SUMMARY AND BACKGROUND

INTRODUCTION

This document represents an update on the unprecedented research efforts undertaken and groundbreaking achievements of an international research project led by Jordan’s Guardian Angels into the PPP2R5D, PPP2R5C, PPP2R1A gene mutations also known as Jordan’s Syndrome. The progress in this short time has been nothing short of extraordinary as the team moves with a great sense of urgency working to improve the lives of the children and families affected and follow linkages to other diseases: Autism, Epilepsy, Parkinson’s, Alzheimer’s, and cancer, to name a few.

Working collaboratively, a remarkable accomplishment in and of itself in the scientific world, the research team has accomplished in this short time, what would normally take a decade. Powered by Jordan’s Guardian Angels, this global project and the foundation behind it are leaving an indelible mark on the rare disease space.

To date, our partnerships with other rare disease groups include The Rare Epilepsy Network (REN), The EveryLife Foundation, Rare Disease Legislative Advocates (RDLA), Global Genes, Rare Revolution Magazine, Patient Worthy, Extra Lucky Moms, Rare., Rare Disease Legislative Advocates and more.

Jordan’s Guardian Angels is also quickly becoming a model for other foundations beginning their rare disease journey, meeting with multiple groups. Team members have met with others who recently received a rare disease diagnosis and are hoping to have the success that Jordan’s Guardian Angels is having in finding a treatment or a cure. Jordan’s Guardian Angels is paying it forward in the rare disease space and hoping that in supporting these groups and many others, they will do the same.

BACKGROUND

Jordan’s Syndrome causes severe developmental disorders in children identified with mutations in PPP2R5D, PPP2R5C, PPP2R1A. Some variants of PPP2R5D, PPP2R5C, PPP2R1A are associated with developmental delays, macrocephaly, hypotonia, and autism. The children may also have seizures.

In July 1, 2021, the State of California approved a general fund allocation to accelerate the research for Jordan's Syndrome and to develop potential therapeutics, testing them in Phase 1 clinical trials. This allocation follows on the prior “scientific discovery phase” funding in 2018.

The funding supports a consortium of investigators at key universities and research institutes around the world who have specific expertise in PPP2R5D, PPP2R5C, PPP2R1A research, mouse modeling, clinical phenotyping, and clinical trials.

With the research done to date, “the toolbox is full” and much has been learned about the protein and how it fits into the molecular signaling pathways in neurons, and what the mutant...
protein does to interfere with normal function. Mice have been generated that have several of the key PPP2R5D, PPP2R5C, PPP2R1A mutations, and research is now moving toward clinical trials. In fact, the natural history study has already started, and additional studies were conducted at the July 2022 family conference. The natural history study is required for the FDA before any interventional treatments will be approved.

The international team of Jordan's Syndrome investigators are working toward two interventional therapies:

1. A repurposed drug that already has FDA approval and will interfere with the aberrant pathway caused by the mutant protein product of the PPP2R5D gene (a phosphatase).

2. A genetic intervention trial, likely an antisense oligonucleotide (ASO), also designed to blunt the effects of the mutant PPP2R5D, PPP2R5C, PPP2R1A gene.

The research is a partnership between the scientists, doctors, patient advocates and most importantly, the families. The science is guided by understanding the nature of the disorder, how children with Jordan's Syndrome are the same or different (especially if they have different variants) and also knowing what is most important to families as far as symptoms to be improved through clinical trials and therapies. We thank each of you for helping our scientific teamwork toward treatments and a cure.

THE RESEARCH TEAM
Significant progress has been made for each of the dual paths approach for the research: treatment (drug) and cure (genetic interventions). With a lot more to discover regarding Jordan’s Syndrome, this gives us the ability to explore two different paths, both racing toward answers.

Our research team meets quarterly for a full day workshop to share data and findings, to brainstorm and look at the big picture together.

The roadmap for stage two of the research is in place and the driving focus amongst team members is a push toward clinical trial readiness.

Individuals with Jordan’s Syndrome continue to be enrolled in the natural history studies with data available from over 120 families worldwide.

Expanded understanding of Jordan’s Syndrome’s clinical features and defined correlations between the biochemical activity and the clinical severity.

A manuscript is about to be published with findings about PPP2R5D, PPP2R5C, PPP2R1A and how different variants impact the individuals living with the syndrome.

Unbiased quantitative global proteomic, phosphoproteomic, transcriptional and metabolic analyses of wild-type and variant cell lines have been performed.

