be done to reverse this process. Dr. Zeltner treated the FD neurons with a panel of drugs that are commonly used the treat the crisis. She showed carbidopa, dexmedetomidine, and propranolol, all reduced the activity of the nerves.

Importance for patients

It's hard to imagine how an experimental model of stem cells can lead to improved medical care. This study bridges the knowledge gap by providing robust evidence that FD nerve cells are primed to behave in a way that makes them hyper-excitable. What is remarkable about her work is the translational nature. Looking at the impact of the drugs we use in clinical practice helps us understand exactly how they are working. Dr. Zeltner's work was published in *Nature Communications*. What makes her work standout, is the lengths she went to arrive at the conclusions, with a series of experiments that look at the problem from all angles. We have spent years conducting clinical trials to prove that these medicines are safe and effective. We now know how they work at a molecular level. Her next step is to explore these findings in a larger group of patients. The Center has a new project in which patients can undergo a small skin biopsy and have their nerves grown in the lab. We want to compare the biological properties of nerves in patients that have frequent, severe, prolonged crises. We suspect that they may be the ones with the most hyperactive nerves.



FD gene linked to missing healthy microbes from the gut

The metabolic engine of FD

The metabolome is the complete set of small chemicals that are found in a biological sample such as blood, organs, or tissues. This is made up of naturally occurring substances produced within the body as well as chemicals such as medicines and toxins that enter the body from the outside. These metabolites produce reactions in the body that can impact health. Measuring the metabolome can provide information on how the internal environment changes with disease states or is impacted by our microbiome. It requires analytical chemistry to quantify the amount of a substance present in each sample.

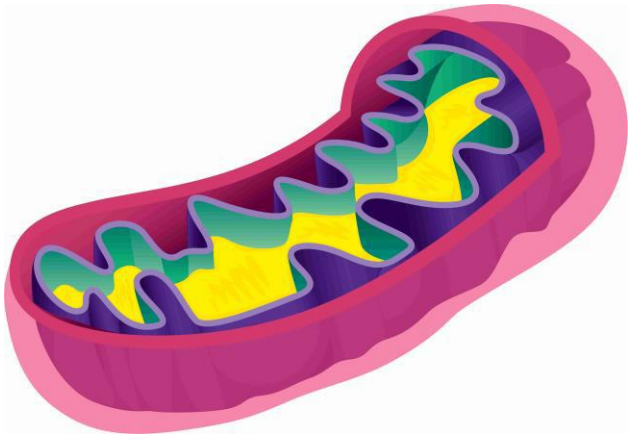
An opportunity

The Montana NIH microbiome grant featured a second aim, which was to look at the metabolomic patterns of FD patients compared to their healthy household relatives in stool and blood. The Montana team convinced the NIH that a comprehensive approach looking at the relationship between the microbiome and the metabolism in FD was a necessary undertaking that may lead to new insights into the cross-talk between the gut microbes, neuronal health and metabolism. The project was carefully set up. The Montana team shipped special kits to the Center that included collection materials, test tubes with reagents, and with an extensive set of step-by-step instructions on how to process the samples. Dr. Maria Cotrina Vidal was the scientist who took charge of recruiting patients, collecting information, and preparing their samples. The Center's team also sent the test results of routine blood work collected at the same time as the biofluid samples.

The results

The first step was to thaw the samples and measure their chemical profiles. Analysis of the blood samples showed that there were 22 metabolites that were different between FD patients and their relatives. Analysis of the stool samples showed similar amounts of different metabolites. What emerged from the data was that there were a cluster of patients that were metabolically distinct.

After mulling things over, the team concluded that 8 metabolites in blood serum and 8 metabolites in stool were of significant interest. In blood, the affected metabolites were all involved in energy metabolism including the breakdown of amino acids and mitochondrial function – which is the organelle within the cell that is responsible for cellular energy. The differences observed in stool samples were associated with the gut microbes, suggesting that perhaps the capacity of the gut to absorb nutrients from the diet could be impacted.



