



2020 – 2021
YEAR IN REVIEW

THE LATEST IN RESEARCH AND CLINICAL CARE
IN FAMILIAL DYSAUTONOMIA

CENTER FOR
NYUDysautonomia

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MESSAGE FROM THE DIRECTOR



When COVID-19 upended nearly all aspects of clinical care in March 2020, our patients and their families quickly pivoted to redefine a new “normal.” People with FD transitioned to virtual learning, virtual day hubs, and virtual offices. They continued their pulmonary care and use of BiPAP to prevent pulmonary complications that would put them at increased risk. Families quarantined for their loved ones, postponed birthday parties, and weddings, and did everything they could to keep their family members safe.

At the NYU Dysautonomia Center, we doubled down on tackling what COVID-19 may look like in patients with FD and how to best prevent this risk and promote health in the time of quarantine. Our office staff devised a telemedicine system to provide virtual visits. Our data team revamped our database to ensure COVID-19 tracking was easy and seamless. Our nurse practitioners stayed ahead of the curve in tackling everything COVID-19 related, from quarantining guidelines to vaccinations and where to find them. Of course, while COVID-19 was here, underlying conditions for patients with FD did not go away. While the pandemic was rampant in New York City, not a day went by that our Center did not respond to the needs and care for patients with FD. We continued to provide comprehensive, quality, interdisciplinary care and collaboration for every patient. Despite ongoing difficulties, we have seen many of our patients graduate, start new jobs, and celebrate new developments in their lives.

Since the inception of the NYU Dysautonomia Center, we have seen how high-quality, comprehensive care has added decades of life for people with FD. Our Center continues to encourage a multidisciplinary approach, emphasizing data and evidence-based medicine, focusing on treating the whole person, and expanding access to care – whether that means seeing patients in the comfort of their home or from across the world.

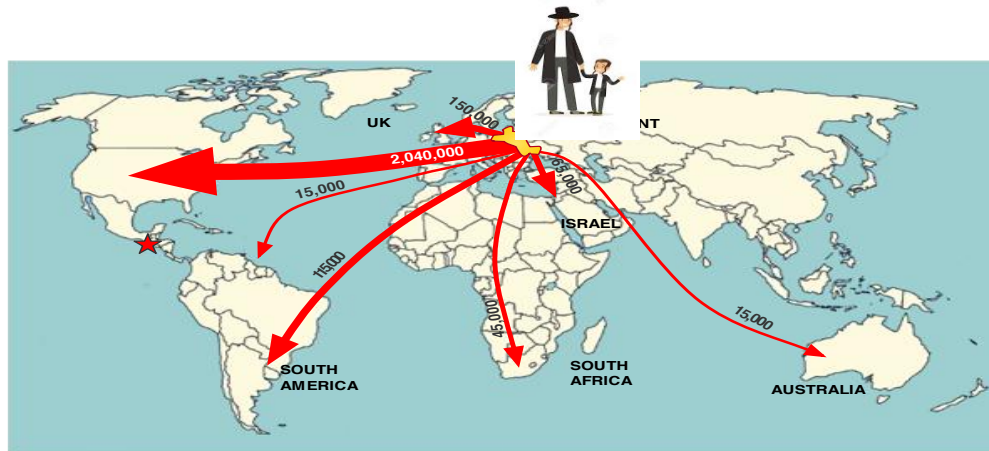
This *Year in Review* publication includes voices from multiple centers in the U.S. and overseas all working towards common goals for FD. We are making strides for better therapies. Some new potential treatment options are highlighted in this publication.

We are excited about the possibility of finally being able to start clinical trials of disease-modifying therapies, hopefully by next year. This is a story about progress and transformation. We must continue to imagine and develop new ways to meet challenges, and together we will write the next chapter of FD.

A handwritten signature in blue ink, likely belonging to Horacio Kaufmann, MD, FAAN.

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

GLOBAL CONNECTIONS

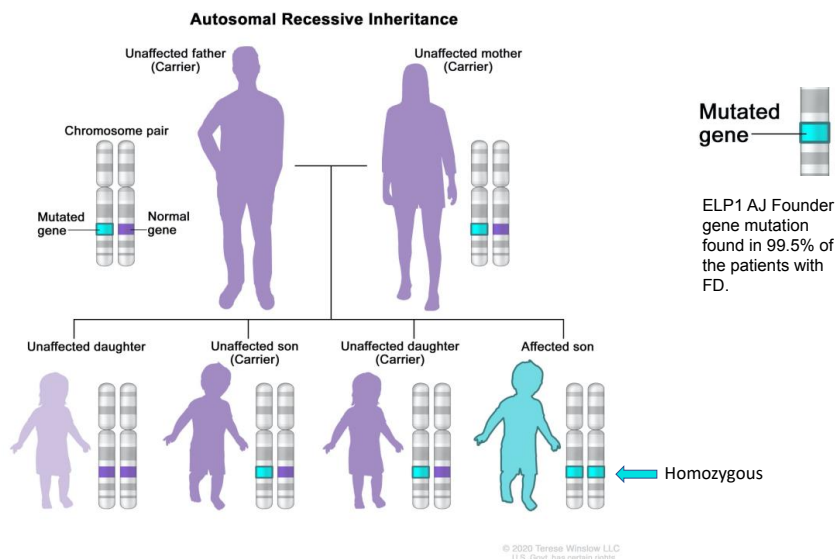


Expanding the FD Family

FD is an inherited disease caused by a mutation in the gene that has the blueprint to make ELP₁, a protein necessary for the development of neurons. FD is inherited in an autosomal recessive pattern. This means that people with FD have 2 copies of the mutated gene, one copy inherited from each parent (Figure 1). People who have only one copy of the normal gene are still able to produce normal amounts of ELP₁ and have no symptoms of FD. They are called carriers. When a carrier has a child with another carrier, their child has a 25% chance of having FD, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier (Figure 1).

Until recently, almost all people that we knew with FD had two copies of the same genetic mutation, called the founder mutation (i.e., they were homozygous for the founder mutation), this is depicted in Figure 1. This mutation was traced back to the 16th century in a Jewish person living in Poland. Thus, however distant a relation, people with FD were related, with both parents descending from the same founder bloodline.

Figure 1

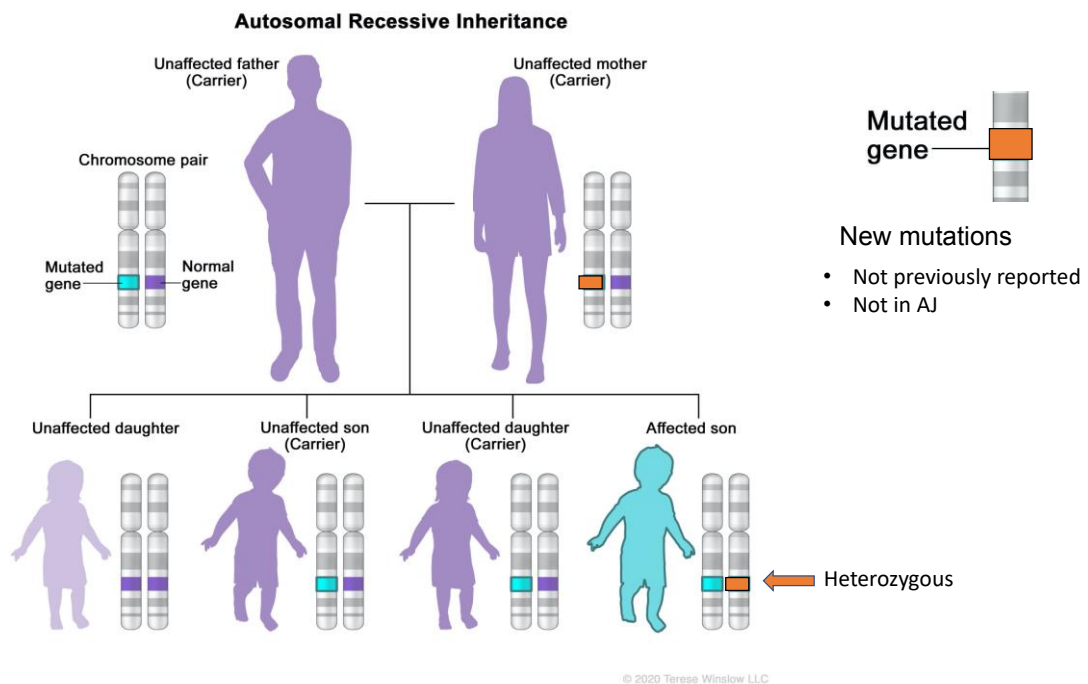


In 2001, a second mutation in the ELP1 gene was identified when it was discovered that a few people with FD had inherited this new mutation together with the founder mutation. In other words, each copy of the ELP1 gene had a different mutation, they were heterozygous (figure 2). Both parents of children carrying this new mutation had Jewish ancestry (Table 1). In 2003, a third mutation in the ELP1 gene was identified, this time in a patient without Jewish but Irish, German, and Sicilian ancestry (Table 1).

