How to SHINE

A GUIDE TO NAVIGATING LIFE WITH SHINE SYNDROME/DLG4 SYNAPTOPATHY

Love Fearlessly! Shine Fearlessly!

SHINE Syndrome Foundation | Established 2021

How to SHINE

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All underlined words in this guide are clickable and linked to corresponding content for your convenience.

Welcome, we are here for you.

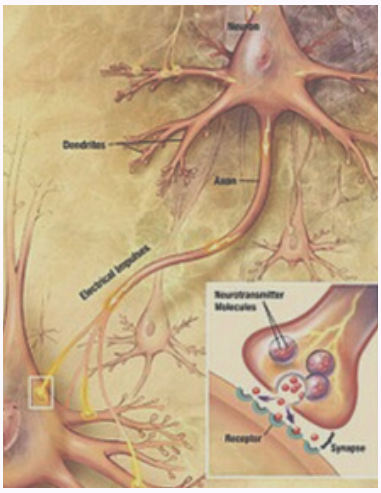
We would like to extend you a warm welcome to the SHINE Syndrome/DLG4 Synaptopathy community. Getting a diagnosis can be an overwhelming experience. You may feel a whole range of emotions, from confusion to grief or even a sense of relief. Wherever you are on your journey, please know that we are here for you.

important tip

Please feel free to share this guide with health practitioners, teachers, family and friends so that they can learn more about SHINE Syndrome and how to best support you, your child and the SHINE community.

This guide includes information to help you learn more about SHINE Syndrome, otherwise known as DLG4-related Synaptopathy, and to connect you with our community. We hope that you use it as a resource that you can refer back to as needed. Please take your time reading and feel free to skip around as you see fit. Given that SHINE is a rare neurological condition, there is a great probability that your support team has little or no knowledge about SHINE. Please share this guide with them. We are here to give you the support, information, and resources you need to be a more confident advocate for you and your SHINE loved one.

What is SHINE Syndrome?



SHINE Syndrome, also known as DLG4 Synaptopathy, is an ultra rare neurodevelopmental disorder. SHINE is an acronym for its most common symptoms.

Sleep Disturbances

Hypotonia

Intellectual Disabilities

Neurological Disorders

Epilepsy

SHINE Symptoms

SHINE Syndrome is characterized predominantly by global developmental delay, intellectual disability, autism spectrum disorder, attention deficit hyperactivity disorder, hypotonia and epilepsy. Many individuals with SHINE Syndrome also present with sleep disturbances, skeletal abnormalities, and/or structural brain abnormalities (seen on an MRI). Families and patients also report symptoms such as: Sensory Processing Disorder, Dyspraxia, Apraxia and Speech Disorders. *SHINE patients do not always have all these symptoms. Symptoms can be experienced as mild to severe.*

Over 50% of people affected by SHINE develop epilepsy. Of those diagnosed with epilepsy, many families have reported that their loved one has been diagnosed with ESES (or CSWS) which is a rare and severe form of epilepsy that stands for Electrical Status Epilepticus of Sleep. For more information about ESES, click ***here***.

Epilepsy can be challenging to detect and diagnose especially when they are brief, non-convulsive or atypical, or generally happen during sleep (like ESES). *If epilepsy or seizures are suspected, please ask for a referral to a neurologist (or epileptologist).* An EEG combined with clinical evaluation is generally needed for a diagnosis. An EEG that captures sleep is recommended.

Please work closely with your medical team for personalized testing and treatment for all neurological symptoms.

The Rarity of SHINE Syndrome

We currently are aware of just over 100 patients in the world, but we know there are more undiagnosed patients out there. People are yet to be diagnosed for a few reasons:

- Families receive a diagnosis like autism, intellectual disability, or epilepsy and discontinue their research or are not offered genetic testing by their medical team
- Cost and access to genetic testing can be a barrier to getting a genetic cause for the patient's symptoms
- Prior to 2019, DLG4 variants were considered VUS (variants of unknown significance). This changed in 2019 to confirm that DLG4 variants may be pathogenic (disease causing). This means that those tested prior to 2019 may not have had tests that include DLG4 or they may not know that their variant changed from VUS to pathogenic.

