Dear members of the SHANK2 community,

Two years ago today we launched the SHANK2 Foundation. At the time, with few exceptions aside from our own kids, the only other cases of SHANK2 we knew of were cited in literature. When our children were diagnosed years before, we only had our doctors and scant research articles to provide us with information. But our doctors were unfamiliar with SHANK2-related disorders and had little to offer us in terms of prognosis or advice. There was no website we could access for general information on SHANK2, and no one to turn to for guidance and support. We were essentially on our own to navigate the unknown.

Simultaneously, scientists were primarily conducting animal model research to better understand SHANK2 and its role in disease. There was no database of clinical information on the unique characteristics, behaviors and learning patterns of individuals affected by SHANK2-related disorders that could inform their studies. And they lacked a venue where they could share their research and brainstorm with other SHANK2 specialists.

Today, a family who learns that their child has a SHANK2-related disorder can do a quick search on the internet and find the SHANK2 Foundation website. There, they can get a basic genetics lesson and understand the role that SHANK2 plays in human functioning. They can join the foundation's private Facebook group and meet so many families from around the globe who have children affected by SHANK2-related disorders, and maybe even connect with people in their region. And while they may learn about the challenges of rearing a child with SHANK2, they may also see that their child could some day place in a Special Olympics ski competition, participate in a triathlon or enter a cycling race. And they can read about the progress that is being made in SHANK2 research. Most important, they can understand that they are not alone and that there is hope.

And scientists studying SHANK2 are no longer siloed and without access to clinical data. With the help of the SHANK2 Foundation, they are learning from each other, brainstorming about the future and accessing the data essential to move forward and help us achieve our mission to improve the quality of life for individuals affected by SHANK2-related disorders.

WE FORGED 2 NEW PARTNERSHIPS THIS YEAR!

BlinkLab Partnership

The SHANK2 Foundation is partnering with BlinkLab to study brain function in SHANK2 patients. BlinkLab is a collaboration between Princeton University and Erasmus Medical Center in the Netherlands striving to make neurobehavioral testing easily accessible to researchers and families. Their mobile app allows researchers to quickly and easily set-up a variety of

neurobehavioral tests such as prepulse inhibition, eyeblink conditioning, and startle habituation. Each of these tests tells the researcher something about how the brain is functioning. While these types of tests have a long history of use in the lab, being able to do them remotely, in a home setting, is a great step forward.

BlinkLab has begun running tests and will then analyze data on approximately ten enrolled individuals from the SHANK2 community. Upon completion, we hope that this data set will not only give us insight into the brain function of SHANK2 individuals and potentially identify biomarkers for SHANK2 individuals, but also serve as a foundation for many future research projects on SHANK2.

Probably Genetic Partnership

Given how rare SHANK2-related disorders are, it is imperative that we maximize our reach to find as many affected individuals as possible. This will not only allow us to support them and their families, but it will also help us gather more data needed to advance research. We are therefore collaborating with Probably Genetic in an effort to expand the SHANK2 Foundation community base. Probably Genetic is a company dedicated to helping undiagnosed rare disease patients get diagnosed. Using social media and their broad network of rare disease organizations, Probably Genetic uses a "symptom checker" to identify individuals eligible for no-cost, at-home genetic testing and free follow-up genetic counseling. The short web-based questionnaire is available through the foundation's website.

DATA COLLECTION

Patient Registry: Two Year Update

Thank you to everyone who has completed the registration process! SHANK2 families who fully register their children provide invaluable information needed by scientists to better understand SHANK2-related disorders. This clinical data allows scientists to develop research programs necessary to advance treatments and ultimately find a cure for those living with SHANK2-related disorders.

The following is an overview of the registry and a summary of our current findings.

