Clinical Research Update

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Since joining the Dysautonomia Center five years ago, we have made great strides in understanding FD and improving clinical care through research. Our major advances in the last year have been finding better ways to control blood pressure without dampening the drive to breathe, which are two of the most dramatic problems faced by people with FD. We have successfully reduced the high blood pressure and the abnormal retention of carbon dioxide in the body by limiting the use of fludrocortisone, reducing the dosage of sedative medications and using non-invasive ventilation during the night (CPAP or BiPAP).

After discovering that positional feedback from the muscles (called proprioception) is lacking in patients with FD [1] and that this deficit plays a major role in their inability to balance and leads to difficulty in walking [2] we have tried new ways to improve mobility and balance in affected people. We have learned how to harness sensors (receptors) from the skin, using athletic tape, to enhance feedback to the brain and allow better fine-tuning of movements. We are now studying whether the athletic tape technique improves walking in people with FD.

The team at the Dysautonomia Center has expanded. Following our work showing that progressive visual loss is the result of a loss of neurons in the eye, Dr. Carlos Mendoza has joined the team. Our goal is to provide comprehensive eye care. In the future, all patients will have a full eye examination when visiting the Center for their annual evaluation.

We are collaborating with the FD Center in Israel, now lead by Dr. Ori Efrati, on a project to define the best strategies to treat the pulmonary complications of FD. The results of this study are being analyzed.

In hopes of spotting renal damage early on and treating it aggressively to halt its progression, we have just begun a study with Dr. Horward Trachtman of NYU. The study aims to identify markers of early renal injury in patients with FD.

Studies of potential gene therapies are ongoing at the Center. A long-term kinetin trial is underway. A phosphatidylserine trial is also underway, and results of IKAP mRNA levels are being analyzed.

The future for people with FD looks brighter than ever before. The FD team is expanding and new treatment options are opening up. We look forward to more good news in the future.

References:

Carbidopa and blood pressure variability in FD

Lucy Norcliffe-Kaufmann, PhD
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Similar to being unable to sense pain or temperature, children with FD are born without the ability to sense their blood pressure [1]. This lack of feedback explains why blood pressure readings spike high one minute and drop low the next. Over the years, this "yo-yo" effect (known as blood pressure variability) takes its toll on organs like the kidney [2]. We recently published the results of the first placebo-controlled trial in FD [3]. We showed that carbidopa, at an average dose of 500 mg/day, reduced the length and severity of nausea and retching attacks [3]. It was safe and well-tolerated. Plus, unlike traditional treatment approaches (clonidine or valium), carbidopa did not suppress respiration.

In the trial, 12 patients collected their urine at baseline and while taking carbidopa. Analysis of those samples showed that FD patients taking carbidopa excreted much less norepinephrine (norepinephrine being the neurotransmitter that causes high spikes in blood pressure). To examine the effect of carbidopa on blood pressure variability in FD, we fitted FD patients on carbidopa with an ambulatory blood pressure monitor. We then went back through the database to compare the results with previous 24-hour ambulatory recordings (before starting carbidopa).

The data shows that carbidopa lessens blood pressure variability by slowing norepinephrine production.

We are optimistic that in addition to being an alternative treatment for nausea, carbidopa might also be good for blood pressure variability. Further research is underway to prove this.

References:

Creation of a new mouse model for testing potential therapeutics for FD
Susan A. Slaugenhaupt, PhD and Ioannis Dragatsis, PhD
Massachusetts General Hospital and University of Tennessee Health Science Center
Team Members: Paula Dietrich, PhD (UT), Elisabetta Morini PhD (MGH), Monica Salani PhD (MGH)

In order to create an accurate mouse model of FD in which we can manipulate mRNA splicing, we introduced an FD transgene (TgFD9), which contains the human IKBKAP gene with the major FD splice mutation, into the Ikbkapdelta20/flox mouse model by mating these two lines of mice. The introduction of a human IKBKAP transgene attenuates the severe FD phenotype that we observed in the Ikbkapdelta20/flox mouse and recreates the same tissue-specific mis-splicing defect seen in FD patients. The new FD mice are not as severely affected as the mice without the human gene. They show a reduced growth rate, but, unlike the more severely affected mice which die soon after birth, the mice with the human gene survive. Staining of their tongues shows that the mice have a reduced number of fungiform papillae and they have several other FD-like features at birth. The creation of this new model has allowed us to initiate a detailed clinical trial of kinetin in these mice and will permit testing of other strategies targeting mRNA splicing. We have already demonstrated that changing mRNA splicing in FD can lead to increased normal IKBKAP in both mice and people. These mice will allow us to determine if increasing normal IKBKAP will lead to improvements in nervous system development.

