JULY 2022 NEWSLETTER

Dear members of the SHANK2 community,

It's been a year since we launched the SHANK2 Foundation. The programs we developed in our planning phase are being implemented, and we are beginning to see results. Our community has expanded, our database has grown, and our research has progressed. Families from all over the world have connected and shared their stories--in fact, two families who had never met before learned that they are related!

As more and more families sign up, the SHANK2 Patient Registry is beginning to yield meaningful data. Furthermore, in May we brought together international researchers who updated their colleagues on their current projects and findings and participated in a collaborative brainstorming session which prompted discussion about future studies. And, within weeks, we will receive a list of potential drug candidates for SHANK2-related disorders that warrant further investigation from Rarebase.

In this newsletter, we are delighted to share more details on these latest developments.

WE RECEIVED OUR FIRST GRANT!!!

This morning we were awarded a small grant from the #RAREis Global Advocacy Grant…the first grant we applied for!

A critical component of our data collection effort includes standardized physical evaluations of our children to help researchers gain a better clinical understanding of SHANK2-related disorders. The #RAREis Global Advocacy Grant will be used to cover the costs of travel for a few families to meet with the only practicing clinician in the United States with an extensive SHANK2 research background. Dr. Yong-hui Jiang, the Chief of Medical Genetics at the Yale School of Medicine, combines his theoretical understanding of SHANK2-related disorders with his clinical observations in an effort to treat patients and develop therapies to alleviate disease symptoms. When meeting with our community members, Dr. Jiang uses standardized evaluation methods to identify a comprehensive clinical presentation of SHANK2-related disorders.

With this documented knowledge, we will be positioned to design and distribute a set of best clinical practices for SHANK2-related disorders to physicians and genetic counselors for more systematic care of affected individuals. This education can be replicated for training and resources for all physicians, worldwide, and will improve the quality of care that all SHANK2

patients receive. As administration of this standardized care expands globally, the ensuing collective data can be used to educate caregivers in how to best support their loved ones from the point of diagnosis on, while contributing to the body of data needed to advance therapeutics.

Details on how to apply to receive financial support from this grant to visit Dr. Jiang will be sent in the coming weeks.

DATA COLLECTION

Patient Registry: One Year Update

First, a big thank you to all of those who have completed the registration process! The SHANK2 Patient Registry collects invaluable information needed by scientists to better understand SHANK2-related disorders and develop research programs that will eventually lead to treatments and a cure for SHANK2 disorders. Without your input, these researchers would be missing the clinical data they need to move forward.

Here's an overview of the registry and a summary of our findings, to date:

SHANK2 Patient Registry basics:

- Overseen and approved by Pearl Institutional Review Board
- Implemented through Beneufit, Inc.
- Free of charge to patients and their families