SHANK2 Patient Registry basics:

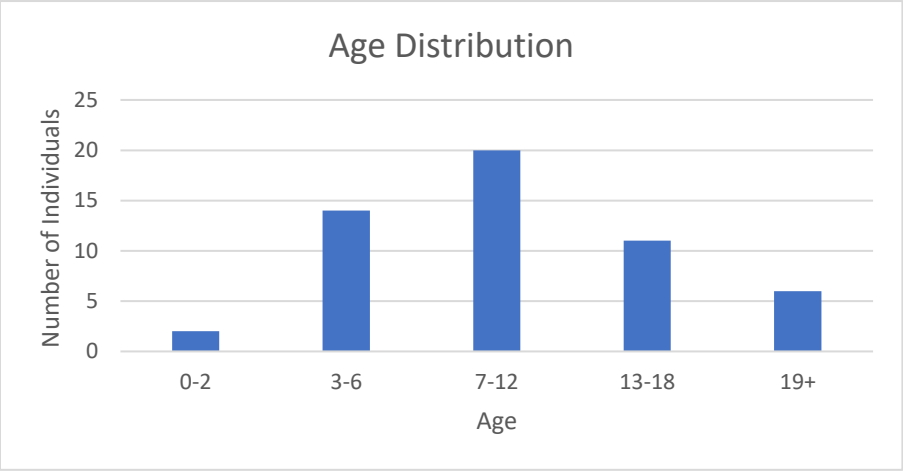
- Overseen and approved by Pearl Institutional Review Board
- Implemented through Beneufit, Inc.
- Free of charge to patients and their families

The registry collects:

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

Demographic Information:

The number of SHANK2 individuals registered continues to grow. Twenty-six new families created accounts over the past year, bringing the number of accounts in our registry to 73. Please note that creating an account is only the first step in contributing to the Patient Registry. It is imperative that you complete all survey questions and submit your child's genetic report. Fifty-three families from 14 countries have registered their children, an increase of 16 registrants from last year. Registrants are fairly evenly split between female and male. Their age distribution is as follows:

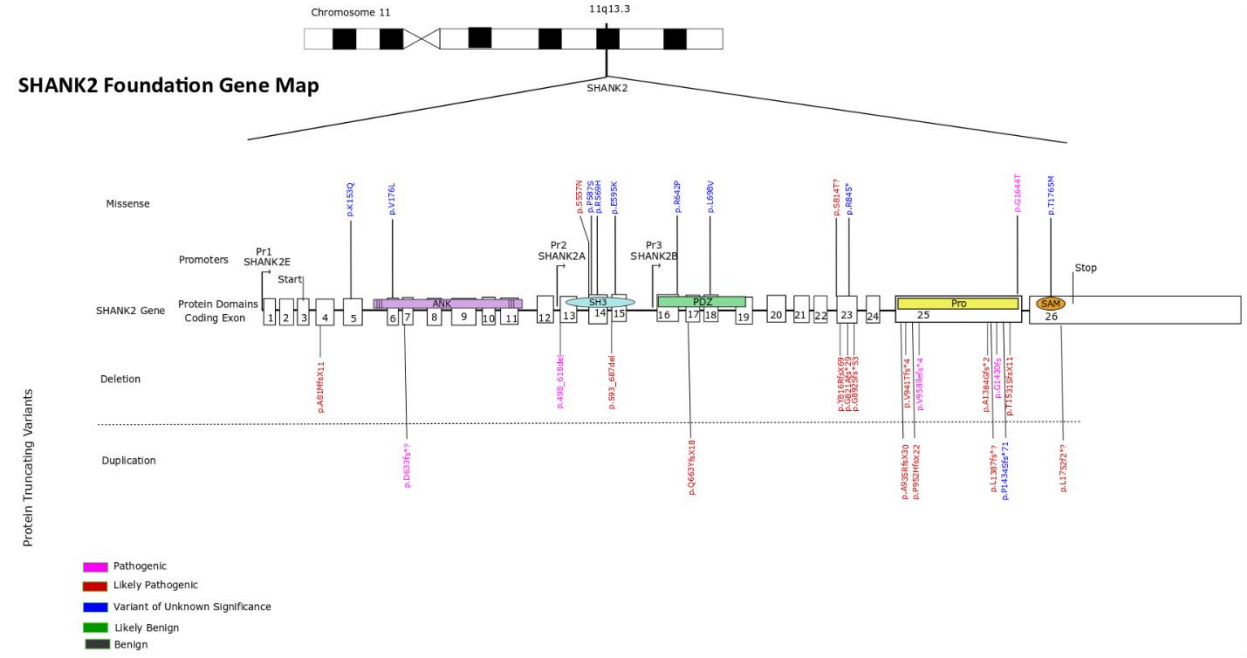


Genetic Information:

We continue to update the SHANK2 Gene Map (below) based on the genetic reports submitted to provide a visual representation of the variants in our community. This tool helps determine how variants in different locations of the gene affect SHANK2 individuals. The genetic report is often the first piece of data that is examined for clinical trials. If you are having trouble getting your genetic report uploaded to the registry, do not hesitate to reach out to us for help (mailto:registry@shank2.org).

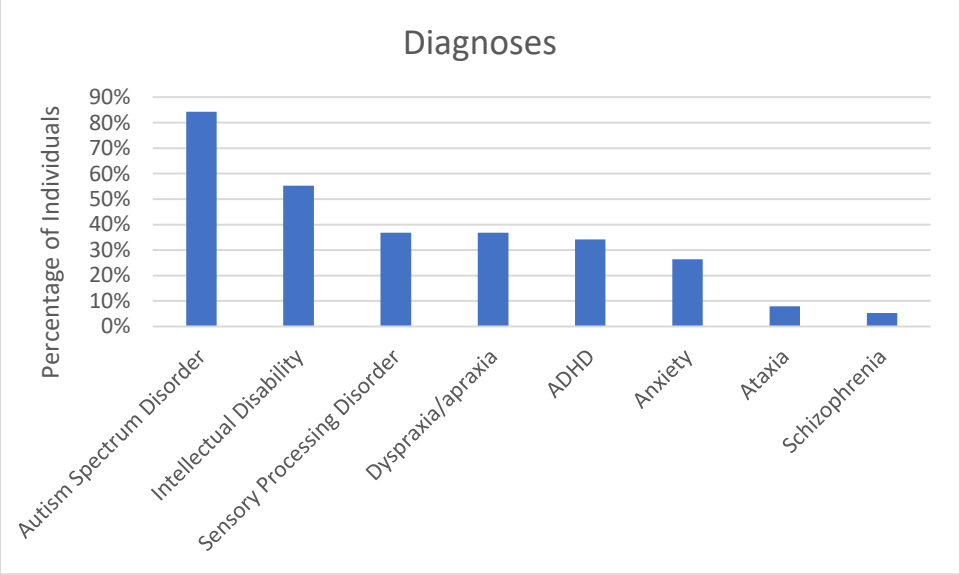
We currently have 30 individuals with genetic reports in the following categories:

	Pathogenic or Likely Pathogenic	Variant of Unknown Significance (VUS)
Missense	3	9
Deletion	11	0
Duplication	6	1
Totals	**20**	**10**



Developmental Information:

The most common diagnosis is autism followed by intellectual disability. Sensory processing disorder, apraxia, ADHD, and anxiety all show a high prevalence as well.



The most common physical characteristics are hypotonia and long eye lashes with 62% and 44% reported, respectively.

Most caretakers listed communication as the most desired area of improvement for their SHANK2-affected loved one. The other areas of academics, motor skills, and social skills were all tied for a distant second.

Some common developmental delays are the following:

- Gross motor skills, such as sitting up and walking, 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.

While the exact percentages have slightly shifted from last year, this data is becoming stable and these results are very similar to what was reported in last year's newsletter.

