

2021 -2022
YEAR IN REVIEW



THE LATEST IN RESEARCH AND CLINICAL
CARE IN FAMILIAL DYSAUTONOMIA

NYU^{CENTER FOR}**Dysautonomia**

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A MESSAGE FROM OUR DIRECTOR



The FD community has a long track record of facing challenges head on and seeking innovative solutions. This requires a dedicated team that never give up. The past years of the global pandemic have meant that we had to adapt to provide high level clinical care and advance research in new ways.

Clinical care at the Center has always been our top priority. While the Center is again open for in-person visits, we have also embraced the new world of telemedicine. Breaking down the geographical boundaries that prevented families from visiting the Center to seek care, has enabled us to reach families in their own homes, no matter where they live through a video screen. At first it might have seemed strange to not meet face-to-face, but the work has been done to make certain we can check a person from head-to-toe with precise questions and at home kits.

The vision and strategy of the Center when it comes to research remains the same. We are continuing to work on symptomatic therapies and genetic interventions that will help patients with FD feel better and live longer. The principles guiding our research program stem from supporting clinical development so that potential new therapies can be brought from the bench to the bedside as quickly and seamlessly as possible.

It takes a village. Our Scientific Advisory Board includes some of the best minds in genetic therapies, committed to FD, who are working on multiple different approaches to curing FD. The more we have different and diverse ideas, the better we will do. I'm very grateful to the Board that keeps on pushing us. Together we are pioneering this journey forward. There is still more for us to do.

Some of our wins over the last year include a psychotherapy program and understanding the social aspects of FD by examining the brain. As we think towards the future, we are laying the groundwork to roll out clinical trials at home, dive deeper into the genome of FD, and expanding our care with international satellite FD Centers of Excellence. Our FD workforce is the key to making sure we are effective. Research happens at many levels. Our team of skilled nurses, doctors, research assistants, trainees, and scientists are always asking what do we need to do to make a difference? Our ability to do world-class research also depends on our collaborators. We are fortunate to partner with outstanding scientists who bring their unique expertise to tackle the unknowns and broaden our understanding. Many of our collaborators have spent years studying other diseases and can apply those learnings to FD.

The coming year gives us a time to focus. The opportunities for treatment are closer than ever. The Center remains committed to our partners at the Familial Dysautonomia Foundation, who continue their unwavering support that makes our work possible. We of course, depend on you. Progress cannot happen without your participation. We believe every patient with FD deserves the opportunity to try new treatments, regardless of where they live, their age, or how advanced their FD has become. We remain committed to ensure that we advocate for everyone. We are making progress.

A handwritten signature in blue ink, appearing to read 'H. Kaufmann'.

Horacio Kaufmann, MD, FAAN,
Director of the Dysautonomia Center



Dr. Alejandra Gonzalez Duarte is the Center's new Co-Director

The long search for a Co-Director to lead the Center is finally over. We launched a worldwide campaign to bring on a talented and experienced physician to drive our program into the future. It was a matter of finding the right person. We knew we needed someone committed, unflappable, and highly skilled. Dr. Alejandra Gonzalez Duarte came on-board as our Co-Director in 2021. No stranger to FD, Dr. Gonzalez Duarte was the first graduate of the Center's Autonomic Disorders Fellowship Program, an intensive hands-on training course for neurologists supported for the last decade by the Familial Dysautonomia Foundation, Inc. Having trained in internal medicine, infectious diseases, neurology, and autonomic disorders, Dr. Gonzalez was a clear leader in the field.

Dr. Gonzalez Duarte is used to complicated patients and rare diseases and does not shy away from taking on the hardest medical challenges. After her NYU FD Fellowship, she returned to Mexico to care for families with a rare genetic mutation that causes familial amyloidosis, a devastating dominantly inherited disease. She became the leading autonomic nervous system disorders specialist in Mexico. She built a clinical research program that helped science make one of the biggest neurological breakthroughs of the last decades, steering to the approval of gene silencing to save nerve function. This landmark achievement meant that RNA therapies became a reality for patients living with progressive neurological diseases. "She helped changed the way we think about and treating diseases," explained Dr. Kaufmann – the Center's Director, "I knew I wanted her on our team".

Returning to Mexico didn't stop Dr. Gonzalez Duarte from staying connected with FD. Soon after the first cases were discovered deep in the heart of central Mexico, she organized for the families to visit her clinic and receive care. She is now helping set up an FD Center in Mexico and train doctors to diagnose and treat FD. What sets Dr. Gonzalez Duarte apart are her incredible skills as a doctor. She is one of the most highly trained specialists in the world. She never stops thinking about her patients and exploring all opportunities to treat their problems. She listens carefully, asks probing questions, and always considers what is best for her patient. Her knowledge of clinical pharmacology is impressive.

The Center is excited to welcome Dr. Gonzalez Duarte into the Co-Director leadership role. She will receive the Seaman Family Professorship Chair, which was previously held by Dr. Felicia Axelrod. "I am delighted to accept the Seaman Professorship, Dr. Axelrod was a pioneer that inspired so many women in the field of autonomic medicine. To take on her legacy and continue the care of FD patients is an enormous honor" – explained Dr. Gonzalez Duarte.



FD Centers of Excellence around the world

Sarahí, was born in Mexico and diagnosed with FD at the age of 13. Struggling to find specialist medical care, her family set out to search for doctors that could understand her complex needs. The problem with genes is that they travel. The FD gene mutation (IVS20+6T>C) occurred around the 1500's in the population of Ashkenazi Jews that was founded in Europe. Many generations later, that population dispersed and now lives all over the world. No longer subject to the geographical constraints imposed by European monarchs, the FD gene is deeply entrenched within the Ashkenazi gene pool, and people are born with FD in many different countries.

The first specialist FD Center was built in New York City, where the first cluster of cases was described. Fast forward to 2022, there is now two additional specialist Centers in Israel, and a fourth opening in Mexico City. The Dysautonomia and Small Fiber Laboratory at the National Institute of Medical Science and Nutrition "Salvador Zubirán" in Mexico City is the only clinic in Mexico that specializes in FD.

There are only a small number of Jewish descendants in Mexico, making FD an even rarer disease in the country. However, in recent years, we began to hear of patients in Mexico that were being diagnosed with FD. What remains remarkable, is that new FD cases in Mexico harbor that original founder mutation, but the parents were completely unaware of their Jewish heritage, until having a baby diagnosed with a Jewish genetic disease. More suspected FD cases are under evaluation. Founded by Dr. Gonzalez Duarte, the Mexican FD Center of Excellence, now has all the necessary tools to perform a detailed evaluation of in a patient with FD and collaborates with many other specialists to provide care of the lung, eye, gastrointestinal, and orthopedic complications of FD. The team in Mexico have visited the Center in New York to train in FD care. These close ties will ensure we have standardized protocols for assessing patients in all our clinics. Our partners in Mexico have a tremendous job in front of them, especially now that the FD gene has been detected in families without known Jewish ancestry. Likely they will find more cases. They remain focused on educating the local medical community to spot FD early so that they can provide the best care as soon as possible.

Nowadays, thanks to our FD partners in Mexico, Sarahí's blood pressure is more stable, her autonomic crises less frequent, and she is now a more active happier child. Reaching patients with FD on a global scale means we must think beyond the obvious locations where we know there are large Jewish communities. The FD gene has left Europe, its worldwide reach has expanded, and so must our care.