Twenty years later we welcome to the FD community two very special newcomers. All patients with FD are special but these two toddlers each brought an added surprise. They were both born in 2017 but diagnosed only recently. One is a girl of African American heritage. The other is a boy, living in Poland. For both children, the diagnosis came as a result of whole-exome analysis, a technique that analyzes all coding regions of a person's genetic code. In that way, doctors can cast a wide net and find mutations they had not thought about. In our two new patients, whole exome analysis was performed because they were chronically sick, and their doctors couldn't figure out why but suspected a genetic condition. Both children were found to have one copy of the FD founder mutation inherited from one parent but novel, yet undescribed, mutations of the gene from the other parent.

In the young girl's case, one parent is from Trinidad, an island in the Caribbean where Jewish people immigrated to in the late 19th century and again in the 1940s. And although this parent was not aware of his Jewish ancestry, he was found to be a carrier of the founder mutation, which makes him a descendant of the Jewish founder. The other parent, however, is a carrier of a novel mutation in the ELP1 gene. Interestingly, when consulting a large database of genes, the same mutation has been reported in 2 other individuals who also have African ancestry. Those individuals in the database were carriers, they only had one copy of the mutated gene, the other copy was normal. But when that mutation is inherited together with a copy of the founder mutation from the other parent, the result is a child with FD. The child is heterozygous with two different mutations, one in each copy of the ELP1 gene, as seen in Figure 2.

Figure 2



The second newcomer was born and lives in Poland. He also is heterozygous for the FD gene (Figure 2), has no known Jewish ancestry but carries one copy of the founder mutation inherited from his father, and the second gene is a new mutation. This mutation has never been described before to result in disease, and according to databases, is also present in two European non-Jewish people.

These novel gene discoveries bring the total number of mutations involved in FD to 5, as shown in Table 1.

Table 1

FD Mutations at NYU Dysautonomia Center

FD Mutations at NYU Dysautonomia Center

Mutation	Other names	Origin	Number of patients	Year Discovered
c.2204+6T>C, founder mutation	IVS20DS	AJH-Founder	99.5%	1993
c.2087G>C	R696P	AJH	4	2001
c.2741C>T	P914L	Irish/German/Sicilian	1	2003
c.1361-1G>T	IVS12-1G>T	African American	1	2020
c.2204+6 C>T	IVS20DS, T-C, +6	Poland (non-jewish)	1	2021

Whole exome analysis allows clinicians to diagnose complex patients even if they have no clue what the patient's diagnosis may be. All new patients recently diagnosed with FD were because of whole-exome analysis. FD was not even suspected in these patients and doctors were puzzled. The difficulty in the diagnosis was, at least in part, because their parents were unaware of their Jewish ancestry, and FD is classified as a Jewish genetic disease.

In the last three years, newly diagnosed patients from Mexico utilizing whole-exome analysis had no known Jewish ancestry. Nevertheless, they were found to have two copies of the FD founder mutation. Despite being unaware of their Jewish ancestry, both parents were descendants of the founder.

In summary, the last six new patients with FD were unaware of Jewish ancestry, and three pathogenic mutations in the ELP1 gene do not originate in Jewish people. Requiring Jewish ancestry delays diagnosis because physicians do not consider the possibility of FD in young patients with suggestive symptoms. Thus, the current criteria that require Jewish ancestry from both parents for the diagnosis of FD is not accurate and should be modified.

STUDY HIGHLIGHT



Insensitivity to pain: not just in FD

Pain is one of our body's defense mechanisms, allowing the ability to detect injury and prevent further damage. One of the most striking features of patients with FD is their reduced ability to perceive pain and temperature. While feeling less pain could sound like a blessing to many people, insensitivity to pain causes a myriad of problems, including burns, lesions, fractures, infections and more.

Impaired sensitivity to pain was mentioned in the first description of FD, by Riley and Day, back in 1949. One of the patients had very little pain when immersing his foot in freezing ice water – they referred to this as “indifference” to pain.

During the following decades, insensitivity to pain became one of the most recognizable features of FD, in addition to the lack of tears and autonomic crisis. These features are so striking that when a child was born with them, the possibility of FD was raised. With the identification of the defective gene involved in FD (IKBKAP or ELP1 gene) a better understanding of this phenomenon occurred. ELP1 is required for the development of both sensory and autonomic neurons, so mutations in ELP1 result in disrupted development of the sensory nerves, the ones transmitting information from the environment to the brain. Identification of the gene also allows the potential for altering the mutation, more on this in another article in this publication.

But with the identification of the gene, something else happened. Many patients coming to the FD center due to a presumed diagnosis of FD, did not have any mutation in ELP1. So, what was their diagnosis? They may have mutations in genes other than ELP1, other genes involved in the development of sensory and autonomic nerves. But finding which one would be like finding a needle in a haystack. Despite that, the Dysautonomia Center kept caring for these patients, carefully collecting information on them to further inform their clinical presentation and care when a gene would be discovered.

A potential solution to the problem came with the advance of genetic testing that allows rapid screening of the whole genome, or at least the exome, the part of the genome that encodes the information to make proteins. This genetic technique is called whole exome sequencing or WES.

Using WES in blood samples obtained from 13 patients with non-FD congenital insensitivity to pain, researchers from the Dysautonomia Center found a surprising result. They found other mutations causing insensitivity to pain in all 13 patients. The mutations were in 9 different genes. Some had already been identified as related to pain disorders, but new genetic mutations not previously described were also discovered.

Interestingly, all patients with these genetic mutations that affect pain sensation had overlapping features with those who have FD, with variable degrees of other features of dysautonomia.

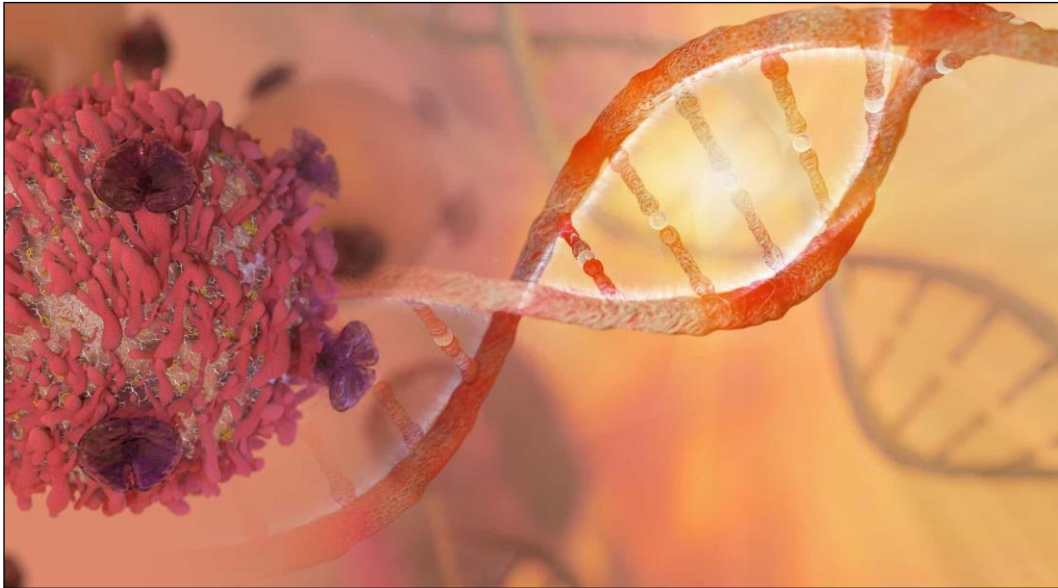
Some patients had Ashkenazi ancestry and had proprioceptive ataxia (those with mutations in TECPR2), some patients had “dysautonomic crisis” with profuse sweating (those with mutations in LIFR2), 11 of the 13 had reduced or absent tears and corneal ulcers, many had gastrointestinal problems, nine patients had dysphagia (difficult swallowing), four had gastroesophageal reflux, and seven had some variation of reduced gastrointestinal motility and constipation.