SHINE Genetics

The human body is made of trillions of cells. Each cell contains 23 pairs of chromosomes (46 total). Each chromosome contains thousands of genes. Most genes also come in pairs and we get one copy from each parent. The role of genes is to produce proteins. Proteins are used to regulate the body's tissues and organs. A gene can stop working or no longer work properly when a variant/mutation occurs. A variant is a mistake that happens, similar to a typo, when the DNA is copied from cell to cell or due to environmental factors.

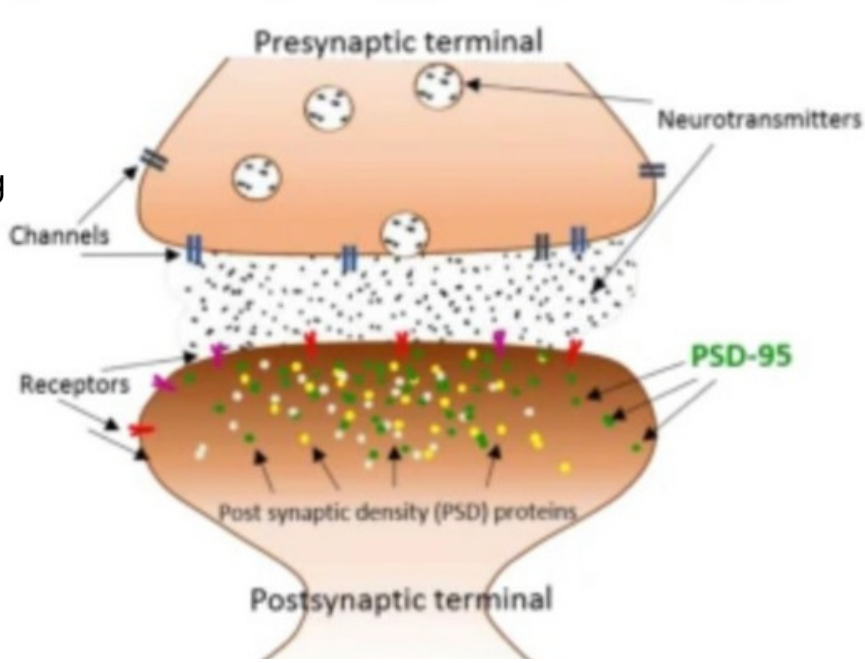
SHINE Syndrome is inherited in an autosomal dominant fashion. This means that only a single copy of the disease-associated mutation is enough to cause the disease. Most individuals with SHINE syndrome are found to have de novo (new) variants in DLG4, meaning the variant occurs for the first time in them and is not inherited from a parent. There are families, however, where there has been sibling reoccurrence of SHINE syndrome. This is hypothesized to be due to a phenomenon known as mosaicism (the variant is present in small amount of the parent's cells, but all of the child's cells).

To learn more about this please visit our informational series on YouTube hosted by one of our medical advisors, Alexandre White-Brown.

SHINE and PSD-95

SHINE Syndrome is caused by variants/mutations in the DLG4 gene. The DLG4 gene is located on the 17th chromosome and is an important gene that encodes the protein PSD-95 (Postsynaptic Density Protein 95). *PSD-95 plays a major role in brain development and function through its implications in synaptic strength and plasticity.*

These mechanisms, along with PSD-95's role in organizing and interacting with other proteins, represent a gene with many capabilities of which, when altered, can induce susceptibility to SHINE Syndrome.



To learn more about this please visit our informational series on YouTube hosted by one of our medical advisors, Alexandre White-Brown.

We are grateful to one of SHINE's medical advisors, Dr. Zeynep Tümer, who created this informative piece for the SHINE community.

VARIANTS IN DLG4 and THEIR PREDICTED EFFECTS ON PSD-95

Prepared by Professor Zeynep Tümer, MD, PhD, DMSc

Department of Clinical Genetics, Copenhagen University Hospital - Rigshospitalet, Denmark

A METAPHORIC EXPLANATION OF DIFFERENT DLG4 VARIANTS (SEE FIGURE 1)

A stretch of three nucleotides (combinations of A, C, G, or T) code for a specific amino acid, and these three nucleotides are called codons. Proteins are composed of amino acid chains. Some codons are called STOP codons, and these signal that the protein chain should stop.

In the next illustration we made a sentence (protein) composed of words (codons) with three letters (nucleotides). The start of the protein is shown with THE and the stop codon with END.

Apart from the normal sequence, we illustrate three common types of variants (mutations) detected in DLG4.