Metabolites involved in mitochondrial function suggest that the cells may be under increased stress, which creates energy deficits that are likely contribute to the death of neurons in FD over time.

The blood samples show signs that there are energy deficits in FD. The amino acids (which are the building blocks of proteins) were being degraded at a faster rate, consistent with "starvation" and muscle wasting. The stool samples suggested that patients may be "holding on" to other substances and salvaging them from excretion. They were saving purines, which require a lot of cellular energy to produce. A similar pattern can be seen in other neurological disease.

One fascinating finding was the high levels of tyrosine in stool. Tyrosine is the chemical substance from which dopamine and norepinephrine are made. These excitatory neurotransmitters are released by the nerves at times of stress during the crisis. Tyrosine is produced in the gut by the bacterial fermentation of tyramine. The stool samples also contained high levels of dopamine. The findings aligned with the work of the Zeltner lab (**page 14**), and suggest that while the nerves are overactive and secreting these neurotransmitters at higher levels than normal, the body is removing them from the gut and excreting them out in stool at a faster rate. They also replicated the findings of differences in choline metabolites.

The importance of these findings for patients

The overall results from the study are intriguing. They suggest that the alterations in the gut microbes may have knock-on metabolic effects, which impair the homeostatic balance of the body at a molecular level. A failure to absorb certain nutrients like choline may be contributing to poor neuronal health, placing stress on the nerves and contributing to their degeneration. The high amounts of tyramine that are being excreted point towards there being an excess, which is consistent with the pattern of sympathetic nerve hyperactivity that is now well established in FD.

The findings point towards a complex interplay between the host, microbes, low ELP-1 protein levels, and the metabolic processes within the body. We do not know how these findings impact the course of the disease, but what we can infer is that the internal environment of a person with FD is shifted. They are under metabolic stress, but doing all they can to hold onto nutrients that aid cellular health, while excreting others that produce unwanted side effects in the body or are toxic when they are present in excess quantities. This provides a biological basis for understanding the disease, and the processes we may need to support to slow down or halt neurodegeneration.

Gastrointestinal bleeds are common in FD, learn about the warning signs

Gastric Bleeds in FD

Dr. Kaufmann pulled the car to the side of the road. It was an emergency call from the Center. An FD patient with another gastric bleed. It can't be he thought. This was the third one in quick succession. He hadn't long been treating FD patients, but it did not feel right. Gastric ulcers with major bleeding are not common, especially in someone young and not using blood thinning medications. The teenage patient had fainted, there was fresh blood in her gastrostomy tube, the ambulance was called, at the hospital her red blood cell count was much lower than usual, the source of bleeding was the stomach.

The stomach and duodenum (the part that connects to the small intestine) live in a harsh world. The delicate cells that line their interior are constantly exposed to an acidic environment. To protect themselves from damage, they have their own mucus shield and release bicarbonate to neutralize the acid. When these defense mechanisms break down, a sore can occur, leading to an ulcer, which eats into the muscles of the stomach and duodenal wall, and may damage the blood vessels resulting in bleeding. Small ruptures that bleed over a long time can make a person feel weak, tired, or dizzy. Larger areas of damage can result in major bleeds with fainting, blood coming out of the gastrostomy, and vomiting blood, which require immediate medical attention to stop the bleeding, heal the damaged area, and prevent a perforating hole.

The clues were there right from the start. Over 70 years ago, when pediatricians Dr. Riley and Dr. Day first reported their observations in FD, they encountered the case of an 11-year-old boy, who died after vomiting blood. We began telling other physicians at the hospital, who were treating FD patients that gastric bleeds appeared to be common. Several years later, Dr. Chethan Ramprasad, a resident was called to treat a gastric bleed in a patient with FD. He had completed medical school and an internship program and had joined NYU to train in gastroenterology with Dr. Lea Ann Chen. He immediately questioned the same: Just how common are gastric bleeds in FD patients? And can we predict who is at high risk? With these questions in mind, Dr. Ramprasad came to the Center to ask how he could help. Eager to learn more about research, he started looking at the FD database, which contains the medical records of close to 700 patients, some spanning 40 years

back. During his residency, he became a regular visitor to the Center, meticulously digging through the cases of GI bleeds to conduct a case-controlled study. His results were published recently in the journal of *Clinical Autonomic Research*.