NEW FACES

One important goal of the Center is to educate clinical scientists in research. Clinical research requires a different set of skills than research at the bench. First and foremost, is always the patient. Research protocols must be developed with precision and innovation, because FD is a rare and complex disease. Bringing early career scientists to work on FD in a clinical setting provides an invaluable teaching opportunity. Many former trainees at the Center have gone on to become doctors, dentists, nutritionists, social workers, and some have set up their own clinics or taken on positions as global leaders in drug development. The Center welcomes two new faces, who are poised to continue in the footsteps of previous FD trainees.



Mechteld Kuijpers is a Project Assistant responsible for maintaining the study databases for FD related projects. She assists the clinical research team at the Center providing support for all the daily activities. She is a graduate of the neuroscience program at Oberlin College. She has a particular interest in sensory function and sight.



María Eugenia Briseño Godínez, MD was a visiting fellow at the Center who took part in a 6 months observership. She is a residency trained neurologist with specialist training in autonomic disorders. She completed an Autonomic Disorders Fellowship at The Instituto de Ciencias Médicas y Nutrición "Salvador Zubirán" and currently runs the Mexico FD Center of Excellence.

The Center has a Visitor Professor Program and a Clinical Observership Program for clinicians and scientists who want to spend time learning about FD and gain hands-on experience. Candidates interested in our undergraduate summer internship program should email a letter of interest to Lee-Ann.Lugg@nyulangone.org.

A NEW TECHNOLOGY GIFT

If we make the shower too hot or accidentally touch a boiling cooking pot, we feel it and retreat immediately. Patients with FD are born without these protective reflexes as they have fewer sensory nerves. They feel heat at higher thresholds and can be unaware of burning themselves when they touch something hot.

Sensation is a hard thing to measure. The NYU Dysautonomia Center recently acquired a new TSA-II analyzer with a generous gift from J Aron Charitable Foundation Inc. With this equipment, we will be able to compare the function of small and medium nerve fibers in our FD population and compare how this changes overtime. The ultimate objective of these measurements is to allow us to use the information to assess the benefits in the clinical trials to come. Applying the latest technology to study sensation in FD will be an important avenue for future research.

TALK THERAPY



Find out how the legacy of Stevie Schwartzberg helped support a psychotherapy program for FD

Ready to talk?

Stevie Schwartzberg was born with FD in the 1980's. His infectious smile and positivity came across immediately. An avid exerciser, he personified what it means to work hard and live well. When Stevie lost his life to FD, his family embarked on a quest to support a psychotherapy program at the Center dedicated to FD. At that time, the therapy program was a pilot project, created by Lily Armstrong, to explore whether talk therapy was helpful for people living with FD. With the support of the Schwartzberg family, the FD talk therapy program has helped change the lives of people living with FD, many of which now have new skills to handle life's challenges. Beginning therapy can feel like a very big deal. It's not uncommon for people to wait too long before seeing a therapist. Unfortunately, it's far too common for people to struggle with their problems for years before seeking help.

Depression and anxiety are a problem for many people with FD and can lead to autonomic crisis, social isolation, and difficulties attending events or medical visits. Although the clinic team were recommending talk therapy, patients often had difficulty connecting with therapists that knew the intricacies of FD. The FD talk therapy program overcomes this hurdle by having Lily Armstrong, who has come to know the FD community thanks to the support of the Montreal Chapter of Dysautonomia and the Schwartzberg family's ongoing pledge. It can be very beneficial to have even a few short sessions of Cognitive Behavior Therapy. Here are 5 signs that you might be ready to give therapy a try.

1) Basic life tasks feel hard

Sometimes we all reach a point when getting out of bed seems difficult and tedious. The stress of relationships, health concerns and other responsibilities can be too much. And yet we often feel better when we share, with vulnerability, the challenges we are currently facing. If the pandemic, physical challenges, or future worries are getting in the way of daily life, reach out for help.

2) Making friends can be difficult for you

If FD has been part of your story, you know the difficulties in relating to others who may not know your daily reality. It can be very stressful to make and sustain deep friendships. Certainly, in a pandemic time, and in a rapid world, carving out time and space for friends is tough. If you'd like some guidance and coaching on how to make and sustain lasting relationships, meeting with a therapist can be a great start.

3) Stress is impacting good sleep

If your sleep cycles have been disrupted as of late, or if you find yourself mindlessly scrolling through social media or news cycles, you may benefit from therapy. Often, the difficulty in maintaining healthy sleep habits is our body communicating important messages to us. In therapy we explore building better habits, including sleep cycles, that means managing stress patterns doesn't have to interfere with good sleep.

4) You spend a lot of time overthinking

If you find yourself dwelling on the past, beating yourself up over mistakes or what you could have done differently in a situation, therapy might be right for you. In sessions, you will talk through your thought patterns and discern together which ones are helpful and those you can let go of. We were not designed to get stuck in the past or overthink. Therapy has proven to be very helpful for those facing similar struggles.

5) You are curious

Perhaps you're just curious or want to take advantage of a great opportunity to learn more about yourself. Therapy doesn't have to be a years-long commitment. And a therapist won't ask you to go more in depth than you want to, especially in the first few sessions. Even getting a fresh start and a new perspective can help you feel more fulfilled.

Many different situations, including those mentioned above, can prompt us to start the therapeutic journey. In any case, you know that your therapist will receive you with the care and compassion that you deserve. Please contact the NYU Dysautonomia Center to receive more information or schedule a session.



Lily Armstrong developed the FD talk therapy program thanks to the gift of the Swartzberg family in memory of Stevie. The program provides access to a therapist with a deep knowledge of FD to support patients of all ages.



The long history of the FD mouse has paved the way for new therapies to be tested

Animal models of FD: A story of perseverance

Mice are indeed very similar to humans in terms of anatomy, physiology, and genetics. Mouse models of human genetic diseases are crucial for a better understanding of disease mechanisms and developing new therapeutics. New drugs can be given to mice in “pre-clinical” studies to look at metabolism and absorption, general safety, and even efficacy. Scientists have long wanted a mouse model of FD.

A big challenge for FD was to generate a mouse that had the classic symptoms of the disease. The mouse has its own FD (ELP-1) gene that is 80% identical to the human gene. Back in 2009, geneticists working on FD started editing the mouse genome to knock out and remove its own ELP-1. This proved more challenging than original thought. Patients with FD still produce some normal protein, despite the gene being misread. A small amount of normal protein goes a long way. Completely knocking out the mouse ELP-1 and removing it all together during development proved fatal.

Path to progress

Back to the drawing board, the team at Mass General Hospital lead by Dr. Susan Slaugenhaupt created a transgenic mouse model by putting the FD splice mutation into the mouse. One thing that is unique about the FD gene mutation is that it is not read the same in all tissues. The brain, for example, seems to read the faulty gene and produce almost no functional protein, whereas other organs appear to correctly read the faulty gene and produce functional protein products. This is known as *tissue specific splicing*. The transgenic mice produced ELP-1 in the same tissue specific manner. But the team were left scratching their heads, the mouse did not recreate the symptoms of FD, because its own ELP-1 gene was still working. Other teams working on FD faced similar problems.

In 2012, the first symptomatic mouse models for FD were generated by husband-and-wife team Drs. Paula Dietrich and Ioannis Dragatsis at the University of Tennessee. They engineered mice to reduce their own ELP1 expression up to 95%. Although their mice had very severe FD symptoms, including poor growth, ataxic gait, loss of pain and temperature

sensation, kyphosis, and nerve loss, it was still not the perfect model as the mutation didn't behave the same as the human FD gene.