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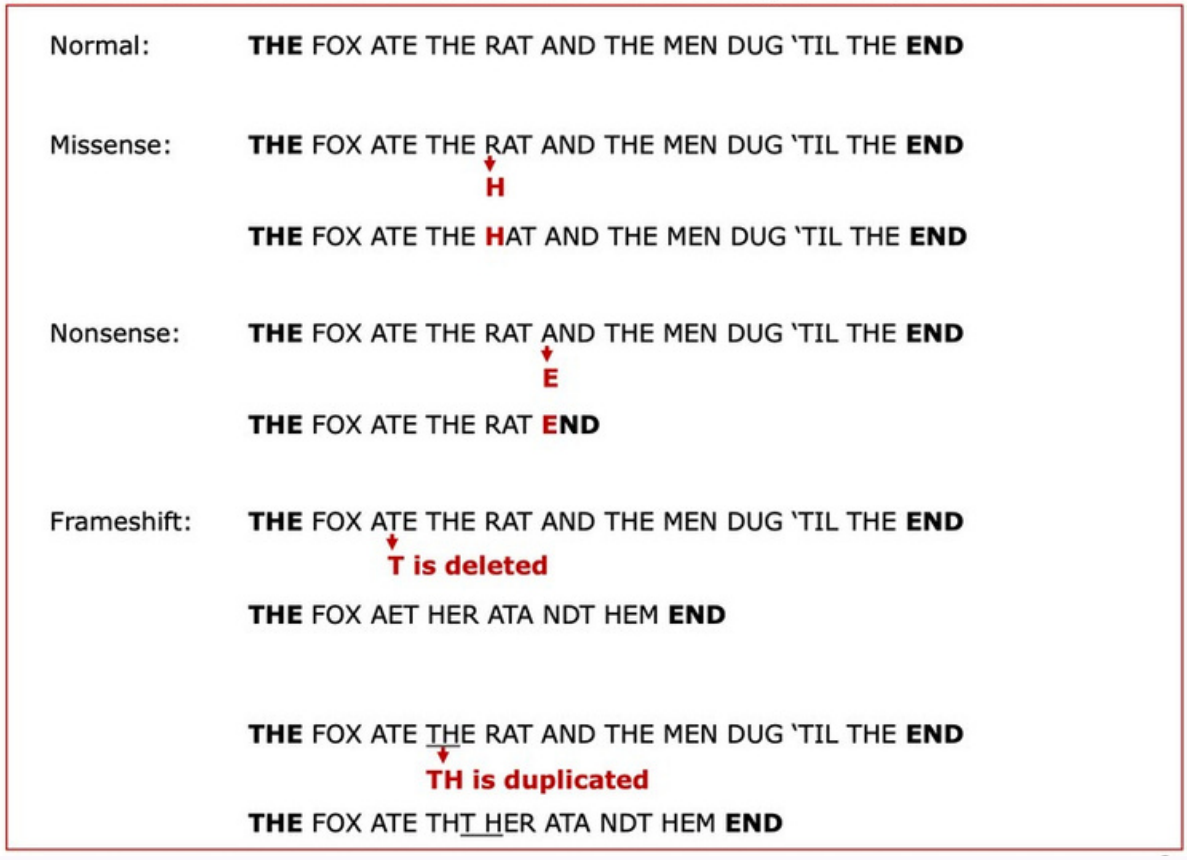
Missense variants: One nucleotide (letter) changes, and this produces a change in one amino acid (word). The results of missense variants are variable. They can be pathogenic or normal, depending on how they change the protein (meaning of the sentence).

Nonsense variants: One nucleotide (letter) changes, and this produces a stop codon (END), and as a result the amino acid chain (sentence) stops earlier.

Frameshift variants: One (or more) nucleotides (letters) are added or removed, and this produces a shift in codon composition (letters form different words). This normally produces a stop codon (END) after a few codons (the sentence stops after a few words).

FIGURE 1 - Explanation of Variants Using Letters, Words, Sentences



Sentences created by Amanda Levy

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DIFFERENT DLG4 VARIANTS AND THEIR PREDICTED EFFECT ON THE PROTEIN

According to their predicted effect on PSD-95, we can divide the disease-causing variants in DLG4 into two groups:

A. Protein truncating variants: Frameshift and nonsense variants (see figure 2)

These variants are predicted to result in two possibilities.
Possibility 1: The protein is not expressed/produced at all due to a mechanism called nonsense mediated decay. This results in the loss-of-function of the protein. This is the most common situation. The normal gene-copy produces a normal protein, but it is not enough for the normal function of the cell.
Possibility 2: If the variant escapes nonsense mediated decay it may create a truncated (shorter) protein which may have a gain-of-function or dominant-negative effect.