Frequency

Dr. Ramprasad went through the database and found 60 FD patients that had at least one GI bleed, with some having multiple events. The rate of GI bleeds in FD was over 20 times higher than seen in healthy children without FD. The average age at the first bleed was 11 years old (identical to the original Riley and Day case). Very few of the FD patients presented with stomach pain, which was unusual. The most common sign of a gastric bleed was fresh or clotted blood in the gastrostomy tube, stool or vomit. Many of the patients had undergone an endoscopy, in which a small camera is fed into the stomach to view the damage. In most cases, the bleeding was associated with an ulcer in the stomach or duodenum.

Association

His next step was to look at the characteristics of the patients that had GI bleeds and those that did not. For every patient with a bleed, he found a matching FD patient of the same age and sex that did not have a GI bleed in their lifetime. This case-controlled approach allows us to look for medical conditions or findings that are associated with someone who has a higher risk of gastric bleeding. His results showed that patients with a gastric bleed were more likely to have undergone fundoplication and/or gastrostomy surgery and were more likely to be prescribed clonidine and valium. This does not mean causality. Dr. Ramprasad observed that the first bleed occurred several years after their surgeries, long after the area had healed, and was never an acute complication. Valium and clonidine are not typical culprits known to increase the risk of a GI bleed.

Gastric bleeds are 20 times more common in FD patients and possibly linked to severe repeated bouts of crisis.

Causality

Although causality cannot be fully established, it is likely given the location of the bleed (almost always in the stomach, away from the gastrostomy tube site) together with the increased need for crisis-regime drugs, the bleeds could possibly be linked to repeated episodes of severe retching and vomiting. During these episodes, the stomach squeezes to build up pressure. These pressures can be even higher in someone with a fundoplication surgery, which essentially wraps the top part of the stomach around the opening, to prevent the gastric contents from leaving. Repeated episodes of retching may over time lead to ruptures or disturb the gastric mucosa.

What this means

These findings are important. We have documented that patients with FD are highly susceptible to gastric bleeds. While in most cases the first gastric bleed occurred in childhood, they can also happen in older patients. Patients who have had one gastric bleed, may have another. Those that suffer from prolonged intense retching/vomiting crises are even more at risk. It is important to note that the gastric bleeds in patients with FD are often painless. The first signs to be alert for are weakness and near fainting. Signs of a gastric bleed include blood in the vomit or gastrostomy tube. Sometimes the blood has a bright red appearance, other times it may be clotted giving it a coffee-ground appearance, or black stools. Dr. Ramprasad has since graduated from the NYU gastroenterology residency leaving an important contribution. He is an example of how a teaching hospital works. Residents that encounter patients with FD can see our patients with fresh ideas. Some like Dr. Ramprasad are committed to making a difference through research projects they can become involved with at the Center.

Supportive therapies and centralized care have helped patients live longer

Survival in FD

Dr. Alejandra Gonzalez-Duarte has pioneered the development of breakthrough therapies that have changed survival in genetic diseases that affect the neurological system. Soon after joining the Center, she was asked to write a review of FD to summarize our current understanding for a special issue on pediatric autonomic disorders of the journal *Clinical Autonomic Research*. She immediately turned her attention to the most relevant question a treating physician can ask: Are we making a difference in survival? For Dr. Gonzalez-Duarte it was an obvious question, and one that she has lost many nights of sleep over, since returning to the Center to take on the role as Co-Director. In the last two years, we have lost several patients in their 30's to FD. Each time we lose a patient, it has an enormous impact on the Center's team. We know our patients, their faces, their families, and their lives, and when one is cut short, we question everything. She wanted to take this opportunity to understand if we were making a difference. For that, she turned to the database.