Dr. Frances Lefcort and Dr. Warren Tourtellotte created a conditional knock out mouse by selectively deleting ELP1 in neural crest cells, which give rise to sympathetic and sensory neurons during development. These mouse models provided valuable insights into disease mechanisms, as the reduction of ELP1 expression was obtained by complete ablation of the mouse gene rather than mRNA mis-splicing. Unfortunately, their mice were born alive but died within 24 hours of birth, and the models could not be used for studying therapeutic interventions that modify mRNA splicing.

In 2016, with the goal of creating an accurate mouse model for FD, the MGH and Tennessee teams introduced the human ELP1 gene with the FD founder splicing mutation into the mouse. This reduced ELP-1 levels by 95%, producing a mouse with the FD symptoms and the tissue-specific mis-splicing observed in FD patients, with very low amounts of normal ELP1 expression in the brain.

The generation of this new mouse model was a breakthrough in the efforts to develop a model system to test the efficacy of new therapeutics. It took a lot of grit. This mouse is now being used for testing the effectiveness of many novel splicing targeted therapeutics for FD, including splicing modulator compounds and exon-specific U1 small nuclear RNAs.

Collaboration

Although the path towards finding an ideal FD mouse has been long, key lessons were learned. Perseverance pays off. The years of permanently engineering mice to stop producing ELP-1 taught us how valuable it is for survival. They also helped us learn that raising ELP-1 helps mitigate some of the worst symptoms of FD. This leaves us optimistic that gene therapies for patients can do the same. They also taught us that collaboration is a key element to success. Dr. Elizabeth Morini has spent much of her career developing FD mice to test new therapies. With several possible treatments in the pipeline, having a mouse to test their safety and efficacy is a critical step in the path towards drug discovery.

TRANSLATIONAL RESEARCH



Microbes in our gut can impact our nervous system

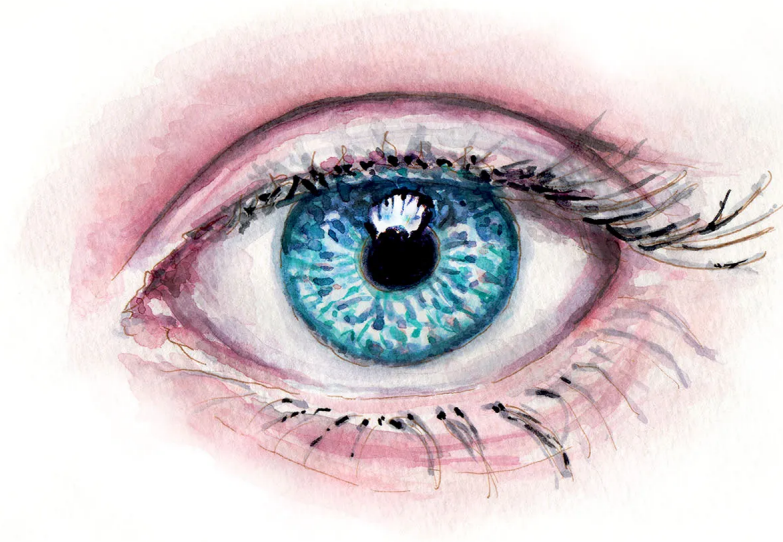
The gut, the eye, and the mouse

Over the past few years, Dr. Frances Lefcort and her team have been focused on understanding two of the hardest problems that people with FD face: gastrointestinal (GI) disturbances and progressive blindness. Dr. Lefcort, a world expert in neuroscience and cell biology, runs a busy lab at Montana State University, tinkering with the ELP-1 gene in mice and analyzing samples from patients. Her scientific research is driven by her curiosity to understand the FD gene, its impact on neurons, and how it interacts with the body, as well as her personal quest to find a cure for the disease that affected her cousin. Her findings have changed the landscape of basic science research in FD over the last years.

The interplay of nerves and microbes in our gut

The GI tract contains over 500 million nerve cells (neurons) in addition to being extensively innervated by the neurons outside of the gut in the autonomic and peripheral sensory nervous system. Those neurons regulate our GI tract activity so if anything is altering their health, GI problems can result. Over the past few years, scientists have learned that the function of those GI neurons is affected by the trillions of bacteria (called the “microbiome”) that live in our GI tracts. Those bacteria secrete signals that affect neurons, and collectively they both respond and affect our metabolism. Thus, by analyzing our metabolism (e.g., in our blood and our stool) and our gut microbiome, it is possible to detect if there are any potential imbalances or deficiencies that could affect our gut function.

To study the GI tract in FD, Dr. Lefcort and her team have analyzed the metabolites in stool and serum samples from FD patients and their family members and their gut microbes. This project is a collaboration between the NYU FD Center and with two other labs at Montana State University, that of Drs Valérie Copié and Seth Walk in addition to the Lefcort lab. These data reveal that significant differences exist between FD patient stool and serum samples and that of their relatives.

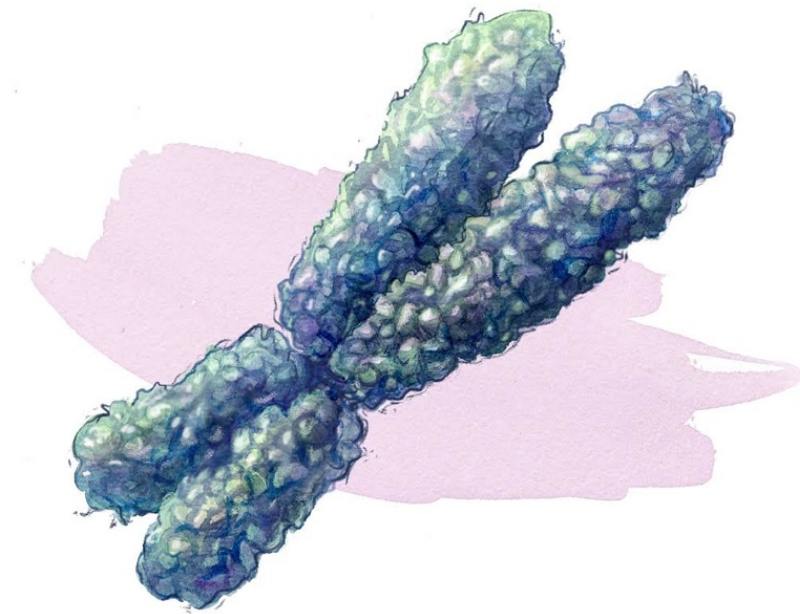


The eyes

The vision of virtually all people with FD diminishes with age. Drs. Carlos Mendoza-Santesteban and Horacio Kaufmann were the first to show that the demise in vision is due to the progressive loss of the retinal ganglion cells. These cells are critical because they are the output cell from the retina: that is, they extend connections to the brain. Without those connections, we can't "see".

Dr. Lefcort's lab and that of Dr. Susan Slaugenhaupt's at MGH, have made mouse models of FD that develop the exact same progressive demise of retinal ganglion cells (see above). These mice provide us with a powerful model system to test potential therapeutics that could prevent the death of retinal ganglion cells in patients. In collaboration with Dr. Claudio Punzo at University of Massachusetts Medical School and Drs. Elisabetta Morini and Susan Slaugenhaupt at MGH, we have shown that reintroduction of a healthy copy of the ELP1 gene into the retina, can reduce the loss of retinal ganglion cells in our mouse model. This approach is called "gene therapy" and given these promising findings in mice, and with funding from the FD Foundation, we will engineer and produce a viral vector that would deliver the human ELP1 gene to the retina of patients with FD. We will first test its effectiveness in mice and if promising, then translate this work to FD patients. Those discussions are underway, and funds will be sought to support a clinical trial. An update will be provided at FD Day.