These results, recently published in the journal *Neurology Genetics*, highlight that insensitivity to pain is not an exclusive feature of patients with FD. The identification of the genetic causes in patients with congenital insensitivity to pain opens the door for the development of genetic therapies, as is the case with FD.

Reference

Palma, J.-A., Yadav, R., Gao, D., Norcliffe-Kaufmann, L., Slaugenhaupt, S., & Kaufmann, H. (2021). Expanding the Genotypic Spectrum of Congenital Sensory and Autonomic Neuropathies Using Whole-Exome Sequencing. *Neurology Genetics*, 7(2), e568. doi:10.1212/nxg.0000000000000568

RESEARCH NEWS



Understanding cancer risk in FD

Cancer is the leading cause of death worldwide. It affects all races in all countries, genders, and people of all ages, although prevalence rates and types of cancer vary widely across all demographics. The epidemiology of cancer allows us to gain more understanding into its causes and risk factors including endogenous cellular processes and environmental risk factors. So, while FD is an extremely rare condition, cancer can occur in FD too, and understanding its prevalence and risk factors is important.

After several cases of cancer in FD patients, we decided to launch an investigation into the incidence and prevalence of tumors in this community. We questioned whether the development of cancerous tumors or the lack thereof could be linked to their genetic mutation.

Because certain types of cancer tend to run in families, the Center expanded the study's population to include relatives of FD patients, classifying them according to their status: carrier, non-carriers, or unknown status. We designed a user-friendly survey that collected comprehensive information. Our team reached out to patients via email, phone calls, or during in-person visits. The information was then characterized by gender, age group, relationship to the patient, tumor type, location and outcome, and this data is currently under analysis.

Depending on the results, we may discover that our patients and their relatives are equally susceptible to tumorigenesis as their corresponding population group. However, if results suggest FD patients and their families are more prone to tumor development, this will enable patient and family counseling on early screening strategies as well as managing modifiable risk factors. These measures can enhance survival and quality of life which is our primary concern. By studying tumor occurrence in FD and their families, we can better understand this condition and its unique features.

We had a very high participation rate and would like to thank patients and families for taking the time to answer the questionnaires. Results will be available soon.



Neurodegeneration, gut microbiome, and metabolic impairment Are they connected?

Drs. **Frances Lefcort**, **Valérie Copié**, and **Seth Walk**, in collaboration with the Dysautonomia Center at NYU, are continuing their research on the gut-brain-metabolism axis in FD, which is supported by a grant award from the National Institutes of Health. Their ultimate goal is to establish whether re-introduction of specific gut microbes through fecal microbial transplantation (FMT) can improve the health of people with FD and, in particular, mitigate the effects of FD on the GI tract and metabolic functions.

We know that the gastrointestinal tract does not function properly in FD, with patients suffering from an array of GI problems including constipation, diarrhea, reflux, and others. We also know that FD patients tend to have problems maintaining a healthy weight, a potential reflection of mitochondrial cellular dysfunction and limited capacity to generate metabolic energy (ATP, adenosine triphosphate, the energy currency of cells) from food.

We have discovered that gut microbiome dysfunction and metabolic impairments accompany neurodegeneration in FD patients, with disease phenotypes that are recapitulated in our FD mouse models. With this knowledge, we are now exploring potential therapeutic strategies such as using gut microbial fecal transplants and/or metabolic supplementation to attenuate FD disease phenotypes. We have first started such studies by cohousing FD mice with healthy sibling control mice, with the objective that their coprophagic behavior might simulate a self-administered oral fecal microbial transplant (FMT).

Stool samples were collected across the animals' lifespan and analyzed for gut microbe composition via 16S rRNA gene sequencing, and small molecule metabolic profiles via nuclear magnetic resonance (NMR) analyses. In addition to observed improvement of the overall health and FD mouse phenotypes when cohoused, our analyses of cohoused mouse stool samples revealed metabolic and microbial community trends that more closely resembled the gut microbiome and stool metabolome profiles of healthy control mice.

Our findings suggest that FMT strategies to restore a healthy gut microbiome may be of significant value as a potentially valuable intervention approach or future therapeutic strategy to mitigate the debilitating symptoms associated with FD and other neurological diseases that share hallmarks of disease with FD.

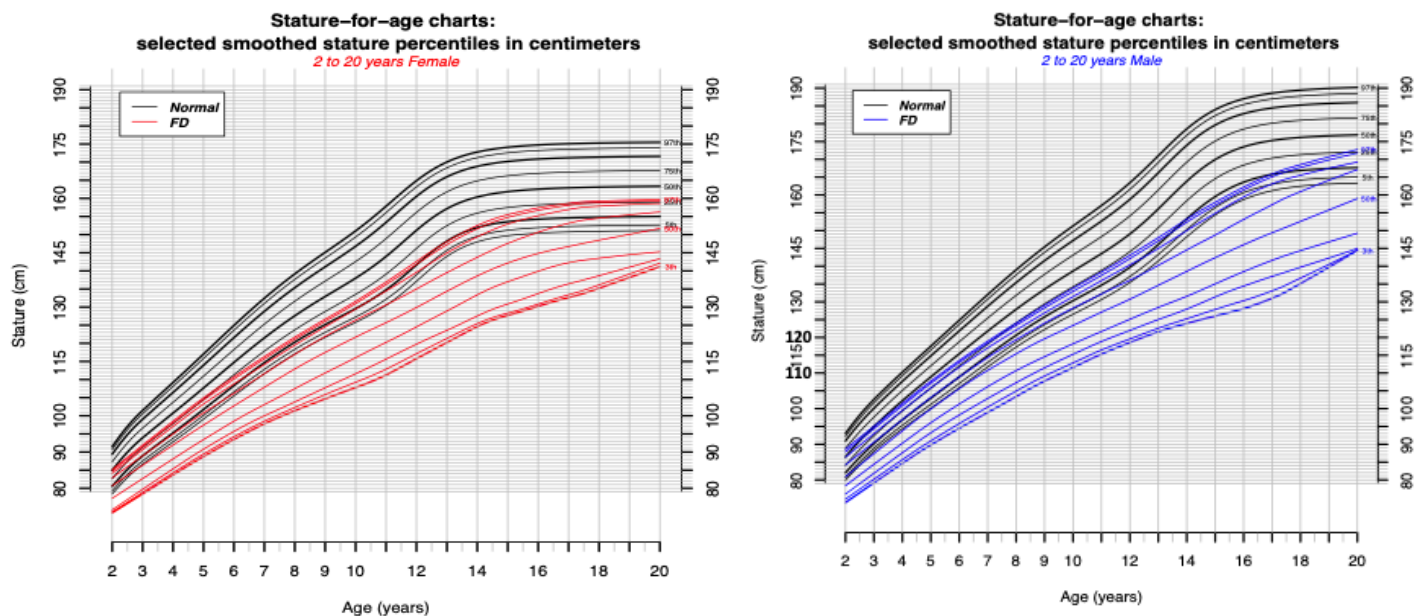


Evaluation of growth and growth hormone in patients with FD

Growth and the ultimate height and weight attained by those with FD is different than in the average population. Those with FD tend to be petite. This often results in heightened concerns in childhood and attempts to improve growth by giving synthetic growth hormone which may improve growth but has added potential risks for skeletal anomalies.

In response to these issues, we developed growth charts by analyzing the collective database from all patients with FD over the last 40 years. The final growth patterns were then plotted with a side-by-side comparison to national and global growth charts developed by the Center for Disease Control and Prevention (CDC) and the World Health Organization (WHO), currently used as global standards to evaluate growth in children. Charts for FD were developed for weight, height and BMI for male and female patients between ages 2 and 40 years old.

Our growth curves show that people with FD experience delayed growth from very early on even starting before birth. Growth is slower than in the average population, and the final weight and height attained are lower. For instance, by the age of 20, most people with FD fall below the 50th percentile of the general population in terms of height and weight, and half fall below the bottom 5th percentile. However, the height of a person with FD reaches a plateau around age 25, compared to age 20 in the general population. Also, weight appears to remain more stable after age 20, compared to the general population where weight tends to increase with age. This contributes to a lower body mass index or BMI in patients with FD.