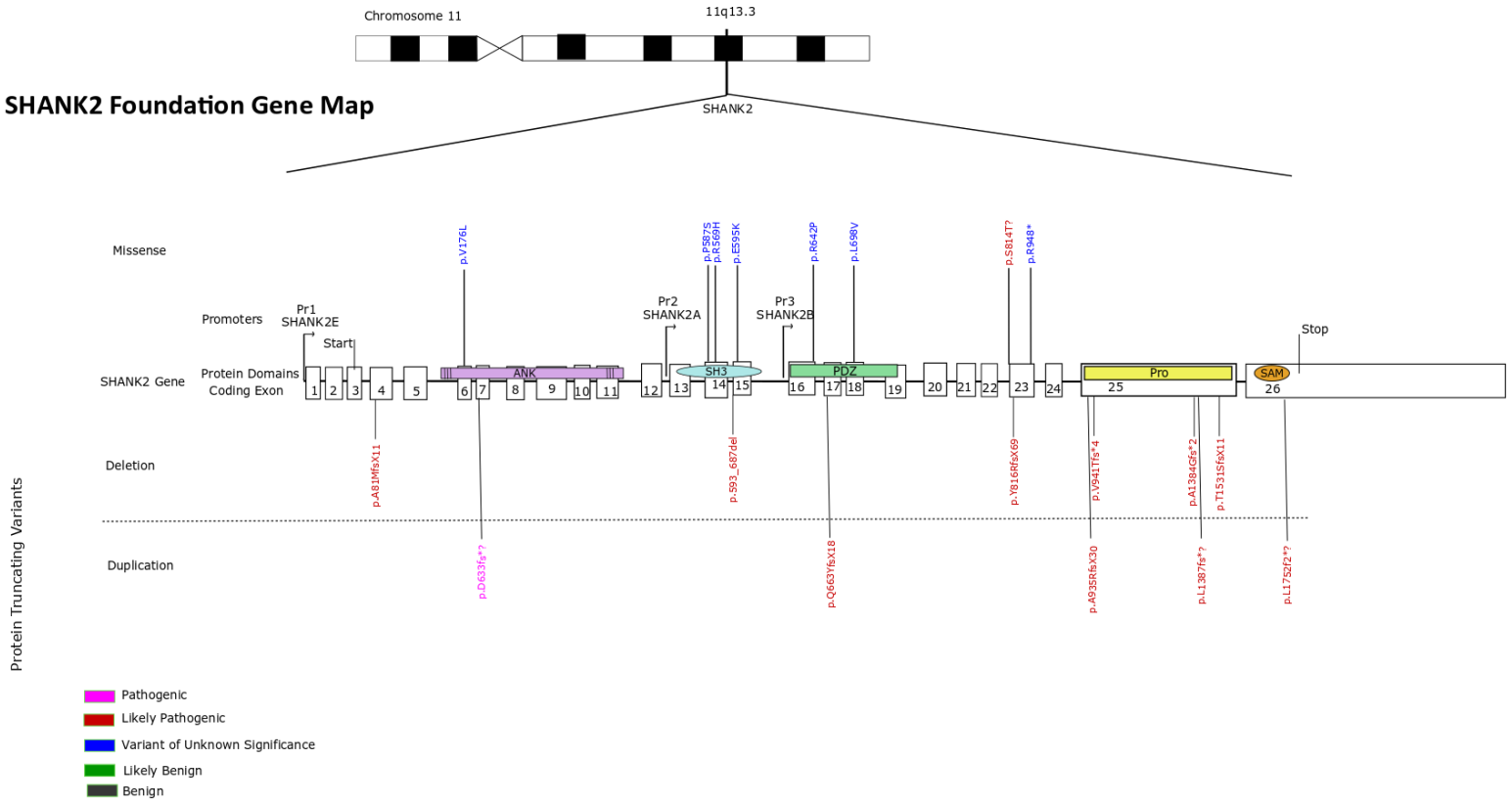
The registry collects:

1. Demographic Information
2. Genetic Information
3. Developmental Information
4. Data from five Validated Surveys

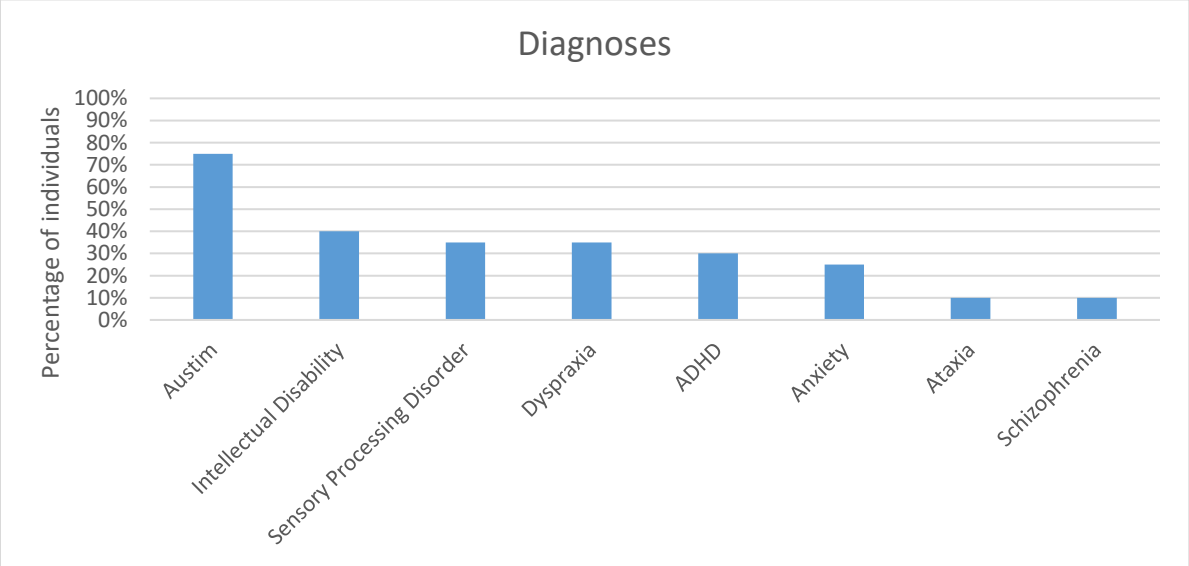
Below is the latest summary from the registry:

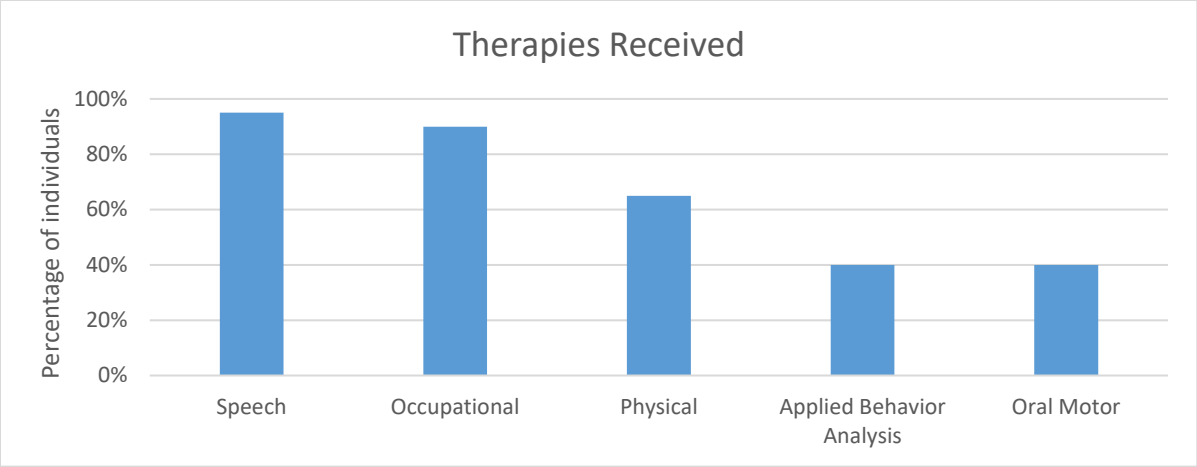
1. **Demographic Information:**
    - 35 individuals from 10 countries
    - Registry information for 13 individuals has been completed
    - Average age of 9 years
    - 55% Female, 45% Male

2. Genetic Information: We've created the SHANK2 Gene Map (below) to visually represent the variants in our community. This tool will help determine how variants in different locations of the gene affect SHANK2 individuals.



3. Developmental Information: The two graphs below summarize developmental characteristics of those registered and the therapies received, respectively:





Common Physical Characteristics

- Hypotonia (66%)
- Long eye lashes (40%)

Areas of Desired Improvement

- Communication was by far the most desired area of improvement.
- Academics, Motor Skills, and Social Skills were all tied for a distant second.