GENETICS RESEARCH



Science Award supports a new collaboration at NYU to understand the GI symptoms of FD

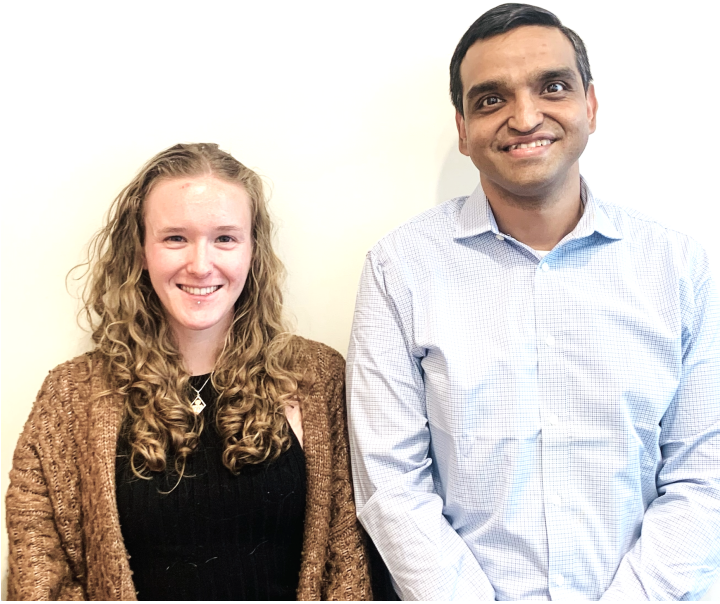
Diving deeper into the genome of people with FD

Almost all FD patients carry the same mutation, but FD is not the same for every patient. Although 90% of FD patients have gastrointestinal (GI) dysfunction, for some this is more problematic than others. The gut is lined with millions of tiny nerve cells, known as the enteric nervous system, that ensure it moves in a rhythmic synchronized fashion for digestion. Nerve studies in patients with FD show a severe reduction in the number of enteric neurons. For one NYU researcher, Dr. Sumantra Chatterjee, this finding piqued his interest as it sounded remarkably similar to another genetically distinct GI motility disorder, known as Hirschsprung disease.

**“Other gene mutations may interplay to determine
who has the most severe FD symptoms”
– Dr. Sumantra Chatterjee**

Hirschsprung disease is marked by absence of nerve cells of the distal GI tract that occur from the failure of the enteric nervous system to develop properly. It is caused by various mutations spanning 24 genes. The most critical mutation, found in around half of Hirschsprung patients occurs within the *RET* gene, which affects the expression of other genes in the developing gut, including *ELP1*. This raises several fundamental questions: (1) How does this genetic interaction between *RET* and *ELP1* manifest clinically? (2) Is the disrupted interaction between *ELP1* and *RET* or with other genes, the primary cause of the gastrointestinal phenotypes in FD patients? Do some FD patients with the most severe GI dysfunction also have Hirschsprung disease? And what are the cellular changes in the GI tracts of these patients?

To address these questions, investigators at the Center for Human Genetics and Genomics within NYU have embarked on a study, funded by the Parekh Center for Interdisciplinary Neurology. This study in collaboration with the NYU Dysautonomia Center will perform targeted sequencing of these 24 Hirschsprung genes in FD patients with GI dysfunction. This will enable us to determine if these patients have additional mutations, beside the known mutation in *ELP1*, which can contribute to the GI symptoms.



Dr. Sumantra Chatterjee and Lauren Fries are key researchers involved in tackling the interaction of different genes to understand the gut in FD.

The research will also involve the creation of new mouse models with deletion of the ELP1 and RET genes to study the gut tissues. This will enable us to detect what types of neuronal cells are affected in these mice which will act as a model for FD patients with GI dysfunction. The catalog of neuronal changes in the mice gut, will help inform our future studies in FD patients

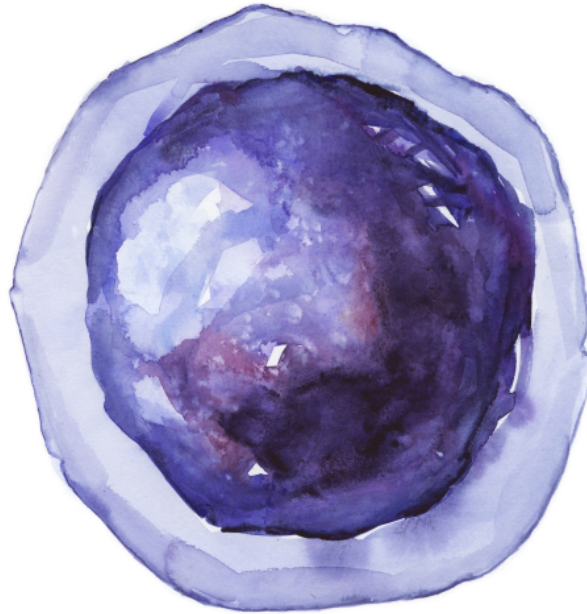
Progress in understanding the GI issues of patients with FD has been a long-standing project for the NYU Dysautonomia Center. Monogenic diseases like FD present interesting opportunities to learn how other genes may interplay to create a particular expression of disease and underlie severity. Investigators have long since struggled to answer why despite 99% of patients carrying two copies of the exact same founder mutation, some may have severe problems that plague their day-to-day life, whereas others may have relatively minor problems that don't interfere with their lives. Each person with FD has similarities and differences.

So-called modifier genes may provide our genetic background and may underlie severity. The FD gene likely impacts the gut in one way (or several ways), but it may be the interaction with other genes that ultimately decide how severe a person's symptoms are. The Ashkenazi Jewish population is unique, because of their history they harbor several different mutations or variants in other genes, such as those involved in cellular health and removing toxic byproducts from our neurons. The genetic risk for developing GI symptoms may answer the puzzle of phenotypic variability.

We believe these studies would not only help understand the spectrum of the gastrointestinal dysfunction observed in FD patients, but will also help in patient management by better classification of the patients. It may also open new avenues for treatment, targeting other genes beyond ELP-1 to restore function.

The initial data on targeted patient sequencing would allow us to propose a larger, longitudinal studies on these patients including assessing the GI tissue for cellular analysis and whole genome sequencing to find potential modifier genes beyond the existing 24 Hirschsprung genes and ELP-1. This is made possible since we have access to a well characterized phenotypic data, housed at the NYU Dysautonomia Center. Diving into the FD genome may help us understand diversity in the population.

NEW CELL LINES



Stem cells created from the skin and blood can help develop new therapies

Reprogramming the cells to find breakthrough therapies

Stem cells are the body's raw materials for making other cells. They are immature cells that can be programmed to make other cells with specific functions. In 2007, researchers discovered that skin cells could be reprogrammed and biochemically coaxed to go back in time and turn into stem cells, which when mixed with the right materials, can go on to develop into any other cell type. These reprogrammed cells are known as induced pluripotent stem cells.

Saving nerves

The team in Israel lead by Dr. Bat-el Bar in collaboration with Prof. Miguel Weil, are ready to start a new study to collect skin biopsies and blood samples from FD patients and family members and transform them back into stem cells. The goal is to eventually make them grow into neuronal cells to test new therapies. These new FD nerve cells can be bathed with different molecules to test whether new (or existing) drugs can protect and preserve the cell, keeping it healthy, and preventing it from dying.