Data from Validated Surveys:

While we have enough registrants to begin seeing overall patterns in diagnoses and development, **we do not yet have enough patient survey data to make the subtler connections**. Of the 53 individuals in the registry, we have fully completed survey information from only 15. That is a 28% completion rate. We would like to make a concerted effort as a community to improve this over the next year. With 73 potential individuals, we could do amazing in-depth analyses of SHANK2-related disorders, if we had this completed data. We could do things ranging from:

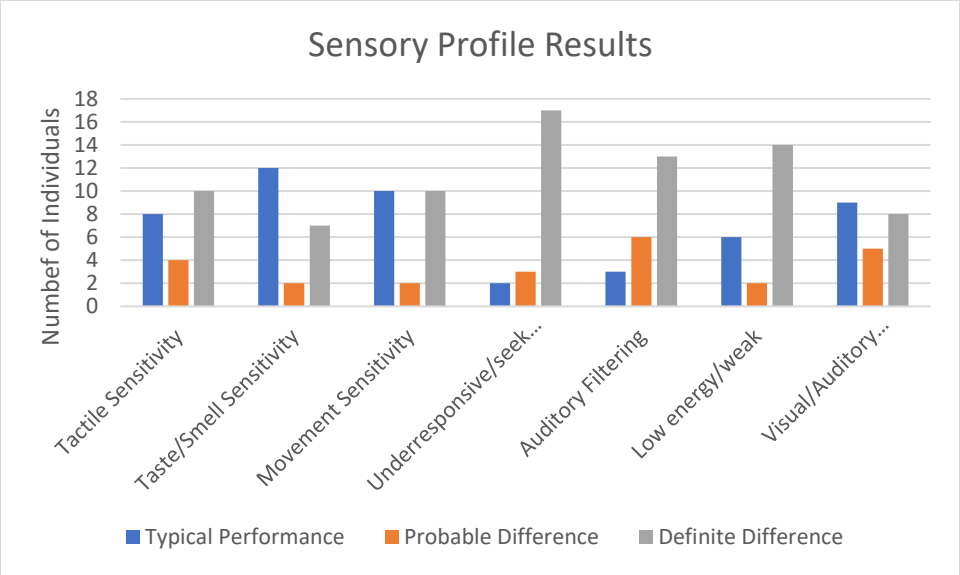
- Pulling out the key characteristics of SHANK2 individuals that could be used for clinical trials
- Identifying the main characteristics of SHANK2 individuals that could be distributed to schools and clinicians who are working with them
- Determining if and how the location of the genetic variant has a role in the individual's characteristics

However, without a more complete set of data, this cannot happen.

Even with the limited data, there are a number of clear trends we can already pull from the surveys.

Aberrant Behavior Checklist: This survey evaluates behavior characteristics across five domains. Almost all individuals exhibit a high level of "hyperactivity". It is fairly common for researchers to talk about the hyperactivity seen in SHANK2 mouse models, but what is seen in mice does not always correspond to the actual patient characteristics. This survey data demonstrates that SHANK2 humans do typically exhibit a high level of hyperactivity. This hyperactivity can have a profound effect on their ability to function well in school or to work in a job.

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. For example, the majority of individuals exhibit significant sensory seeking behaviors. Understanding the sensory profile of individuals can help clinicians, therapists, and teachers design programs to best help the SHANK2 individual.



Genome Connect Health Survey: This survey asks about general health across all body systems. While brain function and psychiatric issues are very common, it is also common for issues to occur in

- Eyes and Vision
- Digestive System

By identifying these common co-morbidities, caregivers of SHANK2 individuals and treating clinicians have an indication of what issues they should be watching out for.

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 SHANK2 individuals are happy, and the overall family quality of life has remained stable over time.

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

We are excited to announce that we have launched our phenotyping study! It took two years for our partners at The Seaver Center for Autism at Mount Sinai in New York City to find ten eligible participants needed to launch the phenotyping study, but they have finally begun! Some of the participants are completing their evaluations, and some are in the scheduling process. The researchers are aiming to assess two participants per month. If your child has been asked to participate and you have not yet responded to scheduling requests, please do so immediately. Upon completion of the study, researchers will have a list of common characteristics seen with SHANK2-related disorders and a more concise and in-depth understanding of the role that SHANK2 plays in brain function and human development. This will guide researchers and

biotech companies in their quest to develop treatments and ultimately a cure for individuals affected by SHANK2-related disorders.