B. Missense variants (see figure 3)

These variants change a single amino acid and they do not truncate the protein. There are exceptions: e.g. if a missense variant is very near the end or start of an exon, it can change RNA splicing and can act like a protein truncating variant. The effect of these variants are not yet known, but they are generally loss-of-function variants. They may though also result in gain-of-function.

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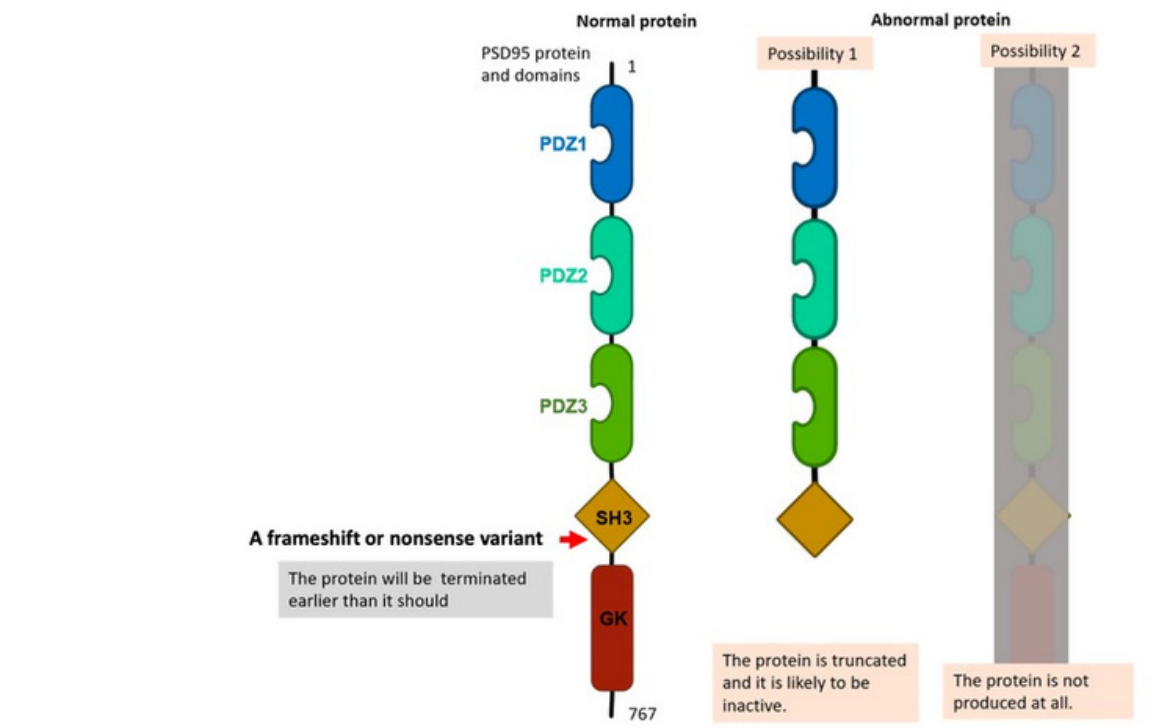
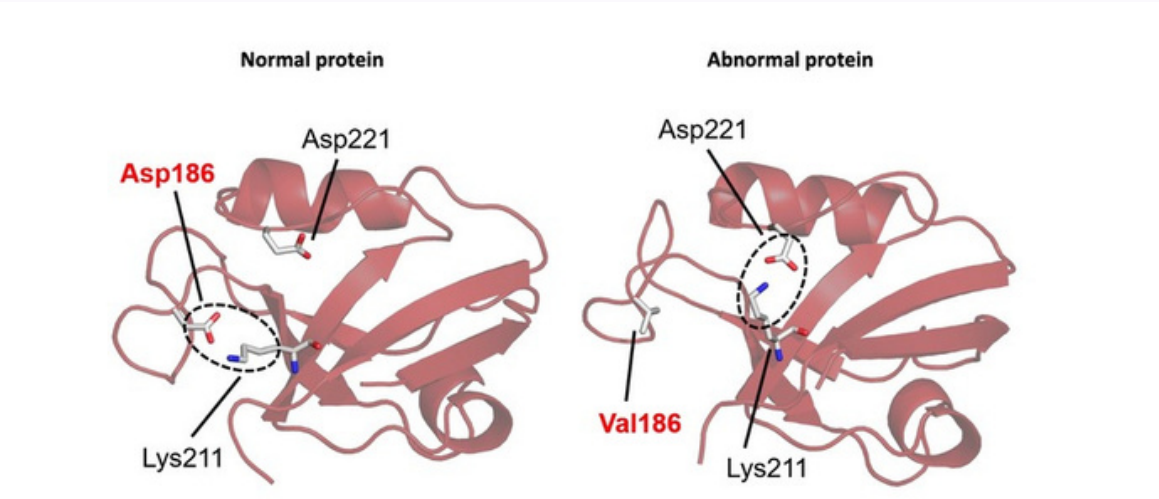
Figure 2 - Protein Truncating Variant