**“Stem cells are an important tool to pave the way
towards personalized medicine”**

– Dr. Bat-el Bar

The stem cells created from skin can also be used to understand the molecular underpinnings of FD. They can be examined to explore their electrical activity and chemical transmission. We can explore their structure and function at a detailed microscopic level to determine why they malfunction and are at risk of dying. ELP-1 isn't only involved in the development of the nervous system, but it also plays a role in the health of our neurons and how they transport chemical messengers (neurotransmitters). Early work shows that stem cells derived from FD patients don't behave the same as those made from health people. They migrate slowly, branch out less, and survive poorly.

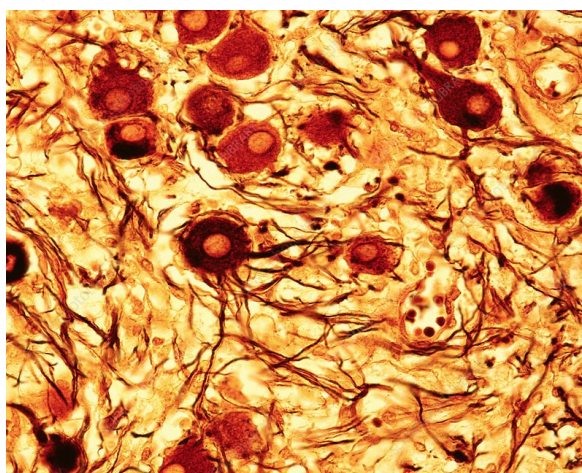
The Israeli stem cell research project will include 20 volunteers with FD and their relatives. The team will reprogram skin cells to behave like stem cells and transform them into neurons at The Ben Gurion University under the supervision of Dr. Gad Vatine. They then plan to screen 6000 FDA-approved drugs to see whether they can improve the function of the FD-cells. The hope is that they will shine the light on potential new therapies that could be targeted to specific people with FD depending on how their cells respond. This approach essentially provides FD cells in a dish as a path to finding new disease-modifying therapies.

Stem cells in crisis

In FD, some nerves are underactive, whereas others are overactive. Dr. Nadja Zeltner is turning our attention to the sympathetic nervous system which orchestrates the body's overall reaction to stress to produce the flight-or-fight response. These nerves reach out to our blood vessels, heart and kidney, speeding up the heart and raising blood pressure. At times of stress, in a person with FD, the brain orders the sympathetic nerves to become overactive. With prolonged stress, this can trigger an autonomic crisis.

The body usually has these sympathetic nerves under very tight control, so that the neurotransmitters released don't rise to excessive levels. Blood taken from patients in a typical crisis show high levels of dopamine triggering uncontrollable vomiting and high levels of adrenaline-like hormones producing high blood pressure and fast heart rates. Even at rest, the sympathetic nerves show a different biochemical profile, almost as if they are primed to start over producing dopamine.

Dr. Zeltner, an FD stem cell expert, began her career coaxing stem cells from FD patients to grow into neurons, and has since perfected her technique to grow sympathetic neurons from blood samples. She received funding from the National Institutes of Health to set up her laboratory and continue her work.



Blood taken from FD patients can be made into sympathetic neurons

The NYU Dysautonomia Center is helping Dr. Zeltner take her research to the next level. Patients can now volunteer to give a small sample of blood, which will be shipped to the Zeltner laboratory, and grown into sympathetic nerves in a dish. The idea is to generate sympathetic nerves from patients with varying degrees of crisis severity; comparing the biochemical profiles of people that have daily crisis to those that rarely have these episodes will allow us to understand why some people have more severe symptoms. She also plans to look at which drugs we use to control a crisis are most effective at calming the nerves and preventing the neurotransmitters from spilling over. Dr. Zeltner also plans to grow other FD nerve cells.

“Growing sympathetic nerves from a small sample of blood will allow us to better understand how to treat the dreaded crisis in an individual patient”

– Dr. Alejandra Gonzalez Duarte

These two stem cell projects are complementary. The first looks at how to save the nerves and the second looks at how to work with the overactive nerves that remain. FD requires an approach from both angles if our goal is to help patients feel better and live longer. To imagine a world in which a person with FD sees clearly, walks well, doesn't have to worry about vomiting or kidney damage, for this to be a reality, we need both projects.

CLINICAL CARE



Tackling the toughest topics, a tracheostomy can be life-saving in advanced lung disease

Problems with breathing

Despite doing all they can to try and protect their lungs, some people with FD face the possibility that they need a life-saving intervention, known as a tracheostomy tube, to support their breathing. The lungs remain the most vulnerable organs in people with FD because of their delicate surfaces and vital function.

Many FD patients require breathing support at night with CPAP or BiPAP machines, which provide air pressure through a tube and mask to keep the airways open and avoid long pauses in breathing (known as apneas). Rarely a patient with FD may have an event which requires them to need BiPAP therapy 24 hours a day. In other cases, FD patients may need to be intubated and ventilated, that is, to place a temporary breathing tube in the airway connected to a breathing machine to provide air pressure and oxygen, to assist with their breathing. Both 24-hours-a-day BiPAP and intubation with ventilation could be lifesaving in the situation when the patient with FD needs immediate help, but this is not a permanent solution. Long-term intubation with a breathing tube in the mouth can lead to scarring and injury of the airway. Also, the patient must remain in a hospital and receive medications to ensure minimal movements to avoid pulling out the tube. Long-term breathing support continuously through a BiPAP mask usually is not done at home because a patient cannot even speak without removing the mask, and with continuous use it can cause injury to the skin. For patients with FD that require long-term help with their breathing with either continuous BiPAP therapy or intubation, a tracheostomy tube may be recommended.

Normally, we breathe through our nose, which filters and warms the air as it travels to the pharynx. The pharynx is behind the nose and mouth. Then the air travels into larynx, the voice box, and through the vocal cords into the trachea. The trachea is a tube-like structure that connects the throat to the lungs. A tracheostomy tube is a plastic or silicone tube inserted through the neck into the trachea. The tracheostomy tube allows the patient to breathe through the tube directly into the lungs. Breathing support such as oxygen can be given through the tracheostomy tube.

A tracheostomy tube can allow breathing support to be given long term to a patient. The patient can go home with a tracheostomy tube and use additional support from the ventilator as needed. When the patient feels better, they can breathe through the tracheostomy tube even without the ventilator. There are special speaking valves, which are easy to attach to tracheostomy tube, so the patient can talk and even sing. A tracheostomy can be temporary and removed when no longer needed. It can also be permanent if the patient needs life-long breathing support. Using a tracheostomy tube also prevents injury to the upper airway and face.

“Tracheostomies are sometimes needed when the lung damage advances, they are a life-saving option for some of our patients”

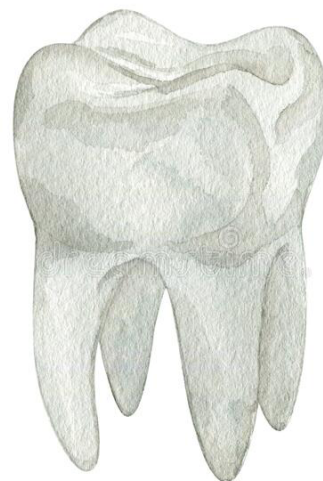
– Dr. Horacio Kaufmann

Problems related to the tracheostomy tube are rare. Patients can have irritation or infection of the skin around the stoma, the opening in the neck where the tracheostomy tube is inserted. Some patients can develop irritation and bleeding or scar tissue around the tracheostomy tube. When tracheostomy tubes are cared for, as instructed by your doctor, these problems are rare and treatable if they happen.

