DLG4-RELATED SYNAPTOPATHY // ISSUE 9 // WINTER 2023

SHINE SYNDROME FOUNDATION

A Letter From The President

LAURA PALMER, MOM TO NOLAN (10)

First of all, I want to say a huge thank you to every family who has attended a COMBINEDBrain biorepository roadshow location! We've collected many samples for both CB and Simons Searchlight, which will help create more diversity in our research studies. We are hopeful the biomarker project will help provide a way to measure changes in our children before and after therapeutic treatments.

In September, two of our board members, Mara and Tim, joined members of the DLG4RF in San Diego, CA for the Global Genes Conference. Two of our members also attended the COMBINEDBrain and NORD conference October 15-17.

We've been working on a few advocacy efforts recently, including developing a Medical Considerations document (page 3), the ICD-10 code process (Page 2), and are in the early stages of an Educational Considerations document.

Lastly, please consider joining the efforts of the SHINE Syndrome Foundation! We are an all-volunteer run organization. We plan to hold 2024 elections on January 16th with new positions beginning on February 1, 2024. Check out this Google Form for more information and details about the available positions.

IN THIS ISSUE

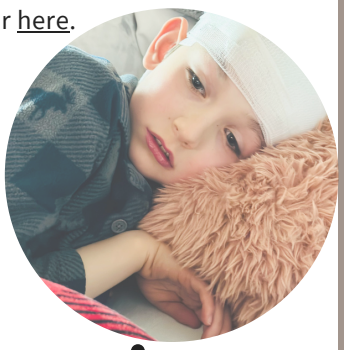
Epilepsy in DLG4 Publication

The first-ever paper describing epilepsy in DLG4 was just published in Epilepsia. The efforts were led by a team at the Danish Epilepsy Centre including Guido Rubboli, Rikke Møller, and Benedetta Kassabian, though there were many co-authors including neurologists currently treating DLG4 patients.

Some of the highlights from the paper include that a subgroup of individuals with DLG4-related synaptopathy have a developmental epileptic encephalopathy (DEE), and around one-fourth of them have ESES (unpublished results). The occurrence of ESES in DLG4-related synaptopathy requires to be properly investigated with 12-24 hour video-EEG monitoring that captures sleep/awake periods.

Another interesting finding is that regression in verbal and/or motor domains was observed in all individuals who suffered from ESES, but also in some who did not. ESES stands for Electrical Status Epilepticus during Slow-Wave Sleep and is a specific EEG pattern found during sleep.

The SHINE Syndrome Foundation has recently partnered with both the Rare Epilepsy Network (REN) and DEE-P Connects as community partners to engage with other disorders that cause DEE. You can read the full epilepsy paper here.



ICD-10 Code Presentation

Patient advocacy is a huge part of our mission. Last fall, SHINE moms Laura Palmer and Colleen Lareau drafted an application for an ICD-10 code for DLG4-synaptopathy. This process is a huge undertaking! An ICD-10 code will benefit our community in several ways: it could help increase diagnostic rates, allowing physicians to document the proper diagnosis and true underlying cause for a patient, help physicians understand disease progression, provide patients access to new medications/treatments, and help with access to benefits and services.

On September 13, Dr. Tümer presented to the CDC on our behalf to create a unique ICD-10 code for our disorder in the Intellectual Disability category of the DSM.

Since the presentation, DLG4 PAG leaders have worked to obtain letters of support for a unique ICD-10 code for DLG4 and have drafted a detailed letter of support, citing incidence rates in various countries and states and the anticipated growth rate for diagnoses we have seen over the last six-twelve months. We have submitted this additional information to the CDC.

Now, we will wait for approval of an ICD-10 code for our disorder. If selected to receive an ICD-10 code, it will be implemented in the next update of the DSM. This means physicians can use the proper diagnosis code within about a year. A huge thank you to Dr. Tümer and Amanda Levy for their work on the presentation!

SHINEing Star

Clarisse just turned 3! We learned the diagnosis of DLG4-related synaptopathy only 10 days after her 3rd birthday. She is French and has two siblings - twins Edouard and Victoire. They have only one year of difference. Mum used to call them "the triplets". Everything has always been difficult for her: to walk, to speak, to manage emotions. She started to walk the week before her second birthday and she finally started to talk. She is determined to succeed until this disease forces her to take a break. The meaning of the name Clarisse is "that brings the light" in Latin… So crazy as this is so close to the meaning of "SHINE" syndrome. She loves to go to kindergarten to play with her friends. She always needs to be with an adult even when she is playing. She loves to dance to announce the beginning and the end of the weekend. This is a funny routine, that allows us to share happy moments. Clarisse likes to go with her caregivers 3-4 times a week. After each session, it's time for a huge hug with Mum. Knowing this disease has been and is still very shocking for Mum, but their family is a very important support.

Fundraising Opportunities

GroupRaise

US families can create a GroupRaise Fundraiser at a local restaurant, invite friends, families, neighbors in your community and give back a percentage of the sales to the SHINE Syndrome Foundation. Contact Melanie Queen at mqueen@shinesyndrome.org to get started!