These curves allow us and outside clinicians we partner with to better care for those with FD by identifying deviations from what is normal for FD. We can then discern if problems with nutrition, metabolism, and hormones are to blame, or if slow and delayed growth fit a normal pattern in FD. These growth charts also help us to evaluate response to treatments aimed at increasing growth.

We also attempt to answer the question of whether an improved body mass index (BMI), a measure of height and weight, can improve recovery and survival in people with FD. We found no significant correlation between BMI and age at death and that an increased BMI does not seem to influence survival in the FD population. A smaller BMI in FD individuals is not a contributing factor for early death.

We hope that the development of FD-specific growth curves will help in the evaluation of possible nutritional or other interventions that might improve growth and overall health. We continue to investigate the causes behind the inability to exhibit normal growth, including chronic respiratory and gastrointestinal disease, and blunted sensory and autonomic neural signaling.

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National Center for Health Statistics. (2009, August 4). *Percentile Data Files with LMS Values*. Centers for Disease Control and Prevention. https://www.cdc.gov/growthcharts/percentile_data_files.htm

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Dr. Alex Gileles-Hillel, Hadassah University Medical Center, Israel

Can we avoid fundoplication in some children with FD?

Severe gastro-esophageal reflux disease (GERD) is a hallmark feature of FD beginning in the neonatal period and throughout life. Impaired swallowing due to lack of sensation and reduced esophageal peristalsis (the wavelike sequence of muscular contraction and relaxation of the esophagus) predisposes those with FD to chronic aspiration of food and gastric contents, recurrent pneumonia and failure to thrive. The first line of treatment for severe GERD in patients with FD has always been Nissen fundoplication surgery and gastrostomy placement and the majority of patients with FD have undergone this procedure. Yet despite these aggressive measures, complications of GERD such as recurrent lower respiratory tract infections are still common and result in significant pulmonary problems including bronchiectasis (permanent enlargement of parts of the airways of the lung). Furthermore, fundoplication may cause significant mechanical complications such as food impaction or achalasia in some patients and has an eventual failure rate of 16%. There may also be an increased incidence of gastroesophageal bleeding in patients with a history of fundoplication as opposed to those without.

Recently, Dr. Gileles-Hillel examined the available evidence for the treatment of GERD in patients with FD using a systematic review and expert consensus guidelines. Due to the considerations mentioned above, fundoplication surgery in children with FD is now not immediately recommended, unless they have very severe proven GERD-related respiratory disease. Instead, guidelines recommend a stepwise approach beginning with acid suppression pharmacotherapy, followed by gastrostomy/gastro-jejunostomy, and then fundoplication only if clinically necessary.

Despite guideline recommendations, little real-world experience has been published on this topic in FD. **Dr. Gileles-Hillel** and his team at Hadassah University Medical Center in Israel have recently concluded a prospective study following 5 children with FD (aged 1-10 years) in whom the initial management was gastrostomy without fundoplication. During the follow-up period, in 4 out of 5 children in the first year after gastrostomy and tube-feeding started, they observed a significant reduction in respiratory complications and hospitalizations as compared to the year before, and only one child eventually required fundoplication surgery due to uncontrolled GERD.

Their data, which is planned for publication soon, provides support to the current guidelines to postpone fundoplication and may reduce the number of fundoplication-related complications. However, they emphasize that each unique patient's condition must be carefully assessed, and medical decisions should be tailored with a personalized approach in mind.

RESEARCH NEWS



Dr. Slaughaupt (highlighted screen) with other researchers including Elisabetta Morini and Dadi Gao at Massachusetts General Hospital Research Institute during a Zoom meeting during the 2020 pandemic.

Developing therapeutic strategies to correct ELP1 splicing in FD

In 2005, **Dr. Slaughaupt** and her team at Massachusetts General Hospital discovered that kinetin, a natural compound used as an anti-aging ingredient in skin treatments, can restore the correct inclusion of the ELP1 exon 20 that is skipped in the nervous system in people with FD. In 2012, their FD project was chosen to be part of the NINDS Blueprint Neurotherapeutics Network, which was created as a pipeline for academic investigators to move promising lead compounds to the clinic. Through this program, they optimized the potency and efficacy of kinetin which led to the creation of a new class of compounds with better drug characteristics. In 2015, Dr. Slaughaupt and her team partnered with **PTC Therapeutics**, a company that focuses on the development of orally administered small molecule drugs and gene therapy that regulate gene expression by targeting post-transcriptional control (PTC) mechanisms in orphan diseases. This partnership allowed for further development of these compounds with the goal of creating an Investigational New Drug (IND) for FD patients. Their collaboration led to the astonishing generation of over 1000 additional compounds with dramatically improved potency, efficacy, and safety.

However, in November 2019, PTC Therapeutics canceled the FD program due to budgetary constraints associated with the development of a drug for such a rare patient population, though they are still committed to work with Dr. Slaughaupt's team and the Dysautonomia Center to bring a drug for FD to the clinic. They are excited by the prospect of a small-molecule drug to correct splicing because it can be taken orally and can get everywhere in the body, and they have shown these compounds to be quite effective in their FD mice models. Given encouraging early results in toxicity testing, what is now needed is to identify funding in order to generate the preclinical data necessary to support an investigator-initiated IND application and a clinical trial in FD patients.

In a parallel investigation, Dr. Slaughaupt started a collaboration with **Dr. Franco Pagani** at ICGEB in Italy and with **Dr. Luk Vandenberghe** at Mass Eye and Ear to develop a treatment to prevent retinal degeneration in FD. The Pagani laboratory has pioneered a novel strategy that uses precisely targeted exon-specific U1 snRNAs to correct exon skipping defects. In the past, they successfully applied this strategy to correct splicing in several genetic disorders, including cystic fibrosis, hemophilia and spinal muscular atrophy. Together, they have developed a novel FD-specific ExSpeU1 that corrects the FD splicing defect, and are currently testing it in FD mice.

RESEARCH NEWS



Dr. Bat-El Bar-Aluma (left) pictured here with Monique, a volunteer working on the FD Database, in her clinic in Sheba Medical Center, Israel.

Longitudinal Pulmonary Function Data from Sheba Medical Center

Lung impairment is a cardinal feature present in all FD patients. Pulmonary manifestations include recurrent aspiration pneumonia, wheezing, and reduction in lung volumes secondary to chest deformity in cases of severe kyphoscoliosis. **Dr. Bat El Bar Aluma** and her medical and research team at Sheba Medical Center in Israel completed a study to further describe the progression of lung disease and help develop effective management and prevention strategies.

For this longitudinal study, lung function data was collected in response to bronchodilators from 52 people with Familial Dysautonomia (25 males and 27 females) that visited the FD center in the Edmond and Lili Safra Children's Hospital at Sheba Medical Center. Data was collected over 8 years, from 2012 to 2020, and included 199 tests.

For analysis, patient data were clustered in two groups according to their initial forced-expiratory volume in 1 second (FEV₁) compared to the predicted for the general population. This is an index of lung function measured by the ability to forcefully blow air. The lower group had an FEV₁ less than or equal to 60% of the predicted value compared to the general population and the higher group had an FEV₁ above 60% of the predicted value in normal subjects. The yearly rate of change was calculated as the average of the differences between all years in relation to age and baseline FEV₁.

They found that in the group with lower FEV₁ the rate of decline was exponential, wherein all pulmonary function parameters drop significantly up to age 20 when pulmonary function decline slowed. In the group with higher FEV₁, however, pulmonary function was stable for years but started to show a decline at later ages, from years 30 to 40.

In this study, there were no differences in the response to bronchodilator therapy between the two groups. This is encouraging and emphasizes an important finding from an earlier study of inhaled bronchodilators by Dr. Bar from 2018, *A Controlled Trial of Inhaled Bronchodilators in Familial Dysautonomia*, that those with greater airway resistance had even more improvement in lung function. So regardless of the degree of bronchial obstruction, both groups stand to improve. Another finding in the 2018 study was that a higher degree of hypoxia at baseline predicted less improvement from bronchodilators, indicating more advanced airway disease such as permanent scarring that is not amenable to pharmacotherapy.

These results reaffirm that efforts should be made to maintain higher FEV₁ from young ages, and by doing so, lung health may remain steady for longer periods into later years of life.