Other Common Characteristics

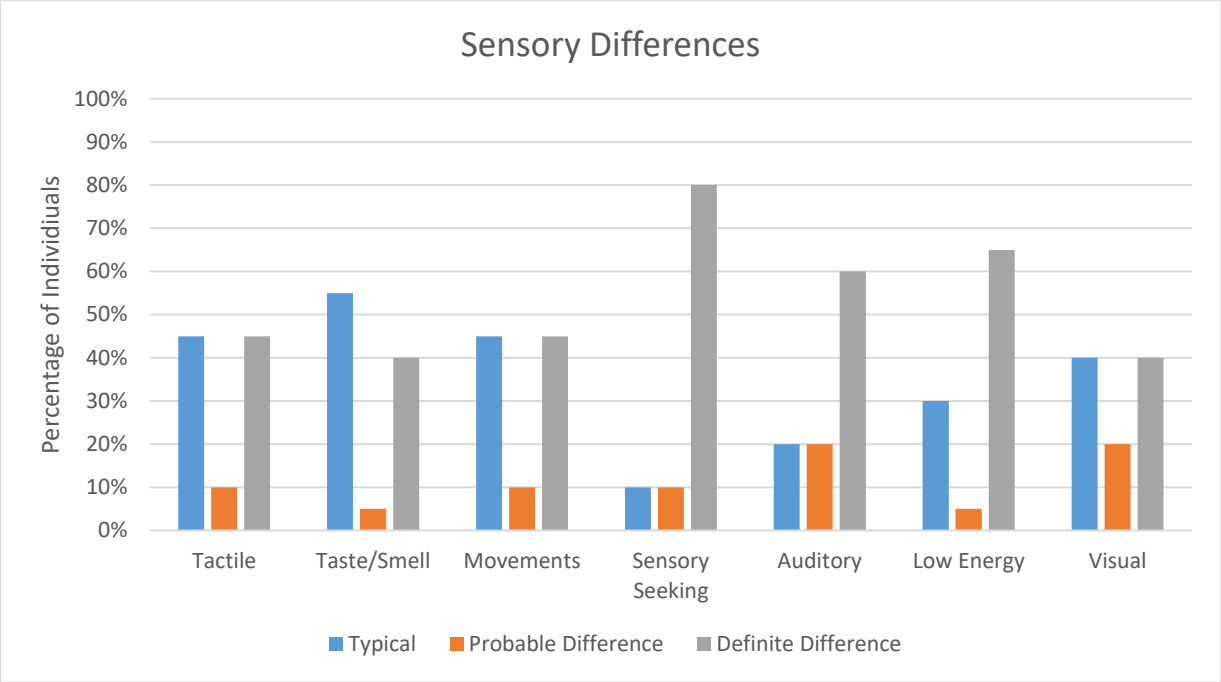
- Gross motor skills, such as sitting up and first steps, are mildly to moderately delayed.
- Play skills, such as parallel play and pretend play, are moderately to severely delayed.
- Language development, such as first spoken word, is moderately to severely delayed.
- Academic skills, such as reading and counting, are moderately to severely delayed.

4. Data from Validated Surveys:

While we do not yet have enough patient survey data to make the subtler connections, there are some trends that are clear even with the small number of patients who have currently completed all the surveys:

Aberrant Behavior Checklist: This survey evaluates behavior characteristics across five domains. Almost all individuals exhibit a high level of "hyperactivity"

Sensory Profile Survey: This survey examines sensory processing over seven different domains (see below). We are starting to see some clear trends in sensory processing difficulties.



Genome Connect Health Survey: This survey asks about general health across all body systems. Aside from neurological issues, a couple of areas that are notable pertain to:

- Eyes and Vision
- Ears and Hearing
- Digestive System

Family Quality of Life Survey: This survey assesses the areas of greatest need in our community in terms of quality of life. Not surprisingly, having a SHANK2 individual in a family has added stress to the majority of families and made social activities more difficult. On the positive side, the majority of parents support each other and work together to help their families.

ORCA: This survey evaluates speech and communication. The majority of our community communicates via spoken language and/or speech devices. The acquisition of language is typically very delayed and the use of the language does not typically adhere to standard norms.

Phenotyping Study

Once completed, the SHANK2 Phenotyping Study, designed by the Seaver Autism Center at Mount Sinai in New York City and funded by the SHANK2 Foundation, will provide researchers with critical information needed to better understand the role pathogenic SHANK2 variants play in human development. Seven members of our community have been deemed eligible for the study, **but we need 3 more patients to begin**. If your child has a de novo SHANK2 variant that is classified as pathogenic or likely pathogenic and English is spoken in your home, please apply today by contacting Tess Levy at tess.levy@mssm.edu.