Population statistics

Advancing clinical care for rare diseases is usually a very slow process. By virtue of the scarcity of cases, most rare diseases communities aren't well organized. Patients are seen at different hospitals, by different medical specialists, and their data is dispersed so it cannot easily be interrogated. This is not the case for FD, which has been treated at NYU Langone Health for the last half a century. This centralized approach allowed us to follow patients within the clinic, implement standard protocols for their care, collect their data, and continuously look at the numbers to evaluate the impact of our treatment choices to create better outcomes. Clinical care shifts rapidly, with new technologies, new diagnostic tools, new drugs, and

new treatment guidelines emerging within the last decade that have revolutionized many diseases. The medicine we practice today, is not the same as the medicine we practiced 40-years ago. We keep saying that early intervention and centralized care improves survival, but are we really doing a good job?

To answer this, she worked with the database, enlisting the help of Dr. Maria Cotrina Vidal to look at survival curves. Only 20% of today's FD population are children. This shift can be explained by the increased awareness of FD in people of Ashkenazi descent that are considering having children. Genetic counselling and tools like selective embryo implantation have enabled families to reduce the odds that they may give birth to a child with FD. Most new cases in recent years have arisen in families that are unaware of their Jewish heritage, but happen to carry the FD gene from an ancestor. The FD gene mutation is considered in genetics as a relatively recent founder mutation. Results from a newly published ancient genome study, show that the FD mutation wasn't found in the medieval cemeteries containing the remains of Jewish families prior to the 14th Century. It gained its footing around 200 years later in the founding Jewish community within the Pale of Settlement.

The results showed that in the last 20 years, patients can expect to live well into adulthood, with the oldest known living patient currently in their mid 60's. At the time that FD was discovered, this was unheard of. Every 20 years, we see survival has improved. Low rates of infant mortality and longer life spans were likely the result of better medical care, including lowering our threshold to test for infections and start antibiotics, daily use of respiratory devices to promote airway clearance, restricting eating and drinking by mouth, and when needed surgical interventions.

Current treatments

In her review, Dr. Gonzalez Duarte went on to conclude that although we were prolonging survival, the aging FD population faced new health challenges. What was quite apparent was that the burden of disease was still catastrophic. Patients living into their adult years face declining vision, loss of mobility, worsening lung disease, kidney failure, and severe morbidity. When the disease was discovered, we knew nothing of this. With improved survival we began to recognize the long-term consequences of FD.

Dr. Gonzalez-Duarte's article provides a comprehensive breakdown of therapies so that the community of treating physicians outside the Center can understand our current guidelines. She describes early interventions that have become standard of care, including the fundoplication and gastrostomy surgeries that many patients undergo at an early age. She discussed eye care, lung care, swallow therapy and non-invasive ventilation, which are mainstay treatments that help prevent major complications. She discussed symptomatic treatments that help patients feel better or prevent the crises including carbidopa, dexmedetomine, and sedatives. She included a summary of the approach to antibiotic therapy and ways to control drooling. Finally, she went on to talk about the new disease modifying therapies that are on the horizon to hopefully slow down the progressive neurological aspects of the disease including poor sight and gait imbalance.

Advances in medical care have improved survival, but more is needed to help patients live better

Implications for families with FD

Most clinicians would be happy to pat themselves on the back and say we improved survival and patients with FD are living longer than ever before. But not Dr. Gonzalez-Duarte. Every day, she faces the complexities of FD side-by-side with patients and their families. In recent years, we have lost several patients to the disease. While some of those deaths were sudden and unpredictable, others were potentially preventable. We cannot let our guard down. Choking is still a huge problem. A few of our patients still choose to eat by mouth. This remains a very dangerous risk. Big food particles can be aspirated into the airway, abruptly block the passage of air, and starve the brain of oxygen. We are urging all of our families to become certified in giving first aid in an emergency. Knowing how to do the Heimlich maneuver to dislodge a food particle trapped in the airway and provide basic life support by performing CPR are important skills that can save a life.