If your child was not chosen to participate in the study, please note that the study findings will ultimately help all SHANK2 individuals.

#RAREis Global Advocacy Grant

We have allocated the funding received by the #RAREis Global Advocacy Grant to six families to cover their cost of travel to see Dr. Yong-hui Jiang, the Chief of Medical Genetics at the Yale School of Medicine. Dr. Jiang is the only practicing clinician in the United States with an extensive SHANK2 research background, and a staunch supporter of the SHANK2 Foundation. By conducting standardized evaluations on the grant recipients, he will bolster the understanding of the clinical presentation of those with SHANK2-related disorders and contribute to the comprehension of the SHANK2 phenotype.

As with the phenotyping study, if your child was not chosen to participate in the study, please note that the study findings will ultimately help all SHANK2 individuals.

If you are interested in participating in future research and clinical studies, the most important step is to complete all registry information. The genetic report is often the first piece of data that is examined for eligibility. If you are having trouble with the registration process or getting your genetic report uploaded to the registry, do not hesitate to reach out to us for help (mailto:registry@shank2.org).

RESEARCH

Second Annual SHANK2 Research Summit

This past May, we held our **Second Annual SHANK2 Research Summit**. SHANK2 researchers from all over the world attended. We shared foundation updates and listened to two cutting edge research talks:

Dr. Aleksanda Badura, Associate Professor at Eramus MC, shared her work on developing a standardized battery of behavioral tests for deep phenotyping to evaluate differences in mouse models of SHANK2, with the goal of finding drug targets that ameliorate deficits. We are excited to see results of different drug candidates.

Dr. Hans Kreienkamp, Professor at University Medical Center Hamburg-Eppendorf, spoke about his work in characterizing the functional readout of different SHANK2 missense variants to better understand the resulting clinical phenotypes. As noted earlier, missense variants are the most prevalent variants cited in our patient registry. We informed Dr. Kreienkamp that we would welcome a collaboration with him to further analyze the role that SHANK2 missense variants play in disease.

We ended the summit with a brainstorming session. We are excited to make it easier for SHANK2 researchers to learn about and contact each other through a voluntary list that is being formulated. This will include a brief biography and SHANK2-related research efforts, as well as contact information. We are also creating a working list of all the SHANK2 cell line repositories that can be used for future research studies. **Thank you to all of the wonderful researchers who continue to be actively engaged in our foundation's efforts. Your ongoing commitment and expanding research efforts are a great source of hope for the future of SHANK2-affected individuals.**

Rarebase/Function Platform Update

Phase I of the Rarebase/Function project has been completed. Using their cutting-edge technology to screen the effects of applying FDA-approved drugs to neuronal cells, Rarebase identified several promising drug candidates for SHANK2 treatment. The SHANK2 Foundation cannot share the specific preliminary results, but we are evaluating the appropriate next steps for the foundation to take in relation to drug discovery efforts.

Patient Derived Mouse Model at MIT

Dr. Guoping Feng's team at the McGovern Institute of Brain Research at MIT continues their work with a patient-derived SHANK2 mouse model. They are investigating how patient-derived SHANK2 variants contribute to circuit dysfunction in autism. Their studies reveal that some single nucleotide polymorphisms in SHANK2 lead to long-lasting changes in the function of neural circuits underlying cognition. These effects are similar to a complete loss of SHANK2, supporting the idea that certain missense mutations can render the entire SHANK2 protein nonfunctional, impacting both behavior and the efficacy of synaptic transmission. Feng and his team hope this work will improve the understanding of SHANK2 variants in the etiology and treatment of autism.