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Nadja Zelter, PhD, Center for Molecular Medicine, University of Georgia

Pluripotent Stem Cell Research for FD

Pluripotent stem cell technology is a powerful research tool, where skin or blood cells from patients are reprogrammed in order for them to turn backwards in developmental time and adapt an embryonic (or pluripotent) character, called induced pluripotent stem cells (iPSCs). **Dr. Nadja Zeltner** and her lab of researchers are employing FD stem cells to understand cellular and molecular mechanisms in FD in more detail. They are able to guide FD-iPSCs in the dish to develop into peripheral sensory and autonomic neurons which are deeply affected in FD and are involved in impairments and symptoms such as insensitivity to pain and autonomic crisis among many more.

A current study by Dr. Zelter and her team, recently funded by the National Institute of Health, has two aims:

First, it aims to better understand why some patients with FD have milder disease symptoms than others. Whole-exome sequencing of 6 FD patients has revealed that the three patients with more severe symptoms harbor additional mutations found in a gene called laminin that is important for a healthy extracellular matrix (ECM), the protein support system found around cells. The three patients with milder symptoms did not harbor these additional mutations. The Zeltner lab is working on understanding how these mutations may lead to more severe FD, how the ECM is important in FD development and how the ECM is related to ELP1.

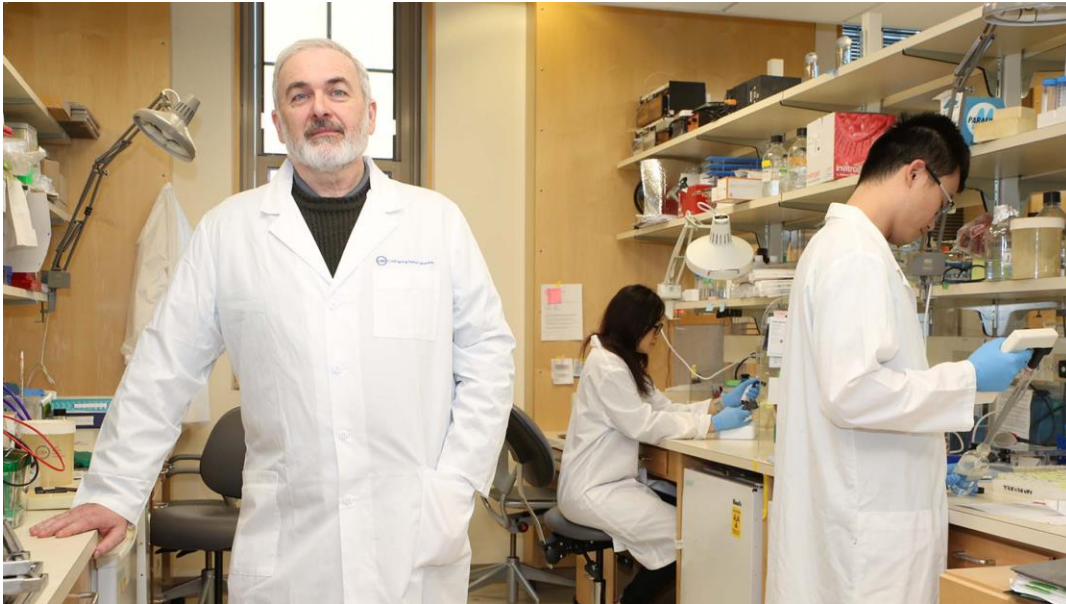
Second, the researchers use the iPSC technology for drug screening approaches. The goal is to develop drug candidates that could be used to halt the degeneration of sensory and autonomic neurons in FD.

The Zeltner lab is also working on understanding the electric activity of sensory and autonomic neurons in FD and how the cells function differently compared to neurons derived from healthy individuals. Again, the goal is to understand the cellular and molecular mechanism and to use this information to design drug screens for FD. The Zeltner lab is working with the Dysautonomia Center at NYU and the Slangenaupt lab to generate more iPSCs from patients with FD and to understand the prevalence of other mutations in the larger FD population.

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UPCOMING CLINICAL TRIALS



Professor Adrian Krainer in his lab at Cold Spring Harbor Laboratory, 2019, photo by Cold Spring Harbor Laboratory at www.cshl.edu

The future of FD: Treatment with Antisense Oligonucleotides

The genome is the complete set of DNA that contains all the information necessary for the creation and survival of a lifeform. In humans, it is organized in 23 chromosome pairs which are made up of approximately 21,000 genes that build proteins. To make these proteins, a cell must first transcribe DNA to RNA which is then used as a messenger and a template. RNA splicing is a crucial step in the process of protein production.

RNA splicing is the mechanism in which a newly made precursor messenger RNA (pre-mRNA) transcript is transformed into a mature messenger RNA (mRNA). This is done by removing introns (the non-coding regions) and joining exons (the coding regions). The result is an mRNA molecule that can be translated into a protein. But missplicing can happen, sometimes sporadically and sometimes as a result of a hereditary mutation such as in FD. FD results from a point mutation in the IKBKAP gene also known as the Elongator Protein 1 (ELP1) gene. The missplice occurs because of a T to C change in base pair 6 of intron 20, in Chromosome 9. The result of the mutation is that exon 20 is skipped, resulting in faulty IKAP protein, which affects neurons throughout the body and primarily a loss in afferent neural signaling in the peripheral nervous system.

Splicing is carried out in a series of reactions catalyzed by the spliceosome, a complex of small nuclear riboproteins (snRNPs, pronounced “snurps”). Splicing can be manipulated by binding synthetic molecules to the pre-mRNA. These molecules are called steric-blocking antisense oligonucleotides (ASOs). Different ASOs can be produced in the laboratory to bind different targets and “correct” abnormal splicing. Binding requires sequence complementarity between the ASO and the RNA, similar to the interactions that hold the two strands of DNA together.

When an ASO targeted to a particular intronic region following IKBKAP exon 20 was administered into transgenic FD mice, it successfully restored exon 20 splicing. This lead ASO promoted the formation of full-length (normal) human IKBKAP mRNA and IKAP protein in several tissues, including the central nervous system.

This method to correct splicing was described by **Adrian Krainer** in the early 2000s and was proven in animal models in the last decade. Then in 2011 it advanced to clinical trials in humans affected by a devastating disease, spinal muscular atrophy, and was so successful at treating both infantile-onset and later stages that it was fast-tracked for approval in 2016, and is now available in over 50 countries. Thousands of children with SMA have been treated with this therapy and are now walking when they likely would otherwise have perished. This is an exciting time in the history of gene therapy. Different ASOs are currently approved and commercially available for the treatment of a few genetic diseases.

New compounds must be tested carefully as trials advance from testing in cells, then in animal models, before testing them in a human organ or the whole body. The **n-Lorem Foundation** was recently created with the mission to develop individual treatments for patients in the United States with ultra-rare diseases caused by genetic mutations. As a result of a collaboration we have just entered into with n-Lorem, it is our hope that in the next year or so, a small clinical trial will begin with an ASO in patients with FD.

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UPCOMING CLINICAL TRIALS



Better treatment of autonomic crisis at home

A phase 2 open-label study of sublingual dexmedetomidine to treat autonomic crises at home is planned to start later this year, 2021. We believe that sublingual dexmedetomidine administered at home in patients with FD can provide comparable treatment of crisis to intravenous dexmedetomidine currently used in an intensive care unit setting, as the most successful drug yet in providing quick and effective cessation of autonomic crisis.

The genetic defect in FD affects mostly afferent (sensory) fibers with cell bodies in the dorsal root and cranial nerve ganglia, and mainly spare efferent (motor) fibers. Due to this imbalance in functional afferent and efferent neural fibers, recurrent episodes known as autonomic crises occur frequently in FD. When the sympathetic nervous system is activated by the central nervous system in reaction to perceived stress, efferent signals raise catecholamine levels. This can occur in response to physical harm such as injury or infection, or a heightened emotional state such as fear or even positive emotions (Norcliffe-Kaufmann et al., 2017). These catecholamines include epinephrine (also known as adrenaline), norepinephrine and dopamine. It is these extreme and uncontrolled surges that are responsible for autonomic crisis, resulting in protracted hypertension, tachycardia, skin flushing and blotching, uncontrolled nausea, retching and/or vomiting, sweating, sometimes inappropriate release of antidiuretic hormone leading to hyponatremia, and behavioral changes (Palma et al., 2014). Autonomic crisis can be a medical emergency.