WAYS TO GET INVOLVED

Ways to support research

Our scientific breakthroughs in FD would not be possible without the support and participation of the FD families in our research efforts. People with FD that participate in our research volunteer their time to help others with FD, through building knowledge. Here are various ways you can get involved to support our efforts.

Know the different types of research. Research studies fall into two main categories. *Observational studies* (like the natural history study) collect standard clinical information about a disease that can be used to observe outcomes and understand the symptoms over time. *Interventional trials* are studies in which you receive a drug or therapy for a given amount of time that is expected to make you feel better or stop the complications of a disease. This will likely involve safety visits to check that there are no harmful effects and check-ins about your symptoms. Regardless of the type of study, your participation is voluntary, you will not have to pay to participate, and you can choose to leave a study if you wish to do so. Research is a choice.

Ask Questions. Our staff can tell you about new research at any time. You can ask questions about the purpose of the study, gauge the time commitments, and determine if you might be a good candidate. Certain studies may be open to people of all ages at all stages of the disease. Other studies might be open only to people that experience a particular symptom. If you don't qualify for one study, you may qualify for another. There is a research opportunity for everyone.

Talk to your friends in the community. Participating in research helps your friends with FD. You should feel proud to have contributed. Share this with your friends. Let people know that you are an FD research warrior. You volunteered your time to a worthy cause. Wear this badge with honor.

Stay connected. We provide regular updates about our research through the Dysautonomia Foundation, Inc. and our website (www.dysautonomia.com). Subscribing to these channels will allow you to learn about new opportunities and new results that are hot off the press.

Talk to us. We want to make the research experience as pleasant as possible for families and your voice is important. We want to hear from you, if you have suggestions on how to improve your visit or maybe you have a topic that you think we should be investigating. Sharing what was good and what was not so good about your experience teaches us how we can design better studies.

CLINICAL TRIAL OPPORTUNITIES

Current research studies open for patients with FD

OPEN and ENROLLING *** NEW
INDUCED PLURIOPOTENT STEM CELLS IN HSAN3 and HSAN4
IRB#: S12-01702
ELIGIBILITY: People with FD
PURPOSE: The aim of this study is to take a small sample of blood from patients with FD, and in collaboration, transform the live cells in to iPSCs to study the mechanism of disease and explore potential therapies. We are particularly interested in studying the stem cells of patients that have frequent and severe crises (**page 14**). This project is part of a collaboration with Dr. Zeltner and an example of how translational research at the bench can help lead to insights into better treatments.
SPONSOR: NIH

OPEN and ENROLLING
THE NATURAL HISTORY OF FAMILIAL DYSAUTONOMIA
IRB#: S16-01774
ELIGIBILITY: Patients with FD of any age
PURPOSE: To use the clinical information collected during routine medical visits to define the clinical features of FD and to see how they evolve over time. The goal of the project is to find biological signals that we can use to track the features of FD to use in clinical trials to test new drug treatments. The study will also measure IKAP protein levels to see how well they correlate with symptoms of FD.
SPONSOR: Familial Dysautonomia Foundation, Inc.

OPEN
UNDERSTANDING THE MUSCLE IN FAMILIAL DYSAUTONOMIA
IRB#: S14-01192
ELIGIBILITY: People with FD of any age.
Purpose: Patients with FD frequently develop muscle atrophy. Moreover, the incidence of rhabdomyolysis (episodes of muscle destruction) is higher in people with FD. To investigate this we aim to examine muscle function in patients with FD and other hereditary sensory neuropathies by studying muscle samples. Small pieces of muscle are taken during scheduled surgery (scoliosis, hip replacement, etc) and studied.
SPONSOR: Familial Dysautonomia Foundation, Inc.

Recently completed research studies in FD

RENAL INJURY MARKERS IN FAMILIAL DYSAUTONOMIA
IRB#: 13-00279, SPONSOR: Familial Dysautonomia Foundation, Inc.
PURPOSE: The first purpose of this pilot project was to identify early, non-invasive biomarkers of renal injury. The second purpose was to establish a panel of renal injury biomarkers to monitor progression.