PSD-95 protein has some functional domains: PDZ1, PDZ2, PDZ3, SH3, and GK.
See, Rodriguez-Palmero *et* al. (2021) or Levy *et* al. (2022) for more details. *Figure adapted from Levy et al. (2022*

Figure 3 - Missense Variant (Example p.Asp186Val in the PDZ2 domain



This is a simulation of the part of the normal PSD-95 protein (on the left) and the abnormal protein with the p.Asp186Val variant (on the right). This is a change of the amino acid asparagine (Asp) to valine (Val). Due to the mutation, Asp182 which is near Lys211 in the normal protein is now away from it. At the same time Lys211 comes near to Asp221. We do not know how this change in the 3D positioning of the protein will affect its function yet, and it should be taken with caution as it is only an in silico protein modelling study. *Figure adapted from Rodriguez-Palmero et al. (2021).*

SHINE Syndrome Foundation

Our foundation is founded and run entirely by parents of children living with SHINE Syndrome. Our board members are listed ***here***. We would like to thank all the other individuals that have helped us get where we are today!

Timeline

In just a few short years, our organization has come a very long way. Explore our timeline to see what we've done recently to expand awareness and support for SHINE Syndrome.

PRE-2019 VUS

RESEARCH HAS NOT YET IDENTIFIED THE EFFECTS OF VARIANTS WITHING THE GENE. DLG4 VARIANTS CLASSIFIED AS VUS OR VARIANCE OF UNKNOWN SIGNIFICANCE

2019 PATHOGENIC STATUS

VARIANTS IN DLG4 WERE CONFIRMED TO BE DISEASE CAUSING OR PATHOGENIC

2019 PARENTS UNITE

PATIENTS INFORMED OF THE PATHOGENIC STATUS OF THEIR VARIANTS. PARENTS FORMED CONNECTIONS AND A FACEBOOK GROUP. WITHIN A YEAR, THE COMMUNITY GREW TO MORE THAN 15 FAMILIES.

2021 DISEASE NAMED

WITH THIS ***PUBLICATION***, DLG4 SYNAPTOPATHY WAS NAMED. SOON AFTER, A FEW INVESTED PARENTS OF SHINE PATIENTS CREATED THE NAME SHINE SYNDROME FOR THE COMMON CHARACTERISTICS OF THE DISEASE.

2021 FOUNDATION FORMED

SHINE SYNDROME FOUNDATION WAS OFFICIALLY FORMED IN DECEMBER 2021 BY A DEDICATED GROUP OF PARENTS OF SHINE PATIENTS

SHINE Research and Awareness

The SHINE Syndrome Foundation has been extremely fortunate to gain the support of a dedicated group of researchers and clinicians around the world. Several of those individuals have also agreed to participate on our Medical and Science Advisory Board in hopes of helping guide us towards research funding opportunities and raising awareness for SHINE Syndrome throughout the medical community.

*To view published research articles on DLG4, learn more about current research and our medical advisory board please visit **here**.*

If you would like to get involved in research and awareness for the SHINE community, please see opportunities below*. Please know that we recognize that all of this can be overwhelming. We encourage you to participate in whatever capacity is comfortable for you and your family.