Many patients with FD have frequent autonomic crises due to a myriad of causes, from silent aspiration to behavioral issues. Crisis can even occur daily in some patients, increasing their risk for acute cardiovascular events and end-organ damage from chronic dramatic swings in blood pressure (Norcliffe-Kaufmann et al., 2017). Autonomic crisis is an enormous burden and threat to the safety and wellbeing of those with FD.

Since autonomic crisis is often elicited by heightened emotional states and is accompanied by hypertension, first-line treatment must always include non-pharmacologic measures to calm the person and reduce their blood pressure. These involve distraction, doing an enjoyable or relaxing activity, deep breathing exercises, meditation, guided imagery, other methods of self-relaxation, and standing up and walking which serves as both distraction from the triggering activity and reduces blood pressure due to failed baroreflexes in FD.

But when non-pharmacological measures are ineffective and agitation, hypertension, tachycardia, nausea, retching or vomiting persist, patients take anxiolytic, sedative, or antihypertensives drugs. Current medications to stop autonomic crisis often include benzodiazepines such as diazepam (Valium), and a non-selective alpha 2-adrenergic agonist, clonidine (Catapres) (Palma et al., 2014). These drugs are frequently effective, but tolerance and respiratory depression with increased risk for sudden death is a major concern with benzodiazepines, and clonidine often excessively reduces blood pressure, increasing the risk for fainting and falls, and can cause rebound excessive sympathetic activity with hypertension. These risks are multiplied as repeated doses are given, and can be dangerous and have the potential to be fatal. So, for the risks these treatments pose and the risks of crisis itself, it is always advised to seek hospital care for crisis unresponsive to 3 successive doses of either diazepam or clonidine. Other drugs that target physical or psychological aspects have been tried with inconsistent results, including beta-adrenergic blockers to lower blood pressure and heart rate, antidepressants, antipsychotics, antiepileptic medications, and cannabinoids.

Dexmedetomidine (Precedex), a selective alpha-2 adrenoceptor agonist, has been the most successful medication for treating autonomic crisis to date and has improved sedation and hemodynamic stability profiles compared to clonidine (Dillon et al., 2017; Palma et al., 2014; Srivastava et al., 2014). But it requires intravenous administration and is only available in an ICU setting. To avoid going to the hospital for severe autonomic crisis refractory to home treatments, attempts have been made to find a safe and effective treatment at home.

Recently, **BioXcel Therapeutics** developed a sublingual delivery form of dexmedetomidine called BXCL501 that is applied on a thin dissolvable film that is placed under the tongue for absorption. BXCL501 is rapidly acting, compares to IV delivery as it bypasses first-pass metabolism in the gut, and mitigates hyperadrenergic activity without excessive sedation. In targeting hyperadrenergic crisis, it has been effective at low doses while being more potent and also easier to wean off than clonidine. And the mucoadhesion properties of the thin film could make sublingual delivery easier in FD patients who might otherwise not be able to control a sublingual tab under their tongue before swallowing due to current crisis and cranial nerve impairment (Norcliffe-Kaufmann et al., 2017). This could make a significant difference in the management of autonomic hyperadrenergic crises in FD.

An additional benefit of planning for this clinical trial has been the development of a rating tool for autonomic crisis. So far, there has not been a tested and validated tool for scoring the severity of autonomic crisis to guide parents and clinicians in treatment decisions. Our tool not only allows for screening of several safety risks related to crisis itself and medications given, but it can offer objective measurement of crisis and response to medications. This can be a game-changer in improving care to people experiencing crisis at home and in the hospital.

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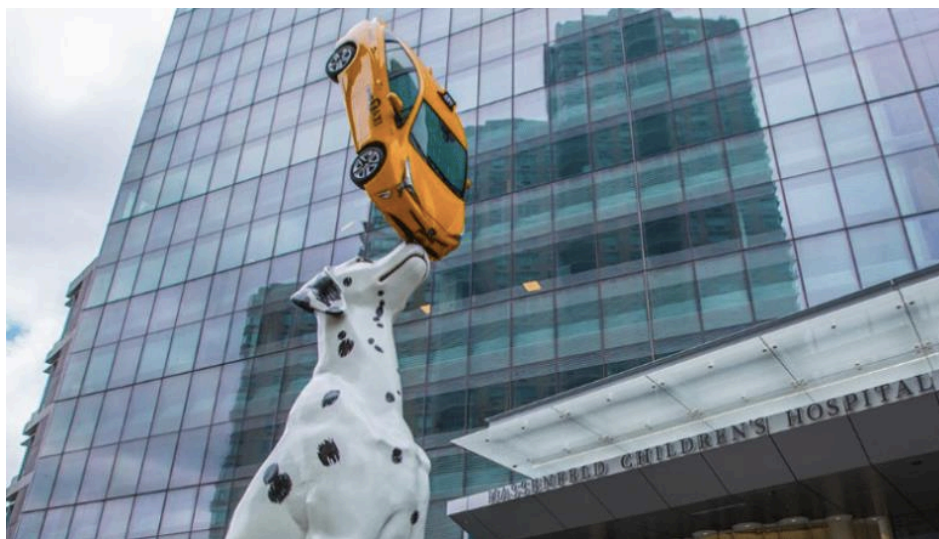
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CLINICAL UPDATE



Telehealth and virtual visits in FD

The NYU Dysautonomia Center has been serving patients with FD since 1970 and is the pre-eminent international facility for treatment of this devastating, progressive disease. We devote ourselves to the care of patients with this complex disorder to provide each patient with a comprehensive individual plan of care. FD patients fly in from all over the country and the world for their annual and interim visits. Typically, FD patients have regular in-person visits with a specialized care team including a pulmonologist, gastroenterologist, ophthalmologist, and neurologist. While beneficial for overall health outcomes, this care model is costly, time-consuming, and can create a barrier to care for those who need to travel significant distances to reach our specialized FD center. Frequent in-person appointments can also increase the risk of infection during the ongoing COVID-19 pandemic.

When the COVID-19 sheltering in place order came to New York City in March 2020, we had to re-imagine what a visit to the Dysautonomia Center looked like. Telehealth offers care options for patients with FD that overcome many of the inconveniences and safety concerns surrounding in-person appointments. The Dysautonomia Center with the help of the FD Foundation implemented a telehealth model that involves web-based video appointments with multiple members of a multidisciplinary care team, and kits with written instructions and video demonstrations sent to patients prior to appointments. These kits are used to measure weight and height, evaluate lung health, listen to heart sounds, record EKGs, assess gait, and look for ulcers or wounds under the supervision of a clinician.

Over the past year, patients and families have expressed overwhelming support for telehealth. Benefits of telehealth identified were a lack of travel time to the clinic, less time away from work, and a reduced risk of infection. Patients also listed a lack of access to WIFI, internet connection problems, and limited physical examination as limitations of telehealth appointments. The feedback received encourages patients and providers at our Center to incorporate telehealth visits into FD care beyond the COVID-19 pandemic. Future work will need to assess the effect of telehealth visits on FD health outcomes.

As always, in-person visits are still open and encouraged for patients and their families. We have made several modifications to ensure the safety of our patients and families including hand sanitizing and washing stations throughout the office, minimizing appointment overlap to reduce the number of people in the waiting room, and disinfecting rooms in between each visit. This model is just one example of how the Dysautonomia Center puts patient safety at the forefront of patient care. We will continue to adapt with the times and ensure that every patient, regardless of their geographic region is cared for and receives the latest information to live the best possible lives they can.

2020-2021 STAFF HIGHLIGHTS



NP Zenith Khan given the Rising Bruin Alumni Award

Zenith Khan was honored in the UCLA School of Nursing Distinguished Alumni Award Ceremony of 2020, the International Year of the Nurse, and received the Rising Bruin Alumni Award. The UCLA School of Nursing has a proud tradition of recognizing their distinguished alumni every year, and Zenith joins an honorable list of individuals who have made exceptional contributions in advancing nursing science, education, leadership, and patient care.

The Rising Bruin Alumni Award award is given annually to a recent UCLA School of Nursing alumni who has demonstrated a high level of excellence in their field. The ceremony honored Zenith beside the Distinguished Alumni who are giants in the field of advanced practice nursing and were pioneers in advancing the field of nursing and recognized for contributions to better patient care, public health, and advocacy on an international level.

