Genetic ALS & FTD: End the Legacy

May 2023 Newsletter

Julie Granning, Editor

A Note from the Chair

May was ALS Awareness Month, and we were all so glad and appreciative of how so many put themselves out there to teach the world about this disease, whether on a video call, the National Mall, or the Today Show. If only the friends and family of the hundreds of thousands impacted by genetic ALS & FTD knew the profound risk we all carry for these diseases, how many more would understand their clear personal connection to these terrible conditions. To push that knowledge forth a little bit more, ETL volunteers Cassandra and Linde shared their very personal stories in an End the Legacy ALS Awareness Month Panel on being healthcare workers impacted by genetic ALS and FTD. We are happy to link to that talk for the first time in this newsletter.

We are also proud, this past month, to have our letter to the editor published online in the journal *Brain*. It is quite shocking to consider the common sense considerations put forth in our letter, and the reasonable responses in the reply, to see how long it has taken for this to be given an airing in the literature. The needs of the genetic ALS & FTD community must never be overlooked again, and we at End the Legacy are glad to be taking this on as the voice for our community.

Finally, we are so excited to offer up our first Peer Support Hour set for June. Having options available for those who would like to connect with others in these often isolating positions is a driving force behind why we exist. I know my own mother Kathleen would have been so happy to speak with others who just understood.

Thank you for staying plugged in and connected as we work together with many others to save our lives and abilities. **-Jean Swidler, Chair**

Advocate **Support** **Educate** **Research**

Mission Statement

The Genetic ALS & FTD community is large and growing. ALS & FTD are terminal conditions, and being at a heightened risk for them can have profound impacts on people and families. We organized Genetic ALS & FTD: End the Legacy to provide educational and support resources to, encourage and promote research about, and advocate for the genetic ALS & FTD community.

Follow us Instagram
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Join Our Team!
You are invited to join us for our weekly team meetings! If you would like to join our strategy/update sessions held every Friday at 9am Pacific, email us at geneticalsftd@gmail.com.

SUPPORT

When we first formed, it was in shared awe of the wonderful resources the Huntington's Disease Youth Organization had established for their at-risk community. Providing support for those in these unenviable positions was something they have done well and we are so delighted to announce our first Peer Support Hour will be held on June 21, at 6:00 p.m CST. As we prepared for this we received wonderful advice and guidance from many mental health professionals (special shout-out to Caitlin and Hope!). MAPT gene carrier and End the Legacy volunteer Linde will be facilitating. **Sign up here** to attend.

ADVOCACY

Taking the call to educate others about this disease and its impacts seriously during ALS Awareness month, our vice chair Cassandra and leader Linde shared very personal, touching, and informed perspectives as both medical professionals and people at risk of genetic ALS. Watch the recording here.

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ADVOCACY

ETL member Debbie took part in lots of activities on a trip to Washington DC. Here is her report: “On May 10, my spouse Marie and I were in Washington DC with I AM ALS, placing 6,000 flags near the Washington Memorial for their ALS Awareness event. On May 11, I was one of the speakers at the event.

On May 11, we visited Senator Vance (OH) and I shared about our family history and made “asks” of him and his office. I spoke about how ALS isn't as ‘rare’ as people once thought and I shared Jean's estimate of 145,000,000 pre-symptomatic C9 people. The meeting was well-received and the office has already reached out to ask how they can push the FDA about NurOwn.

Also on May 11, we met with Rep Wenstrup's (OH) health aide and Senator Brown's (OH) health aide to have the same type of advocacy meetings. Both went very well, and again, we have had positive follow up since returning back to Cincinnati.

As fate would have it, a lady who worked for me 20 years ago, Pat Manhardt, was also on this trip, as she has ALS now. She's the person in the wheelchair in the photo. I have been blessed to be able to visit her over the past couple of years, as she navigates her journey.“

Go Debbie, and all who speak up for those impacted by ALS.

If you want to make sure the Genetic ALS & FTD community is included in any efforts you are involved in, please reach out to us! Email us at geneticalsftd@gmail.com.

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EDUCATE

We hosted PhD candidate and ALLFTD researcher Anna VandeBunte to share information on how cardiovascular health impacts disease progression in genetic FTD, including GRN, MAPT, and C9orf72 gene carriers. The recording is viewable here.