Designing a new drug that targets mRNA splicing to treat FD
Susan A. Slaugenhaupt, Ph.D.
MGH FD Team: Fabio Urbina BS, Monica Salani PhD, Mats Nilbratt PhD, Elisabetta Morini PhD

Last year, our FD project was chosen to be part of the NINDS Blueprint Neurotherapeutics Network. I will provide an update on our exciting work and describe what we are doing to create new FD drugs. More information on the program can be found at: http://neuroscienceblueprint.nih.gov/bpdrugs

The Neurotherapeutics Grand Challenge
Most nervous system disorders lack effective treatment, and most of the potential neurotherapeutic drugs identified in basic research do not make it to human testing:

- Basic researchers often lack the resources to develop novel therapeutics strategies to the point where they can attract biopharmaceutical industry interest
- Biopharmaceutical companies often hesitate to invest in neurotherapeutics development because there are few clinically validated targets or strategies, there is a long track record of failure, and many nervous system disorders affect relatively small populations.

The Blueprint Neurotherapeutics Network
The NIH Blueprint established the Neurotherapeutics Network as a pipeline between academic and industry drug development research. The Network offers neuroscience researchers a “virtual pharma” to develop promising hit compounds from chemical optimization through Phase I clinical testing.

- Researchers receive funding to conduct biological testing, access to a full range of industry-style drug development services and expertise, and control of the intellectual property for drug candidates.
- The Network currently includes projects focused on drugs for age-related macular degeneration, Alzheimer's disease, depression, hearing loss, familial dysautonomia, and Parkinson’s disease.

Each project is directed by a Lead Development Team, which is composed of the principal investigator, industry consultants hired by NIH, and NIH staff. This team maps out a research strategy and oversees implementation of this strategy by a network of contract research service providers.
Antisense Modulation of *IKBKAP* Splicing as a Potential Therapy for FD

Adrian Krainer, PhD
Cold Spring Harbor Laboratory

Genes, which are made of DNA, encode the precise instructions for cells to synthesize individual proteins. These instructions are first copied into “messenger” RNA (mRNA), which then serves as the template for protein synthesis. However, for the mRNA to become competent for protein synthesis, non-coding segments (introns) must be precisely removed, and coding segments (exons) joined in a cut-and-paste process known as mRNA splicing. Virtually all FD patients carry a mutation in intron 20 of the *IKBKAP* gene, which impairs mRNA splicing, resulting in skipping of exon 20, and therefore a reduction in the levels of full-length IKBKAP mRNA and protein.

My lab employs so-called antisense oligonucleotide (ASO) technology to target specific portions of individual mRNAs, in such a way as to change the way in which they are spliced. ASOs are small snippets of DNA/RNA-like material, with useful drug-like properties and the ability to bind to specific RNA sequences with exquisite specificity. We are generating ASOs that optimally correct the FD splicing defect, and thereby increase full-length *IKBKAP* mRNA and protein in cultured patient skin fibroblasts. We will further test and optimize one or more of these ASOs in transgenic mice that carry the human gene with the FD mutation. Finally, we will obtain mice that accurately model the disease, and test our lead ASOs for their ability to ameliorate the symptoms of FD. These pre-clinical development experiments will establish the feasibility of ASO therapy for FD, and provide the groundwork for further clinical development.
Dr. Axelrod presented her traditional update. Information was provided on current patient statistics, focusing on the dramatic decline in birth rate of new FD patients and the continuing diagnoses of new FD patients, resulting in continued growth of the FD population. There has not been a new FD birth in USA or Israel since 2011. However, in the past two years, there have been 9 “new” diagnoses—4 from Israel, 2 from the USA, 2 from the United Kingdom and 1 from South America. Interestingly, both of the USA patients are of Mexican extraction, but only one of these children has identifiable Ashkenazi Jewish heritage. Since both of these children have the common FD splicing mutation, it suggests that we should consider broadening our screening criteria for the general population, as the FD gene may no longer be unique to the traditional Ashkenazi Jewish population.

In the past five years, the Center’s registration has increased by 5% and has reached 662 patients, with 360 (54%) from USA, and 226 (34%) from Israel. However, we do have a diverse international population with growing numbers of patients in Canada, England and South America, in particular Argentina. At present the youngest patient is 18 months and the oldest is 67 years. The adult population continues to increase as 54% are now 20 years or older. On comparison of statistics from 2008 to the present, it can be noted that an increasing number of patients are living independently, are married and are having children of their own. We also noted that 43% of our patients have had a college experience.

Dr. Axelrod also announced this year’s three FD Distinguished Adults – Eugene Budovskiy from Brooklyn, New York, Ben Rainer from Los Angeles, California, and Zoey Schvan from Ottawa, Ontario-Canada.