Dental care

Our teeth have evolved over hundreds of millions of years to be strong and align precisely so that we can chew efficiently. It's surprising how well the teeth of FD patients have been studied. Israeli-based dentist Dr. Mass has done some phenomenal work in studying the teeth of FD patients. His studies show that patients tend to have smaller teeth that become overcrowded or crooked as they grow in. Some patients have abnormalities in the way the jaw grows that may provide less space for the wisdom teeth (also known as third molars). It is not uncommon for patients to have their wisdom teeth removed, even without the issue of impaction. Sometimes patients can develop abscesses, which may go unnoticed as they lack pain perception. They may also grind teeth causing trauma or breakage.

But it is not all bad news. Patients with FD rarely have cavities and the teeth are well-protected by thick layer of hard enamel, which encapsulates the teeth. Enamel is what makes the teeth built to last and endure forces millions of times over the course of a lifetime as we chew our food. It's not clear why patients have extremely low rates of tooth decay, but one possibility is high saliva flow rates. For many patients, drooling is an embarrassing problem, but it may be one factor that is protecting the teeth. Another notable difference is the fact that a substantial number of FD patients do not eat by mouth or eat very little to avoid aspiration into the airway. This changes the bacteria in the mouth and the amounts of sugars the teeth are exposed to. The bottom line is, we need to be vigilant and schedule regular dental exams and cleanings to ensure good oral hygiene and check for problems. Good dental care is an important aspect of caring for someone with FD, whether they eat by mouth or by gastrostomy.



“Removing the wisdom teeth may be a solely prophylactic measure to prevent complications in the future, such as impaction”

- Dr. Shruti Ravindramurthy

Seizures

Anything that interrupts the connections between nerve cells can trigger abnormal electrical discharge, which can spread uncontrollably across the brain, causing a seizure. Seizures can be provoked for example by high fever, illness, or head injuries, or can occur unprovoked – without an obvious trigger. Epilepsy occurs when there is a problem within the brain that causes the hyperexcitability of neurons and results in multiple seizures. Over the years of following patients with FD, it became obvious that seizures are much more common than in the general population. These terrifying events are not well understood. Neurologist Dr. Bhumika Balgobin, who completed her Autonomic Disorders Fellowship at the NYU Dysautonomia Center, set out to try and better understand the causes and triggers of seizures in FD.

Almost two thirds of FD patients suffer from at least one convulsive seizure. On average, patients with FD have their first seizure around the age of 12. For most, their first seizure is provoked by a respiratory illness or fever. However, in one-third of patients, their first seizure was unprovoked and almost all went on to have a second seizure.

Brain imaging studies showed that seizures are associated with abnormalities such as atrophy, structural differences, or benign tumors. When examining the electrical activity of the brain with an EEG recording, almost two thirds of FD patients show patterns of abnormal brain activity like spikes or sharp waves. Patients with unprovoked seizures were more likely to have epileptiform activity on EEG testing.

To put the work into context, the life-time prevalence of a seizure is 12 times more common in FD compared to the general population. A lot of patients have signs of abnormal electrical activity in the brain, but only 20% of FD patients have a diagnosis of epilepsy with multiple seizures. These findings suggest that we need to be alert for seizure-like episodes during an illness, and consider the possibility that recurrent seizures may mean an area of the brain is discharging abnormally, and could indicate a patient has epilepsy. The good news is that there are many options to treating seizures. Commonly used antiepileptic drugs were able to dampen this abnormal brain electrical activity in over 40% of cases.

This is important work. Seizures are very scary and to witness a loved one having a seizure is a harrowing experience. However, we shouldn't jump to conclusions that one seizure means a person has epilepsy. Hypoxia of the brain due to low oxygen levels or very low blood pressure can also produce a seizure. The differential diagnosis is vast. It's important to consider that most seizures in FD patients are provoked, meaning they are triggered by something going on in the body that causes neurons in the brain to momentarily discharge abnormally. To determine if someone with FD has a true epilepsy, in the case of a seizure that has no identifiable trigger or a person has recurrent seizures, we will most often refer a person for a work-up with an epilepsy specialist.

The observations that seizures are more common in FD patients than in the general population is also very illuminating. We don't know the reasons why, but it does suggest that the threshold for having a seizure may be lower. People with FD may be prone to having episodes of abnormal electrical discharge that spreads across the brain and causes uncontrollable movements. It may be that the brain is just more susceptible to seizures because people with FD are wired differently, their neurons may behave differently, they may be primed to become over-excitable, and discharge more erratically at times of stress.



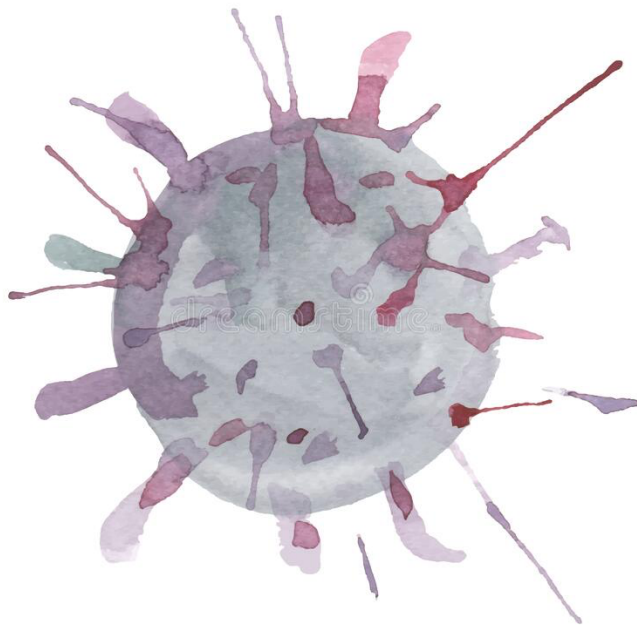
COVID-19 update

In the initial days of the pandemic, there was a lot of fear about how FD patients would handle a COVID-19 infection given their complex medical needs and vulnerability of the lungs. Some patients didn't leave their homes for months as they sheltered in place.

As our experience with COVID-19 in the FD population grows, there are a few notable observations. First, FD patients do not appear to be more susceptible to catching the virus, as occurs in other diseases that have severe immunosuppression. Their immune system can fight the COVID-19 virus. However, they do appear to have an increased risk of systemic complications compared to the general population.

Over 40 FD patients have been affected by COVID-19 infections. Statistics show that around 50% of cases were treated at home with mild symptoms, 25% were treated in the emergency room, and the remaining 25% required hospitalization in the ICU for management. As we have seen in the general population, the most severe complications occurred in patients that were unvaccinated. Those severe complications were most likely to involve the lungs, and the need for mechanical ventilatory support, or affect the muscle due to generalized inflammation. Just like other illness, COVID-19 infections can trigger a crisis. The good news is that all patients survived. Some took a long time to regain their strength and return to their prior health status.

Another notable observation was that FD patients could be reinfected with the new COVID-19 strains that have emerged as the virus mutated in the community. Most patients tolerated the vaccines and boosters very well, but did experience common side effects such as tiredness, a mild fever, or muscle pain. The news is reassuring. The Center is closely following the guidelines set forth by the World Health Organization, which are continuously updated. The Center's blog (www.dysautonomiacenter.com) provides regular updates and advice on managing COVID-19 symptoms and how to avoid infections.