Upcoming Educational Webinars

We have our next educational webinar scheduled on June 27,at 9:00 AM Pacific/12:00 pm EST, with researcher Jolien Perneel, a PhD Candidate who is working in renowned genetic FTD researcher Dr. Rosa Rademakers lab. They will be presenting on findings related to genes people may have in addition to ALS/FTD genetic mutations that could alter the risk of developing disease. Sign up here to attend.

If you are interested in presenting to the Genetic ALS and FTD community, please reach out! Email us at geneticalsftd@gmail.com.

RESEARCH

Patient-Led Research

Our letter, titled, "A new diagnostic entity must enable earlier treatment in gene carriers," was just published in the journal *Brain*. It was written in response to an article by Dr. Benatar concerning pre-diagnosis periods in ALS gene carriers. Our letter made three points: 1) we are already patients, even if not showing symptoms, underscored with a statement by the FDA to that effect; 2) we want access to care and clinical trials long before any phenoconversion occurs; 3) we participate in studies but think it is time to move past observation to treatment, and it is likely that earlier administration of treatment will be more effective, just like in animal studies.

A reply to our letter was published. It was co-authored by Drs. Benatar, Al-Chalabi, Wu, and Anita Crowley. The reply brought up rebuttal points. Among them, they cautioned that gene carriers being seen as patients would have their gene status in their medical records, which could open them up to insurance discrimination. This is surely a matter for individuals to consider, but we would hope that the medical field would look out for our best health outcomes. Also, they raised the need for more research to define a point of disease emergence, which we enthusiastically agree with and feel strongly that only by bringing the thousands of carriers not in research but instead into clinical care into the fold, will the best and the most detailed picture of disease emergence be painted.

Finally, they asserted that pre-symptomatic treatment would be considered off-label. We think the last point is a non-issue, considering the consensus in the field that ALS and FTD disease processes begin prior to symptom onset and the statement on the matter that was made at our recent FDA patient-led listening session, "...from the FDA's perspective, we do consider the presymptomatic stage in genetic mutation carriers as part of the ALS disease process."

Reasearch Study News: ETL was proud to provide a letter of support to assist with a grant request by genetic ALS researchers at DIALS. We are happy to speak on behalf of the genetic als and FTD community for others upon review and request.

Member Spotlight

Tucker Olson, Interviewed by Mindy Uhrlaub

You come from an SOD1 family. As a pre-symptomatic gene carrier of ALS, can you explain your—and your family's—experience with clinical trials?

From records obtained through research on our ancestors who first immigrated from Romania to the United States during the late 1800s and early 1900s, the earliest record I have found that likely indicates (SOD1) ALS dates back to 1939. At that time, ALS was poorly understood. It wasn't until 1993, shortly before my grandmother succumbed to the disease, that the SOD1 mutation was discovered as the cause of ALS.

To the best of my knowledge, my uncle was the first person in our family to participate in an ALS clinical trial. My aunt shared that there was limited information available about the trial at the time, and for an unknown reason, my uncle's participation was immediately halted.

Shortly after my father's SOD1 ALS diagnosis in 2008, he enrolled in what our family was told was the first ALS clinical trial targeting the underlying cause of the disease, the SOD1 gene mutation. The drug being trialed, pyrimethamine, was repurposed from its original intended use, which was the treatment of malaria. My father participated in Phase I of that trial. To take part, either my mother or a friend of his would travel with him every other week from Fort Wayne to Mt. Sinai Hospital in New York, New York. My father made the trip ten times that year, which was quite a challenge for someone battling a muscle-wasting disease. After the trial period, my father continued to take pyrimethamine. Although a publication in 2017 reported significantly lower cerebrospinal fluid Cu/Zn superoxide dismutase in SOD1 participants, the drug was not ultimately approved. Sadly, my father succumbed to the disease in May of 2013, after five years of battling ALS.

I don't believe that my aunt was made aware of any actively recruiting clinical trials targeting our family's SOD1 mutation when she was diagnosed with the disease in 2017. Further complicating matters was the nearly two-year delay between the initial symptoms and the disease diagnosis. Such a time delay is often considered exclusionary criteria for clinical trials.

While not necessarily an "interventional clinical trial" but rather a clinical study, my older sister and I participate in the Pre-fALS Study at the University of Miami. Every 18 months, the researchers arrange and cover our travel expenses to assist their ALS biomarker research.

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Are there any trials for QALSODY that include pre-manifest carriers? Are you eligible? How does this make you feel?