In the words of her nominator who was a student of hers at UCLA, "Zenith taught me to think beyond the patient and see the person behind the term 'patient.' Zenith is compassionate for all individuals regardless of socioeconomic status or other factors. She acts ethically, is highly skilled, and has a positive attitude that is unmatched." We know that Zenith is a rising star, and she will make a world of a difference in the field of Dysautonomia and promoting the health and wellbeing of those with FD.

Zenith was also nominated for the Edith Cavell Award at NYU Langone Health Nurse Practitioner Awards for her desire to make a change in the healthcare system in a year like no other. In the words of her nominator, "Zenith Khan is an amazingly heartwarming person. Every day she shows great compassion to her patients and an utmost consideration for their care. She always has a joyful and cheerful demeanor regardless of the situation that is irresistibly contagious and has the incredible gift of bringing a smile to everyone in her care. Zenith's love and affection for her patients and their families truly makes an inspiring difference worthy of recognition."

Already a board-certified Family Nurse Practitioner with her Master's degree in Nursing from UCLA, Zenith also completed her first year of NYU's Doctor of Nursing Practice program this year, where she is conducting her doctoral project on advancing clinician knowledge of familial dysautonomia, afferent baroreflex failure, and other autonomic disorders. She chose to enroll in NYU's prestigious nursing program to be prepared at the highest academic level for advanced clinical practice and raise knowledge and awareness of FD.

2020-2021 STAFF HIGHLIGHTS



Dr. Patricio Millar making his name known in the world of Dysautonomia

Patricio Millar has been appointed faculty in the Department of Neurology at NYU Grossman School of Medicine. He came to us with specialized training in neurology and subspecialty training in movement disorders at FLENI, the leading neurological institute in Buenos Aires, Argentina. There, he helped design rating scales to assess unmet needs for patients with neurological disorders and contributed to clinical diagnostic algorithms for identifying and diagnosing patients with rare neurological conditions alongside world-class recognized experts.

Dr. Millar joined the Center in July 2019 as a research fellow. Within the FD program, he performs comprehensive neurological and blood pressure evaluations during clinical visits, which extended to innovative ways to complete a thorough telemedicine neurological evaluation during the COVID-19 pandemic. He has developed expertise in the management of blood pressure irregularities caused by afferent baroreflex failure and uses that knowledge in the care of people with FD.

During the past year, Dr. Millar has been invited to lecture on autonomic disorders both locally and internationally. He gave Neurology Grand Rounds at NYU, and talks for patients and caregivers on how to identify and manage autonomic dysfunction, a plenary lecture at the Mexican Academy of Neurology, and lectures for doctors and patients for the World Parkinson Coalition.

Dr. Millar published a book chapter focusing on gastrointestinal autonomic dysfunction. And he has recently been appointed a member of the Data Safety Monitoring Board for a clinical trial for dysautonomia in patients with another rare genetic disorder, Menkes' Disease, in patients who have survived into adulthood.

His specialized background makes for an excellent clinician addressing and providing the complex care the FD community requires.

2020-2021 STAFF HIGHLIGHTS



Alejandra González-Duarte, MD, PhD We are delighted to announce that Dr. González-Duarte has returned to NYU as a Clinical Associate Professor. Dr. González-Duarte received a medical degree from La Salle University in Mexico City, completed two residencies in Internal Medicine and Neurology in the Salvador Zubirán National Institute of Health Sciences and Nutrition, neuroAIDS fellowship at Mount Sinai Medical Center, and Autonomic Nervous System Disorders Fellowship at NYU Dysautonomia Center. She recently graduated from Anahuac University with a PhD in Bioethics. She has most recently worked as Head of the Dysautonomia and Small Fiber Laboratory in Mexico City, National Researcher and Research in Medical Sciences.



Lee-Ann Lugg Lee-Ann Lugg is the program coordinator and administrative lead at the Center. She has been a critical part of our team for 8 years and has an excellent understanding of how things work and more importantly how to keep things running smoothly. Lee-Ann has recently been accepted into the Master of Public Health program at NYU School of Global Public Health for the Fall 2021 semester. Her concentration will be in Social and Behavioral Sciences.



Jose Martinez Clinical Trials Manager Jose Martinez is celebrating 12 years of working at the Dysautonomia Center. He joined us in 2009 in this position and has been a vital asset to safe, quality clinical care and the success of our clinical research. Mr. Martinez sees patients to provide direct care in clinical trials ranging from blood draws, EKGs, patient questionnaires, collecting data for analysis, and publishing study results. He has managed over 35 clinical trials sponsored by either NIH or biopharma. In 2020 Mr. Martinez was first author in the publication *Impact of depressive symptoms on self-perceived severity of autonomic dysfunction in multiple system atrophy: relevance for patient-reported outcomes in clinical trials*, published in the international peer-reviewed biomedical journal Clinical Autonomic Research, and has co-authored numerous studies in other acclaimed biomedical journals.



Kaia Dalamo, DNP, FNP-BC, RN Dr. Dalamo was nominated for the Edith Cavell Award at NYU Langone Health Nurse Practitioner Awards for being a force of motivation and change at NYU Langone Health. In the words of her nominator, “Dr. Dalamo is an inspiring colleague and a true motivator. Despite working with patients that have incurable diseases, she continues to encourage them to live their best possible lives. Her presence in the office encourages us all to do better and strive to achieve better clinical care.” Earlier this year Dr. Dalamo designed the first rating scale for recognizing and assessing autonomic crises. This should be useful to titrate medications and monitor the effects of treatment. Validation of this tool is planned to begin this year. An artist herself, Dr. Dalamo also organized and hosted this year’s annual “The World Through My Eyes” FD Day art competition, expanding it from previous years’ photography focus to include all art forms. For this, she and Dr. Kaufmann also collaborated with leading New York and international artists and curators to organize a judging panel for all entries.



Siobhan Bhirangi, MPH Siobhan graduated with a Master's in Public Health from NYU's School of Global Public Health this spring, 2021. She has been working as a project assistant at the Dysautonomia Center since June 2019. She has enjoyed learning about the complexity of FD and other autonomic disorders and the research efforts to improve patient's lives at the Center. In addition to graduate school and her work at the Center, Siobhan completed research with the Department of Population Health at NYU Langone Health. Her work focused on substance use disorders among low-income New York residents with mental health conditions. She also worked as a co-editor for a literature review on healthcare policy for the organization Polygeia, a student-led Global Health Think Tank. In the fall, Siobhan will be attending medical school at Lake Erie College of Osteopathic Medicine in Elmira, NY to become a Doctor of Osteopathic Medicine. She hopes to continue to advocate for all patients and to be a force of change in healthcare.



Celeste Camargo, MD A visiting trainee from Brazil, Dr. Camargo first visited the Center as a second-year medical student. She has worked on several projects, including the investigation of cold-induced sweating in patients with synucleinopathies, psychosis in patients with multiple system atrophy and is currently investigating the incidence and prevalence of cancer in people with FD. Dr. Camargo presented on FD at the American Autonomic Society annual meeting in 2019. After graduating from medical school, she returned to the Center as a trainee to expand our research on cancer in FD patients to their relatives. Dr. Camargo will begin neurology residency training at Rutgers University Medical Center in New Jersey this summer, 2021. She expresses gratitude to Dr. Kaufmann and the Dysautonomia Center and the people with FD she has met and worked with at the Center for mentoring her and for inspiring her passion for medicine.



Dr. Jose Alberto Palma-Carazo, MD, PhD Dr. Palma recently joined Novartis as medical director for gene therapies. While Dr. Palma is no longer involved in direct patient care, he still works one day a week at the Center where he conducts research activities and clinical trials. In his new role, Dr. Palma is breaking new ground advancing the development of gene therapies for neurologic disorders and continues advocating for the FD community. We are grateful for his continued dedication and strategic thinking.



Dr. Maria Cotrina-Vidal, PhD Dr. Cotrina-Vidal moved from her Clinical Scientist position at the Dysautonomia Center earlier this year to grow into a management position within NYU. She now coordinates the Clinical Research Program of the Neurology-Stroke unit at NYU Langone Hospital in Brooklyn. She is still deeply connected to the Dysautonomia Center and FD research and community as she is completing an analysis of growth patterns and factors that affect height and weight in FD, as well as creating a guide on nutrition for FD families. Because of her personal connection with the rare diseases community, Maria is happy to chat or assist FD families that would like to contact her.