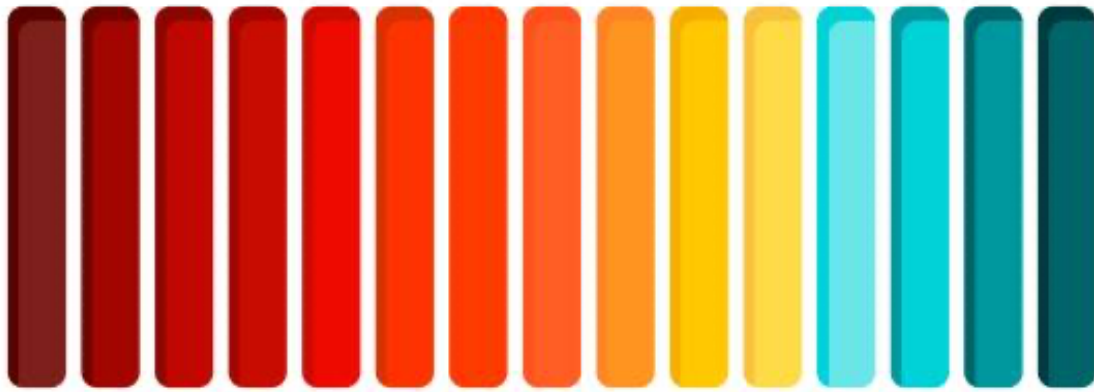
“We still need to have our guard up to avoid catching COVID, but the Center is here to help those that do get sick with the virus”

– Zenith Khan, NP

We know that this has been a difficult time for the FD community and we cannot ignore the social aspects of the COVID-19 pandemic. Isolation, anxiety and uncertainty have been part of our lives for the last 2 years. We are fortunate that we can follow the science-based recommendations and apply these to our FD patients. The best is to avoid an infection with handwashing, social distancing, and masking. If someone does become infected with COVID, we suggest they call the Center (212-263-7225), and be alert for any signs of worsening breathing. Some patients may need hospital support.

As we get better at managing COVID and new drugs to treat an active infection are available, we have hope that the COVID-19 pandemic will be a distant memory for the FD community and we remember the good parts – more time with family, better access to telehealth, and hope that science can move rapidly so that treatments enter the clinic sooner than before.

CLINICAL TRIALS AT HOME



Personalized medicine requires precision measurements

A new scale for crisis paves the way for a clinical trial of a crisis drug at home

There is no doubt the global pandemic changed the world. Medicine was forced to evolve, and clinical trials were rethought to continue while people sheltered at home. Telemedicine became the new normal and people in clinical trials met with their doctors through video conference calls. We all made our best efforts to stop clinical trials grinding to a halt and allow research to continue.

The Center was no stranger to telemedicine, almost a six years ago, researchers started using telemedicine visits to follow people in the first carbidopa trial, who otherwise would not have been able to participate as they did not live close the clinic. “We were probably one of the first groups to reach out to the FDA and ask if we could implement home assessments to track a patient’s progress in a clinical trial” explained Dr. Horacio Kaufmann.

As the pandemic ebbs and flows, telemedicine is now mainstream and “at home” research visits are widely used in clinical trials. There are several advantages over the traditional model of bringing people back into the clinic. The Center has always strived to understand how our patients are functioning in their daily lives. Seeing people over the screen, in their own environment, provides a new level of understanding and perspective compared to an in clinic visit.

“Having this type of detailed information is a vital tool in the fight against the FD crisis and the search for new medicines”
– Dr. Kaia Dalamo

Still, trials need endpoints, which are measures chosen to test whether a new treatment works by the numbers. Despite recent advances in the management of an autonomic crisis, patients with FD still experience breakthrough episodes that leave them retching and vomiting for several hours. The problem with testing new drugs for the FD crisis, is that there are no good scales to measure a crisis. In the past, we used scales developed for chemotherapy-induced nausea, but many patients found them difficult to fill and hard to relate to.

This challenge was taken on by Dr. Kaia Dalamo, a specialist FD Nurse Practitioner at the Dysautonomia Center. Together with the team, she helped create a specific measurement tool for autonomic crisis in FD. It's called ACSAS, the Autonomic Crisis Symptom Assessment Scale. Since then, it's been used to help people with FD both in the hospital and at home to help assess if new medications are helping.

The new scale goes beyond just nausea, retching and vomiting and considers many of the other classic symptoms of an FD crisis like high blood pressure, fast heart rates, skin flushing, excessive salivation, and sweating. It's designed to be used before and after medications so that we can see their impact in resolving the symptoms. It precisely captures the severity of an FD crisis overtime by numerically scoring the extent of distressing symptoms. It also includes behavioral changes like agitation and excessive movements (rubbing, thrashing).



With a new crisis trial set to start using sublingual dexmedetomidine (Precedex), supported by BioXcel Therapeutics, the scale will become the benchmark for charting its efficacy. We encourage all patients with FD who experience a breakthrough crisis to reach out to the Center. They can monitor their experiences and help collect vital information to personalize their medications and target specific symptoms. “We need better scales” explained Dr. Dalamo. “It is essential that we chart the crisis while a patient is at home so that we can find the right combination of drugs that help control the symptoms”. FD is never one size fits all when it comes to treating a crisis. At least now we have the tools to objectively measure if what we are trying helps.



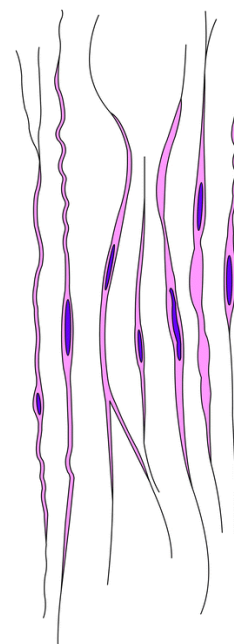
von Economo neurons found in highly social mammals are reduced in FD

The brain and social behaviors in FD

When “Z” arrived in New York, his heart stopped, his breathing ceased, and he died shortly after in hospital surrounded by his family. It was a devastating moment and one I will never forget, explained Dr. Lucy Norcliffe-Kaufmann. Despite the heavy sadness, his parents made one thing clear, Z was adamant about donating his brain to science to help his friends with FD. Even in his death, he gave back to the community. “I was so touched by his gesture, it felt like an enormous responsibility to do something important”, she explained. Brain donation is one of the most sensitive topics. When someone chooses during life to donate their brain after death, there are unprecedented opportunities to understand a disease process.

That opportunity arose a few years later. Dr. Patrick Hof, a neuropathologist at Mount Sinai School of Medicine, had been studying autism. Hof was interested in a specific type of nerve cell in the brain, named after Constantin von Economo, an Austrian psychiatrist born in Romania. Von Economo cells have a spindly shape and are found only in specific regions of the cortex. These cells receive a lot of sensory information coming from the body and are critical in quickly processing these signals to allow us to interact socially and control behaviors. They enable us to recognize errors and create self-awareness. Von-Economo neurons are only present in highly intelligent animals that have complex social structures, like whales, apes, and humans. People with autism and other psychiatric conditions that distort thoughts, disturb language, or lead to withdrawal from social contact have fewer von Economo neurons.

Dr. Hof and his team started examining the brains of FD patients in his lab under the microscope. The research was many years in the making. They meticulously stained sections, identified different neurons based on their shape, and counted them. Taking advantage of their existing brain bank, they were able to compare FD brain regions to healthy people who had no history of social or psychiatric issues. It was the first time the brain of a person with FD had been examined at a cellular level. A brain MRI, for example, enables you to see areas of the brain and sometimes regions of blood flow, but they don’t have a high enough resolution to see single cells.



The differences were startling. The FD patients had very low numbers of von Economo neurons. These cells are critical regulators of self-control and emotional-based decision-making skills. The team then decided to trawl back through the clinical charts of the patients, to look at the behavioral and social difficulties that they experienced during life. Most of the patients had difficulties forming friendships, delays in speech, or crippling anxiety attacks that triggered vomiting crises. All of them had encountered struggles with their emotions.