As a preface, it's important to note that there are over 150 variants of the SOD1 mutation known to cause ALS, referred to as pathogenicity. Out of those 150+ variants, only a small handful are associated with rapid disease progression. Individuals with rapid progression typically have a disease course of six to eighteen months, compared to the average of 3660 months. Some people with rapidly progressing variants may have a longer disease course, just as some individuals with SOD1 variants not associated with rapid disease progression may experience a swift rate of progression.

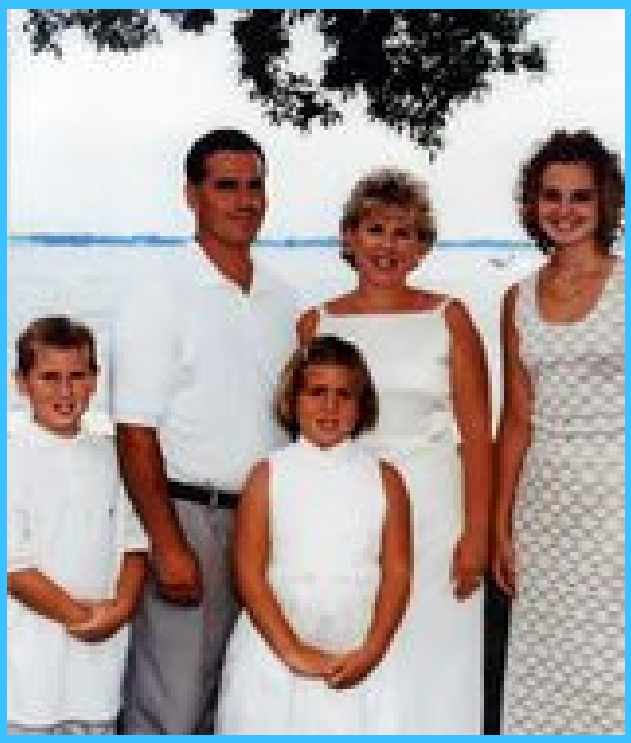
Those with rapid progression are likely to experience a "spike" in their neurofilament levels within a 12-month period before the disease becomes clinically recognizable. This spike occurs due to a rapid number of cells dying within the body, which can be detected through biomarker tests.

Currently, there is an ongoing trial referred to as the "pre-symptomatic trial" for individuals with an SOD1 mutation, known as the ATLAS Study. The key eligibility criteria for the trial are:

- Be 18 years of age or older.
- Not have any signs or symptoms of ALS.
- Have an SOD1 mutation that is considered to have high/complete penetrance.
- Have an SOD1 mutation that is associated with a rapidly progressing disease course, or otherwise have your SOD1 mutation approved by an independent adjudication committee.
- Have a plasma neurofilament level below the predefined threshold.

Since December 2017, I have known that I inherited the SOD1 mutation from my father. Geneticists have informed me that our family's mutation has a high rate of penetrance, with some referring to it as being completely penetrant. However, they have also told me that my specific SOD1 mutation does not belong to the handful of variants considered to have a rapid rate of progression. Instead, they described disease progression as "variable." Some individuals with my variant progress rapidly, some progress on par with the often-described "average disease course" of three to five years, while others progress at a much slower rate. Within my family, the average disease course has been five years. Essentially, I knew that my SOD1 mutation would have to be approved by the independent adjudication committee for inclusion in the clinical trial. I underwent the ATLAS Study's screening process at the nearest trial site, Northwestern Hospital (Chicago, IL). However, my enrollment was rejected due to the variable disease progression within affected family members.

Interview continues next page



How does the FDA approval of Tofersen's QALSODY affect you and your family?

The FDA's approval of Tofersen, now marketed as QALSODY, brings a sigh of relief for my family and other families affected by SOD1 ALS. Furthermore, I believe it represents a step forward in advancing future treatments for this terrible disease. I remain hopeful that QALSODY's approval will serve as a signal to the rest of the pharmaceutical industry, indicating that a cure can ultimately be found soon.

However, when it comes to treatment access, the immediate net benefit for my family and me remains uncertain. In a conversation with my local ALS clinic in the fall of 2022, I was told that even if QALSODY were to be approved, it would be unlikely to be provided there. This means that we would still need to travel monthly over two hours away to a larger hospital, in a larger market, for the potentially invasive treatment. I worry that others may face similar barriers to treatment in their respective regional areas.

Let's keep our growing community strong and informed!

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