AN OPEN-LABEL PILOT TRIAL OF COGNITIVE BEHAVIORAL THERAPY IN FAMILIAL DYSAUTONOMIA
IRB#: S16-01823. SPONSOR: Familial Dysautonomia Foundation, Inc.
PURPOSE: To evaluate the effect of cognitive behavioral therapy in the severity of anxiety, depression and self-esteem in adults with FD.

A STUDY OF GUT FLORA IN FAMILIAL DYSAUTONOMIA (MIBIOM)
IRB#: s16-00718. SPONSOR: National Institutes of Health (NIH)
PURPOSE: To develop a better understanding of the microbiome in FD to help understand GI motility problems in FD, which are common despite the absence of known pathogens.

THE EFFECTS OF BRONCHODILATOR THERAPY ON RESPIRATORY AND AUTONOMIC FUNCTION IN PATIENTS WITH FAMILIAL DYSAUTONOMIA. SPONSOR: Familial Dysautonomia Foundation, Inc
IRB#: S13-00004
PURPOSE: Assess the effects of ipratropium and albuterol in patients with FD.

CARBIDOPA IN FAMILIAL DYSAUTONOMIA (BLOOD PRESSURE)
IRB#: S13-00065. SPONSOR: Food & Drug Administration Office of Orphan Product Development
PURPOSE: The goal of this study was to use carbidopa and evaluate the effect in blood pressure peaks and variability, norepinephrine levels, and crisis in FD. The results were published in *Hypertension*.

PROPRIOCEPTION AND SENSORIMOTOR CONTROL IN HSAN
IRB#: s16-00530: SPONSOR: National Health and Medical Research Council of Australia
PURPOSE: The purpose of this study is to understand disturbances in walking in FD patients.

THE USE OF CARBIDOPA IN FAMILIAL DYSAUTONOMIA (NAUSEA)
IRB#: R09-0011. SPONSOR: Food & Drug Administration Office of Orphan Product Development
PURPOSE: The study objective was to determine if carbidopa reduces the spillover of dopamine into the circulation and decreases the frequency of nausea in FD patients. The results were published in *Neurology*.

PHOSPHATIDYLSERINE (PS) IN FAMILIAL DYSAUTONOMIA – DOSE TITRATION STUDY
IRB #: 11-02100. Sponsor: Familial Dysautonomia Foundation, Inc. and Country Life LLC (which donated PS).
PURPOSE: This study was a safety, tolerability and proof of concept efficacy study of PS in patients with FD.

KINETIN IN FAMILIAL DYSAUTONOMIA
SPONSOR: Familial Dysautonomia Foundation, Inc.
PURPOSE: To evaluate the safety, tolerability and efficacy of kinetin, a nutritional supplement, that corrects the splicing defect in FD patients.

NATURAL HISTORY PROJECT

We need you. The closer we can follow you, the sooner we can understand your issues and the closer it brings us to finding a treatment. Our Natural History Study is currently open and recruiting patients with FD.

There are several ways be involved:

- Patients with FD who are evaluated at the NYU Dysautonomia Center in New York or at a satellite center in Israel or Mexico will have the option to be enrolled in the Natural History Study.
- If, for whatever reason, you are unable to visit in person, you can still send medical records from your local doctors to be included in the database.

What type of clinical information should you send?

- Your most recent sleep study report
- Your most recent swallow study report
- Your most recent office visit notes from your neurologist or other specialist
- Your most recent chest-CT or chest x-ray report. Ideally, you should also send a CD/DVD with the images.
- Your most recent eye evaluation, ideally including retinal optical coherence tomography (OCT) and other visual function tests
- Your most recent pulmonary function tests
- 24-hour blood pressure recordings
- Results from regular blood or urine tests
- Notes from hospital admissions or surgical admissions
- A current medication list

These tests are routine for patients with FD as part of their standard medical care. They help screen for potential problems and determine when treatments are necessary. If you are still unsure of what to send, send us any your information from any visit to a doctor.