COMMUNITY

Second Annual SHANK2 Day Conference

We held our **Second Annual SHANK2 Day Conference** in December of 2022. Researchers and family members joined together to connect and engage with the foundation. We heard talks from four researchers, briefly described below:

Dr. Thomas Bourgeron, Professor at Institut Pasteur in Paris, gave a compelling talk about the use of aggregate genomic data to better understand risk and resilience in developmental diversity and mental health outcomes. With more risk and resilience factors better characterized, we can begin to think about how to drive development in favor of resilience. The SHANK2 Foundation

strives to have more complete genomic data of SHANK2-affected individuals for these purposes, as well.

Fraser McCready, a PhD Candidate in Dr. James Ellis's lab at University of Toronto/Hospital for Sick Children in Ontario, spoke about his work using a cell culture model, in which cells from SHANK2-affected individuals are reprogrammed into neurons and then characterized for cellular phenotypes. He has found that SHANK2-affected neurons displayed increased dendritic length and an increased number of synapses compared to control neurons, demonstrating overconnected circuitry, which can be rescued in culture with a glutamate receptor agonist. For larger scale drug compound screenings, multielectrode arrays are being used in the lab that give results on network activity differences and compounds that can rescue these deficits.

Dr. Lace Riggs, a Postdoctoral Associate in Dr. Guoping Feng's lab at Massachusetts Institute of Technology, gave a talk about her work, demonstrating that there is behavioral hyperactivity, repetitive behaviors, and anxiety in mice with a *Shank2* deletion. Correlated with these behavioral differences, there is hyperexcitability in the dorsal anterior cingulate cortex, a brain region involved in these behaviors.

Paola Negrón-Moreno, a Graduate Student in Dr. Yong-Hui Jiang's lab at Yale School of Medicine, told us about her experiments in demonstrating hyperactive locomotor activity in *Shank2* mutant mice, as well as an increase in exploratory behavior. She also collected and analyzed survey data in partnership with The SHANK2 Foundation that correlated well with her mice studies, in which SHANK2-affected individuals are reported to have prolonged interests in both novel and familiar objects.

It was therefore a common theme throughout the research talks, consistent with registry data, that there is a hyperactivity phenotype evident when SHANK2 function is disrupted. This is true from both a behavioral standpoint and from a brain communication standpoint. With this knowledge, more drug compounds can be screened to determine if these symptoms can be targeted and ameliorated.

Aside from the wonderful research talks, we heard foundation updates and a personal diagnostic odyssey from Polly for her son, Jarret. Genetics are complicated, and there is always the possibility that a combination of genes play a role in an individual's phenotype, which leads to the clinical heterogeneity seen in autism. However, the more we know and can document, the more hope there is for effective treatments in the future.

Geraldine Bliss, the President and Co-Founder of CureSHANK, shared the journey and evolution of CureSHANK, a nonprofit foundation whose mission is to accelerate the development of treatments for SHANK-associated disorders. The SHANK2 Foundation continues to appreciate the guidance and insights from CureSHANK.

We ended with a brainstorming session, in which researchers and family members shared ideas and goals for the future of The SHANK2 Foundation with us. Recordings are available to the SHANK2 community by request through our website. **We thank everyone who attended and participated. As we prepare for our Third Annual SHANK2 Day Conference this coming**

fall, feel free to reach out with any suggestions or recommendations. We hope to see you all there!

Facebook

We are so pleased with the success of The SHANK2 Foundation's private Facebook group! Since last year, membership has increased by 64% and the number of countries represented has grown by 73%, with 87 members from 19 countries. Just this morning we welcomed our newest member from Papua New Guinea. The Facebook group is a safe venue where families can share their triumphs, concerns and questions.

One-on-one Meetings

Since the inception of the foundation, we have met privately with numerous families in virtual meetings. We are available to meet with you if you would like to learn more about the foundation, share your stories or ask us any questions. Please reach out to us (mailto:contact@shank2.org) if you would like to arrange a meeting.

Thank you to all the families, researchers and clinicians for your continued support and involvement!

Warmly,

Polly, Ben, and Alex
Board of Directors of the SHANK2 Foundation
http://shank2.org