**“Examining the brain at a cellular level has changed
the way we think about FD. The brain is involved
and processes emotions differently”**

– Dr. Horacio Kaufmann

The results were published in the *Journal of Neuropathology and Experimental Neurology*. What is not yet known is whether these von Economo neurons fail to develop during embryogenesis or don't grow because they lack sensory inputs. Regardless of the underlying cause, the research paves the way to think about FD differently. We were always focused on FD being a peripheral disorder, affecting nerves outside the brain. Now we have evidence that it also affects neurons within the brain. As difficult as it may have been, Z and the other patients whose brains were examined have provided concrete evidence that FD leads to changes in the regions of the cortex that are involved in self-control and emotional processing.



Constantin von Economo (1876 – 1931) discovered large fast conducting neurons specific to the cortex, which emerge after birth, reach their maximum number at the age of 4, and play an important role in social behavior and mental diseases.

We now know that the anatomy of the FD brain differs from a healthy person. That knowledge can be put into action to tailor therapies aimed at boosting the social emotional skills by different learning techniques. It doesn't mean that FD patients cannot form social connections, what it means is that they may do this differently using other pathways that are less affected.

OPPORTUNITIES

Current research studies open for patients with FD

OPEN and ENROLLING *** NEW

INDUCED PLURIPOTENT STEM CELLS IN HSN3 and HSN4

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.

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 how they evolve overtime. 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. and PTC Therapeutics, 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 increased 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 obtained during programmed surgery (scoliosis, hip replacement, etc) and studied.

SPONSOR: Familial Dysautonomia Foundation, Inc.

Recently completed research studies in FD

COMPLETED

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.

COMPLETED

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.

COMPLETED

A STUDY OF GUT FLORA IN FAMILIAL DYSAUTONOMIA (MIBIOM)

IRB#: s16-00718. SPONSOR: National Institutes of Health (NIH)

PURPOSE: Better understanding of the microbiome in FD might help also understand GI motility problems in FD, which are common despite the absence of known pathogens.

COMPLETED

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.

COMPLETED

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.

COMPLETED

PROPRIOCEPTION AND SENSORIMOTOR CONTROL IN HSN

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.

COMPLETED

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.

COMPLETED

PHOSPHATIDYL SERINE (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.

COMPLETED

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 being evaluated at the NYU Dysautonomia Center in New York or 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 routinely recommended 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 copy of the questionnaire as soon as you schedule your appointment (212-263-7225). It can also be filled online.

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 overtime 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 to use this information to support their scientific work.

How is my information protected? The information collected in the natural history study is stored in a secure encrypted server supported by NYU Langone Health MCIT. 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. Information and support for this can be provided. Data shared for research is de-identified, entered into a secure online data collection platform (RedCap), with controlled access. If you no longer wish to participate, you may request your data be removed.

DYSAUTONOMIA CENTER

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Nadja Zeltner, PhD
Patrick Hof, MD
Shruti Ravindramurthy, MD

Support for the Program

Familial Dysautonomia Foundation, Inc.
Food and Drug Administration
MSA Coalition
J Aron Charitable Foundation Inc
Montreal Chapter of Dysautonomia

National Institutes of Health
Michael J. Fox Foundation
PTC Therapeutics
Anonymous donation

2021-2022 HIGHLIGHTS

N-Lorem Foundation selects FD to develop an antisense oligonucleotide treatment for a clinical trial

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

Dr. María Eugenia Briseño-Godínez (Maru) joins the Dysautonomia Center for 6-months as a Visiting Scholar

Ms. Zenith Khan completes key project design step in NYU's Nursing Doctorate Program

Ms. Lee-Ann Lugg received her promotion

Dr. Horacio Kaufmann leading investigator for a clinical trial of a new drug for low blood pressure

Dr. Patricio Millar-Verneti presented at the American Academy of Neurology

First brain pathology report in FD published with Dr. Patrick Hof

HSAN4 foundation officially launched in March 2022

Research grant provides funding for a brand new QST machine to measure small fiber nerve function

Dr. Elizabeth Morini appointed Instructor in Neurology at Mass. General Hospital

The annual FD art competition celebrates its Bar Mitzvah year

Dr. Nadja Zeltner awarded NIH grant to generate FD Cell lines

Israeli FD Lung Specialist Dr. Alex Gileles-Hillel volunteers as a medic at the frontlines in the Ukrainian crisis

New scale for the FD crisis created

Telemedicine home kits deployed by the FD Foundation to enable telemedicine annual comprehensive evaluations

Center opens in Mexico to provide care to FD patients

Dr. Alberto Palma appointed as Medical Director for Gene Therapies at Novartis

Dr. Lucy Norcliffe-Kaufmann appointed to lead 23andMe's Parkinson Disease Program

Dr. Sumantra Chatterjee receives funding from the Parekh Center for Neurology to work on FD

Former project assistant Valerie Itkina graduates from NYU Dental School

Dr. Bhumika Balgobin graduates our Fellowship Program and joins NYU as an Assistant Professor and Attending Doctor

WAYS TO HELP

Stay up to date: New studies for patients with FD open throughout the year. There are several places where you can learn about new research opportunities: sign up for our blog at DysautonomiaCenter.com; follow the Dysautonomia Center on Facebook and Instagram; read the FD Foundation's Dyscourse magazine; and ask the team at your annual evaluation visit. Periodically calling to find out about new research opportunities is important. Our staff can tell you about new studies and discuss which clinical trials may be right for you.

Give samples: You can consent to giving a small sample of blood. We can use this to measure the levels of the ELP-1 protein and create stem cells that can be grown into nerve cells. This research will help us understand how to preserve neurological function in patients with FD. You can also donate muscle samples when undergoing routine surgeries.

Send your doctors reports: Have you visited your eye, kidney, or lung doctor recently? By sending us your clinical results or reports, we can add the information to our natural history study and help better understand how to treat patients with FD. We are always happy to talk with your local doctors.

Support the Familial Dysautonomia Foundation: No single organization has done more to change the face of treatment of FD. The Foundation's unwavering support over the last 50-years has helped to centralize the care of patients with FD and to bring new treatments to the clinic. The Foundation and its chapters around the world have regular fund-raising events to support the cause. They make it possible for us to make important equipment upgrades, have a mental health program, maintain a dedicated team, and provide 24h emergency care to families at times of need.

Tell your friends. Talk to your friends about studies that you participate in. This will hopefully encourage them to be consider participating. Research in rare diseases like FD relies on having a committed community. Each time you give up your time for research the knowledge gained helps pave the way for other potential treatments.

Consider brain donation. Donating your brain to science can help shape research in unprecedented ways. This allows us to truly understand how FD impacts the nervous system and verify the accuracy of our research hypotheses. This is a sensitive topic and we can help guide you and your family through the process.

Participate when you can. Our progress depends on your willingness to volunteer for research. Some research projects are entirely observational and follow your clinical data overtime. Others may involve you trying a new medicine. Your information is always secure and not shared without your consent.

Talk to us. Having your voice and knowing what symptoms bother you the most will help us focus our research to meet your needs. The likelihood is you are not alone, others may be facing similar problems, which science can help understand.

Welcome new faces. We have new staff, trainees, rotating neurologists, visiting professors who would be happy to share what they are doing at the Center. Welcoming great minds to FD will help research progress.

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 with the brain and the body
5. Patients have similar symptoms, but the severity may vary from patient to patient
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 injuries, have difficulty localizing pain, and regulating their body
9. Lung disease is common and requires a proactive approach to treatment
10. The NYU Center has existed for over half a century and is dedicated to FD patients 24/7

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