The FD Questionnaire: The FD Questionnaire was developed over several years to provide doctors with the information they need in clinical practice. It is a series of questions that cover all the body systems, how they function, and identify common complications at different stages of the disease. The questionnaire is specifically designed for patients with FD, to be filled on a yearly basis. Filling it out will help families prepare for their visits with doctors. The FD Center will send you a link to the questionnaire as soon as you schedule your appointment (212-263-7225).

What will happen with my information? The information received will be stored in specially designed databases. It will be used by the research team to answer pressing clinical research questions. It allows us to look at trends over time and examine which treatments are truly effective for treating FD. It allows us to look for patterns to provide guidelines that will shape clinical practice. The study is designed to support clinical trial readiness to speed up drug development to improve the lives of patients with FD. The goal is to help other researchers working and collaborating on FD and support their scientific work with this information.

How is my information protected? The information collected in the natural history study is stored in a secure encrypted server supported by MCIT at NYU Langone Health. Access to identifying information is restricted to NYU Langone Health administered terminals. Patients should transmit their medical records through data-protected safe channels, including MyChart and NYU Langone Safe-Email Portal. Support for this can be provided. Data shared for research is de-identified and entered into a secure online data collection platform (RedCap) with controlled access. If you no longer wish to participate, you may request that your data be removed.

DYSAUTONOMIA CENTER

Staff

Dr. Horacio Kaufmann, MD
Professor, Director

Dr. Alejandra González-Duarte, MD, PhD
Associate Professor, Co-Director

Dr. Jose-Alberto Palma, MD, PhD
Associate Professor

Dr. Lucy Norcliffe-Kaufmann PhD
Adjunct Associate Professor

Dr. Zenith Khan, DNP, FNP-BC
Specialist Nurse Practitioner

Dr. Kaia Dalamo, DNP, FNP-BC
Specialist Nurse Practitioner

Dr. Patricio Millar-Vernetti, MD
Research Instructor, Neurology

Lee-Ann Lugg, BS
Program Coordinator / Administrative Lead

Mechteld "Mecky" Kuijpers, BA
Junior Scientist

Mike Yates
Project Assistant

Jose Martinez, MS
Clinical Trials Manager

Matthew Hertzberg
Social Work Intern

Lily Armstrong, MA, LPC
Licensed Professional Counselor

Collaborators

Susan Slaughenhaupt, PhD
Frances Lefcort, PhD
Bat-el Bar, MD
Mikhail Kazachov, MD
Elisabetta Morini, PhD
Leela Raju, MD
Sumantra Chatterjee, MD
Carlos Mendoza, MD
Vaughan Macefield, PhD
Alex Gileles-Hillel, MD, PhD
Joel Gutierrez, MD
Nadja Zeltner, PhD
Patrick Hof, MD
Shruti Ravindramurthy, MD
Chethan Ramprasad, MD

Support for the Program

Familial Dysautonomia Foundation Inc.
HSAN IV Foundation
Food and Drug Administration
Biogen Inc.
Anonymous Donations
National Institutes of Health
Theravance Biopharma Inc.
Montreal Chapter of FD
J Aron Charitable Foundation Inc.

2022-2023 HIGHLIGHTS

Dr. Alejandra Gonzalez-Duarte receives Carl Seaman Family Professorship for Dysautonomia Treatment and Research

Dr. Zenith Khan completes her Doctor of Nursing program

Dr. Horacio Kaufmann invited to give a plenary lecture at the Movement Disorders Conference

Dr. Nadja Zeltner publishes her work on FD stem cells in *Nature Communications*

Dr. Seth Walk publishes his work on the Microbiome in *Nature Communications*

Dr. Kaia Dalamo runs the NYC Marathon for FD

Dr. Alberto Palma and his wife welcome their first son David

Dr. Valerie Copie publishes her work on the metabolic profiles of FD patients

Dr. Gonzalez-Duarte publishes results of survival in FD in *Clinical Autonomic Research*

Case-controlled study of GI bleeds in FD published in *Clinical Autonomic Research*