RESEARCH

SHANK2 Research Summit

We held our first SHANK2 Research Summit on May 15, 2022. Leading SHANK2 researchers from around the world had the opportunity to meet virtually and discuss the latest in their SHANK2 research efforts. **We are so grateful to all of those who participated in this very important meeting!** Talks were given by:

Dr. Eunjoon Kim: Professor and Director of the Center for Synaptic Brain Dysfunctions, Institute for Basic Sciences at KAIST (Korea)

Dr. Thomas Bourgeron: Professor and Head of Human Genetics and Cognitive Functions, Institut Pasteur (France)

Dr. Yong-Hui Jiang: Professor and Chief of Medical Genetics, Yale School of Medicine

Dr. Guoping Feng: Associate Director of the McGovern Institute, MIT

There were also two panel discussions in which all researchers had the opportunity to converse about the current state of SHANK2 research and its future.

Here are some highlights of the day:

Dr. Eunjoon Kim focused his talk on the relationship between NMDA-receptor (NMDAR) functioning and SHANK2. NMDARs are localized at excitatory synapses in the brain and are important for normal brain processes. Dr. Kim and his team observed that during the critical period of synapse development and maturation in SHANK2 knockout mice, an overactive functioning of NMDARs early on reversed and became underactive with time. Decreased NMDAR functioning is linked to repetitive behaviors and social deficits. By limiting NMDAR early in development in SHANK2 knock-out mice, Dr. Kim's team was able to normalize NMDAR functioning later on. They learned, however, that other SHANK2 mutant mice (not knock-outs) exhibited different patterns of change in NMDAR functioning over time, demonstrating different SHANK2 mutations can lead to different types of NMDAR dysfunction and may require different timing and targets of treatment. His team has uncovered and continues to investigate a number of treatments to correct NMDAR levels in mutant mice.

Dr. Thomas Bourgeron and his team strive to identify the underlying genes that cause ASD, understand the mechanisms at play, and establish treatments to address symptoms. He stated that while certain disorders correlate directly with single gene mutations, others, including SHANK2, may result from "multiple hits," a combination of genetic variants that lead to disease. Dr.

Bourgeron and his team spent over a decade building a live mouse tracker, allowing his team to gather in-depth behavioral data around the clock. Dr. Bourgeron's SHANK2 knock-out mice studies have led him to conclude that these mice lack social motivation and are hyperactive. The hyperactivity is not corrected when given Ritalin. On the other hand, in his SHANK3 knock-out mice that received lithium treatment, he and his team observed a reduction in hyperactivity, restored synaptic functioning, and a boost in SHANK3 protein. They are currently conducting a clinical trial with 22 children affected by SHANK3 mutations under the age of eighteen. Specific research studies using lithium in SHANK2 animal models and patients are still needed to determine whether lithium can play a similar role in correcting SHANK2 phenotypes.

Dr. Yong-hui Jiang shared the lessons he has learned in his journey to develop molecular treatments for two diseases he has studied for decades, Angelman Syndrome and Prader-Willi Syndrome. Throughout the process he has come to understand the value and limitations of mice models and realized the tradeoffs between understanding pathophysiology versus focusing on treatment. Dr. Jiang discussed the scientific advances that led to the trial of antisense oligonucleotide (ASO) therapeutics to rescue the phenotype of patients suffering from these diseases. ASOs can be affective in increasing the expression of genes that are not producing the necessary amount of protein for normal functioning, consequently reversing disease symptoms. In 2020, a clinical trial using ASOs that included five patients ranging in age from five to fifteen years old began. Parents have reported significant improvement in their children who are in the trial. Despite setbacks, the trial was expanded in 2022 to include younger children. In the case of a SHANK2 disorder, one copy of the gene is not working properly and the resulting reduction in protein production leads to symptoms. If these trials are successful, ASO treatment may be beneficial for many other developmental disorders including SHANK2.