Consider hosting an end-or-year Facebook Fundraiser. Get started at the DLG4-Synaptopathy (SHINE Syndrome) public Facebook page (linked above).

Thank You!

Thank you for supporting our Kendra Scott Gives Back Fundraiser, raising almost $1000. And a huge thank you to the Clorox Company employees. Employees were given an amount to donate to a charity of choice and we are so thankful many of them chose the SHINE Syndrome Foundation, bringing in close to $2,500 for DLG4 research!

KENDRA SCOTT

The Clorox Company

Medical Care Considerations for DLG4

After publishing a DLG4 chapter in Gene Reviews, the same team of MAB advisors helped create a user-friendly Medical Considerations Document that families can take with them to medical appointments and/or their PCP to know which issues may be important to monitor in a patient with SHINE Syndrome.

Our organization received a grant from Horizon Therapeutics to translate the document into two other languages and also print this document to send to families.

This document can also be found on our website at www.shinesyndrome.org or via this link. We hope to have translated versions in Spanish, French, and Dutch in the near future. We will share these once the translation has occurred.

Through this grant, we will also create high-quality printed copies of the English document. Once we have a distribution process in place, we can send them via mail to families who request one using this form.

Team Florian Hikes for SHINE

Le dimanche 27 août, la Team Flo-Flo a complété le Trail du Bélier, une randonnée de 15km à flanc de montagne dans les Alpes françaises. Un groupe de famille et amis de Florian, qui est atteint du syndrome SHINE, l'a accompagné dans cette aventure munis d'une joëlette (un fauteuil tout-terrain adapté) et portant fièrement des t-shirts et un drapeau SHINE Syndrome. Un exploit impressionnant et un example émouvant d'inclusion et de sensibilisation à cette maladie génétique rare.

On Sunday August 27th, Team Flo-Flo completed the "Trail du Bélier" (which translate to the Ram Trail), a 9-mile mountainside hike in the French Alps. A group of the family and friends of Florian, who has SHINE Syndrome, accompanied him in this adventure using a Joëlette (an adaptive all-terrain wheelchair) proudly wearing SHINE Syndrome t-shirts and a flag. It was an impressive exploit and a moving exemple of inclusion while raising awareness for this rare genetic condition.

Variants of Uncertain Significance

While most of our SHINE patients are labeled as pathogenic or likely pathogenic, we do still have a few patients who are considered “VUS” or Variants of Uncertain Significance. If this applies to you, there are several ways you can further investigate your child’s variant.

One way is to participate in patient registries, such as Simons Searchlight or the Brain Gene Registry. Both of these options have genetic counselors who can review your report and potentially advise you on the pathogenesis of your child’s variant. Both of these options are hyperlinked above.

Another option available to SHINE families is to reach out to Dr. Zeynep Tümer, clinical geneticist at Copenhagen University Hospital via email. She is happy to review reports for any family who has questions about their variant. You can email Dr. Tümer at asuman.zeynep.tuemer@regionh.dk.

It is beneficial to have the correct classification for your child’s variant so their data can be counted and included in analysis of DLG4 data and progression of disease.

Some of our SHINEing Stars enjoying winter festivities!




Global Genes Conference

On September 19th to 21st, Mara Gervais and Tim Stuart had the opportunity to represent the SHINE Syndrome Foundation at the Rare Advocacy Summit hosted by Global Genes in San Diego. It was an opportunity to create more awareness for SHINE Syndrome, the intricacies of what having a DLG4 mutation entails and the research efforts that are underway for our disorder.

It was also a great place for networking with researchers, biotechs, pharmaceutical companies, and other PAG leaders. Seeing all these various parties gathered around the sole purpose of improving the lives of rare disease patients and their families was inspiring. It gave us many ideas of avenues to explore and actions to take and a renewed sense of motivation.

From left to right: Payal Patel (DLG4RF, Marie-France Gervais (SSF), Tim Stuart (SSF), and Sabrina Merchant (DLG4RF) at the Global Genes conference in San Diego.

Research Updates

I*Hebrew University, Israel*
The AAV vector was generated and is ready to be tested on human derived neurons and 3D model systems.

Cincinnati Children’s Hospital, Ohio
The mouse colony is still being scaled up. The mice in the colony are doing well. Initial assays are currently in design and a new MD/PhD has started work with the mice.

Copenhagen, Denmark
Dr. Strømgaard received a grant earlier this year from the Lundbeck Foundation. His team has onboarded a post doc and a PhD student working on disease mutations in PSD-95 (and other PSD proteins) and their putative relation to biomolecular condensates. Dr. Tümer and Amanda Levy have been working on updating OMIM, the ICD-10 code presentation, and starting work on a non-viral approach to study the variants. Additionally, the team at the Danish Epilepsy Centre has finished their study of 35 DLG4 patients with epilepsy. See page two for more information about the epilepsy publication.

CHEO, Canada
CHEO is working on our repurposed drug screen for DLG4. They are currently using 4 lines (2 DLG4 patient iPSC lines and 2 control lines) and evaluating morphology, neural activity, protein quantity, and marker localization using techniques including Western Blots and immunostaining.

HAPPY HOLIDAYS!