Dr. Elisabetta Morini receives a second NIH Blueprint grant to develop new therapies for FD

Former visiting medical student Dr. Celeste Camargo was accepted into Rutgers' Neurology Residency Training Program

Dr. Patricio Millar joined the Editorial Board of the journal *Clinical Autonomic Research*

Clinical Trials Manager Mr. Jose Martinez celebrates 12 years at NYU's Dysautonomia Center

Dr. Gonzalez-Duarte appointed Chief of the Visiting Scholars Program at the Dysautonomia Center

Dr. Millar co-authored a chapter on genetic autonomic disorders for the forthcoming book *Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease*

Dr. Frances Lefcort will retire from Montana State University after 29 years of success!

Dr. Vaughan Macefield publishes a review on gait ataxia in FD in *Experimental Physiology*

The MGH Team publish the results of super kinetin in the *American Journal of Human Genetics*

The MGH Team partners with researchers in Italy to explore RNA-based therapies in FD mice

Dr. Lefcort and team publish results of ELP-1 deficiency on nerve cell survival

10 FD QUICK FACTS

1) FD is caused by a mutation in the ELP-1 gene (which used to be known as IKBKAP)
2) Over 99% of patients inherit 2 copies of the Ashkenazi (founder) mutation dating back to the 1500's
3) Most parents of newly diagnosed children with FD are unaware of their Jewish heritage
4) FD affects the development and survival of the nervous system within the brain and the body
5) Patients have similar symptoms, but the severity may vary
6) There are symptomatic treatments that help patients feel better and live longer
7) Currently, FD has no cure
8) Patients have less sensation, are at risk of injuries, have difficulty localizing pain, and regulating their body
9) Lung disease is common and requires a proactive approach to treatment
10) The NYU Dysautonomia Center has existed for over half a century and is dedicated to FD patients 24/7

10 THINGS YOU SHOULD KNOW

1) Basic life support training is a must. We recommend that all family members living with a person with FD receive training to know how to administer basic life support (including CPR and airway clearance techniques). Refresher courses should be completed on a regular basis.
2) Therapy is available through the Center. We support clinician social workers to run dedicated group sessions for patients and parents. Please contact the Center (212-263-7225).
3) You can call and ask about new research at any time. Our staff would be glad to talk to you about new studies you might be interested in. We will guide you through the enrolment process. Depending on the level of involvement, you may be able to consent virtually.
4) Your information is secure. Your data is stored behind a secure firewall, on an encrypted database. Your personal identifying information is never shared without your consent.
5) You will never be charged for research. Research is voluntary and free. You will never have to pay to participate. Our research is sponsored by grants and donations.
6) The tests done in your annual visit are all part of clinical care. Your comprehensive annual check-ups are for medical care and are not research studies. You can learn about how to take part in our research projects at the visit. If you wish to participate, you will work with our staff to obtain your consent and schedule a time that works for you.
7) Subscribe to our blog to receive important updates. Visit www.dysautonomiacenter.com and sign up to subscribe to our blog. You will receive updates on treatment guidelines and research progress directly to your inbox.
8) We will work with you to make your visit a good one. If you have concerns about your visit, don't know what to bring, or want to know more about what to expect, call our staff to talk it through.
9) Our emergency phone line is open 24/7 all year. The on-call phone is carried by our medical staff at all times. Whenever there is an emergency, families can reach a dedicated expert for advice. It is the same number as our office (212-263-7225). You will be connected by NYU's after-hours phone service team.
10) If you are admitted to NYU we can see your progress live. The NYU EPIC system allows us to follow your progress in real time, coordinate with the hospital ward teams, and support you during your visit.

STAYING CONNECTED

www.dysautonomiacenter.com

www.facebook.com/dysautonomiacenter/

@nyudysautonomia

https://familialdysautonomia.org/news/newsletter

https://nyulangone.org/locations/dysautonomia-center

NYU Dysautonomia Center
530 First Avenue, Suite 9Q
New York, NY, 10016
+1 212 263 7225
www.dysautonomiacenter.com