Dr. Lucy Jane Norcliffe-Kaufmann, PhD Dr. Norcliffe-Kaufmann has taken a position as Senior Director of clinical science at Theravance BioPharma. For the last 15 years, she organized the clinical research program at the Dysautonomia Center and authored the seminal papers that changed our understanding of FD and led to new therapies. We are forever grateful.

2020-2021 CENTER HIGHLIGHTS

Expert review on dysautonomia published in the *New England Journal of Medicine* (top world medical journal)

New HSAN genes discovered, published in *Neurology Genetics*

Frequency and burden of
gastrointestinal symptoms in familial dysautonomia, published in *Clinical Autonomic Research*

Carbidopa for
Afferent Baroreflex Failure in Familial Dysautonomia: A Double-Blind Randomized
Crossover Clinical Trial, published in top cardiovascular journal *Hypertension*

Longitudinal changes in the macula and optic nerve in familial
Dysautonomia, published in *Journal of Neurology*

Elbow
proprioception is normal in patients with a congenital absence of functional
muscle spindles, published in *The Journal of Physiology*

Guidelines in the management of neurogenic dysphagia published in *Parkinsonism & Related Disorders*

α -Synuclein in blood exosomes immunoprecipitated using neuronal
and oligodendroglial markers distinguishes Parkinson's disease from multiple
system atrophy published in
Acta Neuropathologica

What is the best method to diagnose a vasovagal
syncope? Published in *Clinical Autonomic Research*

Expanding the Genotypic Spectrum of Congenital Sensory and Autonomic
Neuropathies Using Whole-Exome Sequencing, published in *Neurology Genetics*

Genome sequencing analysis identifies new loci associated with Lewy
body dementia and provides insights into its genetic architecture, published in *Nature Genetics*

Limitations
of the Unified Multiple System Atrophy Rating Scale as outcome measure for
clinical trials and a roadmap for improvement, published in *Clinical Autonomic Research*

Three decades of Clinical Autonomic Research and
Beyond, published in *Clinical Autonomic Research*

Can Autonomic Testing and Imaging
Contribute to the Early Diagnosis of Multiple System Atrophy? A Systematic
Review and Recommendations by the Movement Disorder Society Multiple System
Atrophy Study Group, published in *Movement Disorders Clinical Practice*

Von Economo Neuron Pathology in
Familial Dysautonomia: Quantitative Assessment and Possible Implications, published in *Journal of
Neuropathology & Experimental Neurology*

Clinical Trials for Neurogenic Orthostatic Hypotension: A Comprehensive Review of Endpoints, Pitfalls, and Challenges, published in *Seminars in Neurology*

Afferent Baroreflex Dysfunction: Decreased or Excessive Signaling Results in Distinct Phenotypes, published in *Seminars in Neurology*

Acute Sensory and Autonomic Neuronopathy: A Devastating Disorder Affecting Sensory and Autonomic Ganglia, published in *Seminars in Neurology*

Muscarinic Receptors Cause Postganglionic Cholinergic Dysautonomia, published in *Annals of Neurology*

White Matter Hyperintensities in the Synucleinopathies: Orthostatic Hypotension, Supine Hypertension, or Both? Published in *Movement Disorders Clinical Practice*

Validation of the Neurogenic Orthostatic Hypotension Ratio with Active Standing. Published in *Annals of Neurology*

FD Scientific Advisory Board meets virtually due to the ongoing pandemic

Telemedicine service started for FD patients during the COVID-19 pandemic

The Natural History Study enrolls patients at sites in the US and at two sites in Israel

Increased collaboration with centers in Israel to understand COVID-19 in people with FD

Montreal Chapter of the Dysautonomia Foundation renews grant to support a mental health program

Theravance BioPharma continues grant to support research for neurologist Dr. Patricio Millar

Clinical Trials Manager Jose Martinez celebrates 12-years at the Center

Dr. Kaufmann gives neurology Grand Rounds at the University of Washington Medical Center and UCLA

Dr. Patricio Millar gives neurology Grand Rounds at NYU on autonomic failure

Dr. Alberto Palma gives neurology Grand Rounds at the University of Cincinnati

Dr. Kaia Dalamo and NP Zenith Khan become founding members of the American Autonomic Society Advanced Practice Providers Special Interest Group

Dr. Patricio Millar accepted into NYU Langone Health TRAIL Leadership Training Program

Jonathan Perez joins the team as a student intern performing data entry for the FD Natural History Study

CURRENT RESEARCH STUDIES FOR PATIENTS WITH FD

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. 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.*

ENROLLING

A STUDY OF GUT FLORA IN FAMILIAL DYSAUTONOMIA (MIBIOM)

IRB#: S16-00718

ELIGIBILITY: Patients with FD age 4 and older and their family members

PURPOSE: Maintaining a healthy weight is a problem for many patients with FD. This study aims to better understand the microorganisms that live in the gut of patients with FD and whether these play an important role in digestive function. In this project, we want to understand if differences in the microorganisms in the gut of patients with FD affect the energy derived from food. We will compare diets between tube and orally fed subjects to better understand the differences and also we will compare it with healthy controls. A better understanding of the microbiome in FD might help also to understand whether fungal overgrowth in the GI tract of FD patients is associated with persistent diarrhea in the absence of known pathogens.

SPONSOR: *National Institutes of Health – Institute of Diabetes, Digestive, and Kidney Diseases*

OPEN

UNDERSTANDING THE MUSCLE IN FAMILIAL DYSAUTONOMIA

IRB#: S14-01192

ELIGIBILITY: People with familial dysautonomia 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.*

ENROLLING

BRAINSTEM REFLEXES IN FAMILIAL DYSAUTONOMIA

IRB#: S07-938

ELIGIBILITY: People with familial dysautonomia of any age.

PURPOSE: To understand if dysphagia and dysarthria in FD are due to a reduction in the number and/or excitability of afferent trigeminal nerve fibers. To achieve this, we are studying brainstem reflexes in familial dysautonomia using electrophysiological techniques.

SPONSOR: *Familial Dysautonomia Foundation, Inc.*

NATURAL HISTORY INFORMATION

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 to be involved:

- Patients with FD being evaluated at the NYU Dysautonomia Center in New York, at the Hadassah Hebrew University Medical Center or at the Sheba Medical Center in Israel will have the option to be enrolled in the Natural History Study. All three centers share the same database regardless of the different locations.
- If for whatever reason, you are unable to visit New York or Israel, you can still send medical records from your local doctors. In addition to receiving medical recommendations from the FD doctors, your information will 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 specialists
- 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, 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 your information from any visit to a doctor.

The FD Questionnaire: The FD Questionnaire has been developed over the years to provide doctors with the information they need. It is a series of questions that cover all body systems, how they function, and identify common complications at different stages of disease. The questionnaire is specifically designed for patients with FD, to be filled every year. Filling it out will help families prepare for their visits with doctors. The FD Center will send you an electronic copy of 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, an idea originally implemented by Dr. Felicia Axelrod. 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 to use this information to support their scientific work.

Official sites for the Natural History Study of FD: In the United States - NYU Dysautonomia Center, 530 First Avenue, Suite 9Q, New York, NY, 10016. In Israel - Sheba Medical Center, Tel Hashomer, Derech Sheba 2, Ramat Gan, Israel and Pediatric Pulmonology and Sleep, Hadassah Hebrew University Medical Center, Jerusalem, Israel.

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 and entered into a secure online data collection platform (RedCap), with controlled access.

DYSAUTONOMIA CENTER

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DYSAUTONOMIA CENTER

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Biohaven Pharmaceuticals

The US Food and Drug Administration

MSA Coalition

Theravance Biopharma Inc.

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, read the Foundation's Dyscourse magazine, and ask the clinicians at your annual evaluation visit.

Give samples: By giving a small sample of blood, we can measure gene production and protein levels, which can help test the outcome of different treatments 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.

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.

Call us: Keep in touch. Periodically calling to find out about new research opportunities is an important way to find out what is new at the Center. Our staff can tell you about new studies and discuss whether our clinical trials may be right for you. Dr. Maria Cotrina is available to answer questions about studies you may be interested in joining and how to enroll.

Tell your friends: Talk to your friends about studies that you participate in. This will hopefully encourage them to 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.

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