Dr. Guoping Feng spoke of his work on SHANK3 gene therapy and the various factors that must be considered when developing treatments for neurodevelopmental disorders. For example, although a single gene disruption may lead to autism, many other downstream genes may also be affected which can complicate therapeutic target strategies. One therapeutic strategy is to target the mutated gene itself, as Dr. Feng has done in animal models with a SHANK3 deletion. Here, he highlighted another factor that must be considered. While SHANK3 expression can lead to the rescuing of behavioral phenotypes in young animals, if SHANK3 expression is not restored until adulthood, only some behavioral phenotypes, but not all, are rescued. Therefore, the timing of treatment may be critical when using gene replacement therapy. Treatment dosage is also an important consideration to prevent overexpression of the targeted gene. Dr. Feng also spoke of how researchers are exploring alternative approaches to targeted therapies that aim to treat specific phenotypes. He used the thalamic reticular nucleus (TRN) as an example. The TRN is a group of neurons that filter out stimuli and allow an individual to focus. Many ASD risk genes are highly expressed in the TRN, which possibly explains a number of ASD symptoms, including sleep disruption and ADHD. Dr. Feng and his team have identified a compound that may correct these issues in mice. Finally, he spoke of the non-human primates he and his colleagues have implemented in their research of neurodevelopmental disorders. Given the greater similarity between non-human primates and humans, compared to mice, non-human primate research offers a better understanding of how mutations manifest into behavioral

phenotypes and has more translational relevance for predicting the efficacy of candidate treatments in human testing.

MIT Mouse Model Study Update

Dr. Guoping Feng is a Poitras Professor of Neuroscience and Associate Director of the McGovern Institute for Brain Research at MIT. Using cutting-edge cell-type specific technologies, Dr. Feng and his team are investigating how SHANK2 variants contribute to the behavioral, cognitive, and affect-related features of autism. So far, these studies demonstrate that SHANK2 mutations can lead to long-lasting changes in the structure and function of neural circuits that are implicated in autism. More recently, Dr. Feng's newest team member, Dr. Lace Riggs, garnered research support through the BRAIN Initiative to further investigate the role of SHANK2 in the development of corticothalamic circuits--making it the first SHANK2-related investigation to be funded by the National Institutes of Health. Dr. Feng and his team hope this work will help improve our understanding of SHANK2 variants in both the causes and treatments of autism.

Rarebase/Function Platform Update

We recently received an update on our research collaboration with Rarebase. The SHANK2 Foundation is one of 25 rare disease organizations included in the *Function Platform* created by Rarebase, a public benefit precision medicine company that leverages cutting-edge technology and biology to discover and develop treatments for the millions of people worldwide living with a rare disease.

Rarebase is screening FDA-approved drugs in neuronal cells with the goal of identifying disease modifying therapies for rare neurological diseases. To date, they have identified several promising drug candidates for SHANK2 that require additional evaluation. The next step is to test these compounds in cell models harboring disease-causing SHANK2 gene variants.

We will continue to provide updates as the Rarebase research project progresses. Learn more about Rarebase at rarebase.org.

FAMILY SUPPORT

Facebook Group

The SHANK2 Foundation private Facebook Group has grown to include 53 members from 11 countries! Over the course of the year, we have shared stories about our kids up and downs, tried therapies and supplements suggested by other community members, and welcomed those who had never before connected with another SHANK2 family.

We are so grateful to Sarah Schmidt, a parent in our community, who regularly creates the fantastic posts that make all of this happen.

Zoom Meet-ups

We held two family "meet-ups" in 2022, hoping to further develop relationships among families in the SHANK2 community. Although only a small number of families attended, the conversations were interesting and enlightening. If you would like to participate in future family "meet-ups," please email us at contact@shank2.org, and keep an eye out for polls posted on Facebook about potential dates and times for these meet-ups.

SHANK2 DAY 2022

Get ready for the second annual SHANK2 Day conference! Although we intend to hold SHANK2 Day on November 13th ever year (as a nod to the location of the SHANK2 gene at 11q13), this year the event will be on December 4th, due to a conflict with other industry meetings. Please join us for presentations by international SHANK2 experts and community members, brainstorming sessions and so much more. More information will be sent in the coming weeks.