SHINE Action Opportunities

- Please consider sharing photos ***here*** for our social media bank to help spread awareness of SHINE Syndrome.
- Read more about our community ***here***. We'd love to share your personal SHINE story. Please email us if you are interested in sharing your story: contact@shinesyndrome.org.
- Join ***Ciitizen*** (U.S. only) and have medical records in one place. This will streamline and expedite access to medical records when a researcher or medical professional needs the whole picture. Reach out to contact@shinesyndrome.org with questions.
- Complete the SHINE Syndrome Census ***here*** so we can learn more about how many patients exist, their ages, locations, etc and help attract researchers and aide SHINE Syndrome in being better recognized in the medical community.

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SHINE Research Opportunities

- Simons Searchlight is a research registry for DLG4 Synaptopathy and other rare genetic neurodevelopmental disorders. They collect data and blood samples and share the information with leading researchers around the world to improve the lives of people living with rare neurodevelopmental disorders. Participation is open worldwide to people who speak English, Dutch, French, and Spanish, and more languages are coming soon. People of any age with a DLG4 Synaptopathy diagnosis and their family members can sign up ***here***.

- In partnership with CoRDS the SHINE Syndrome Foundation has created a registry focused specifically on questions based on typical characteristics of DLG4-related Synaptopathy patients. Participation in this registry is critical to building a data set to describe the history and characteristics of the disease. Learn more and sign up ***here***.

- Dr. Zeynep Tümer (one of our medical advisors) is leading a research initiative to study DLG4 and PSD-95. You can participate by sharing your variant with the team. A detailed explanation on how to share this information can be viewed ***here***. Alternatively, it can be completed ***here***.

Join Our Community

Our community continues to steadily grow across the globe. We'd love to get to know you and be a part of your support system. For community information and patient stories please visit ***here***.

Please join our private Facebook support group ***here.*** The group primarily functions as a support group for families. We warmly welcome, support and appreciate our DLG4 adult patients and caregiver members. Select DLG4 researchers are also welcome and participate only to help answer questions related to research. While respecting group rules, you can ask questions and participate with no judgment and cheer for each other as progress is made.

Please also join and share our public Facebook foundation ***page*** where we share SHINE Syndrome Foundation news and all things pertinent to DLG4 Synaptopathy. This is a great resource for your family and friends to stay current and informed about SHINE.

We are here for you! If you prefer private support or Facebook is not your thing, please reach out to Courtney, our Director of Patient & Family Engagement at croche@shinesyndrome.org.

SHINE Syndrome Foundation: How to Get Involved

At SHINE Syndrome Foundation, we strive to build awareness for our growing community as well as to help provide funding for researchers around the world who are searching for answers and working to unravel the secrets of SHINE Syndrome. Through sharing our stories on our website, increasing visibility on social media, and participating in fundraising efforts, we can connect with newly diagnosed patients, provide a community for the families living with SHINE, and assist in finding strategies and treatments for those in need. Thank you to all who have participated in our fundraising efforts.

For more information on fundraising, please visit ***here***.

Visit and share our ***Bonfire store*** for SHINE Syndrome merchandise and help spread awareness while advocating for the community.

Though we understand that not everyone will be able to contribute financially, we appreciate anyone willing to share the word about SHINE Syndrome on social media or among family and friends. You can click on the icons below to follow our public social media accounts.

Resources

"A hero is an ordinary individual who finds the strength to persevere and endure in spite of overwhelming obstacles."

Epilepsy Management

Epilepsy Foundation: epilepsy.com

Danny Did Foundation: dannydid.org

Child Neurology Foundation: childneurologyfoundation.org

Autism

ASAN autisticadvocacy.org

Autism Society autismsociety.org

Sensory Processing Disorder

Star Institute: spdstar.org

Apraxia

Apraxia Kids: apraxia-kids.org

Rare Diseases:

Global Genes: globalgenes.org

NORD: rarediseases.org

Stay Up to Date on SHINE Syndrome

Visit our ***website*** to stay current on SHINE news.

To make sure that you don't miss anything important, please ***sign up*** for our newsletter.

If you are a parent, please join our ***private Facebook support group*** for the latest information. Please share our ***public Facebook page*** with family and friends so they can stay current with the latest news.

How to SHINE CHECKLIST

- [ ] Join Facebook Support and Foundation Pages
- [ ] Sign Up for the Patient Registries: Simons, CoRDS
- [ ] Share Variant for Research with Dr. Tümer and the epilepsy team
- [ ] Sign up for SHINE Newsletter
- [ ] Share 'How to Shine' Guide with Support Team, Family and Friends
- [ ] Help Fundraise for SHINE

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