Additional induced pluripotent stem cells and allelic series have been created to get a better understanding of the different variants and how they compare.

A plethora of alpaca-derived antibodies and nanobodies pertinent to the study of Jordan’s Syndrome have been developed and the JGA team colleagues for ongoing studies in their labs.

High resolution cryo-EM structures have been developed providing important basis for the drug discovery in targeting the mutations.

Gene editing technologies have been used in the lab at a cell level to repair the mutations.

Advanced mice studies have shown that the animal models are faithful models of Jordan’s Syndrome in that they recapitulate the most common symptoms of the disorder. Our team is also using mice to study the link between PPP2R5D, PPP2R5C, PPP2R1A and Parkinson’s Disease, looking at why the link occurs and to enable treatment.

FDA-approved drugs are being screened on the cell level and in mice in hopes of finding potential drug candidates.

Behavioral studies in PPP2R1A mice at both the neonatal and adult stages are underway. The work highlights the two subgroups with different levels of severity.
• The cohort of PPP2R5C affected patients was significantly extended and all variants were characterized for A/C subunit binding and/or lirpin-α1 binding impairments. There are many striking resemblances between PPP2R5D and PPP2R5C affected cases, both in terms of clinical features of the patients i.e., ID/DD, hypotonia, tendency for macrocephaly, occurrence of seizures, and in terms of biochemical impairments of the genetic variants.

JORDAN’S GUARDIAN ANGELS 2022

FOUNDATION AND COMMUNITY UPDATE

Jordan’s Guardian Angels as a foundation is pushing the envelope every day. The team is focusing on growing the Jordan's Syndrome community, expanding the foundation's reach in the rare disease space and continuing fundraising efforts to bolster research efforts.... just to name a few.

Our Jordan’s Guardian Angels community has grown to more than 285 families in over 35 different countries. The online Facebook community continues to grow on a weekly basis. The numbers of families connected has expanded with nearly 100 new families joining in the last two years. Many of our families were referred directly to the Facebook page by their medical professionals all over the world.

As our global presence grows, team members at Jordan’s Guardian Angels are strongly focused on inclusion for all of our families. That includes building the Ambassador Program, utilizing members of our community from around the world to ensure that there is language and resource support for every family. Ambassadors span across regions and languages including Spanish, French, German and Italian. Families can connect with their local community and access local resources as well as participate in virtual and in-person regional events. It's a true testament to our community coming together to expand how we support each other in all of our regions across the globe. Additionally, many of the key documents created by Jordan’s Guardian Angels are now available in several languages with more to come.

Partnerships between the foundation and the community continue to flourish. The foundation is providing our families with tools and support to learn about their diagnosis and go forward and spread awareness with medical professionals, in schools, and beyond. The foundation has created a children’s book in multiple languages telling the story of Jordan’s Syndrome and encouraging children to accept differences and make a new friend. Kits for media and medical professionals have been created to spread awareness and information, as well as fundraising resources and a standard of care booklet that helps families navigate their Jordan's Syndrome diagnosis. Team members also provide daily, weekly, bi-weekly, monthly, and quarterly forums for families to support each other.

Jordan’s Guardian Angels continues to provide information to medical professionals as well. More and more information on Jordan’s Syndrome is becoming available and it is imperative that doctors, genetic specialists, therapists, and others in the medical field become acquainted with Jordan’s Syndrome. The foundation is continuously updating genetic databases with new information, reaching out to children’s hospitals to make Jordan’s Syndrome a household name.
Our families are also digging deep to make sure that the research moves forward, hosting fundraisers where they live or virtually. The Jordan’s Guardian Angels team does the same, hosting major fundraising events throughout the year.

The international Jordan’s Guardian Angels research team comes together in person and in virtual labs regularly to share data and knowledge. The team sits down together to drive the conversation forward, collaborate and work as a team on this unprecedented effort.

In July 2022 our families came together with the research team for an in-person conference in New York City. More than 300 people were in attendance, with more attending virtually as well. Previously our families came together in March of 2019 in California.

DISTRIBUTION OF CASES WORLDWIDE

More than 250 cases in more than 35 countries*

Likely approximately 250,000 undiagnosed cases worldwide

Scan this QR code with your smartphone to view an interactive map.

The interactive map can also be found by visiting www.jordansguardianangels.org/our-community/
In an effort to make Jordan’s Syndrome and Jordan’s Guardian Angels household names, outreach and awareness efforts are front and center.

In 2021, Jordan’s Guardian Angels launched a podcast called ‘A Rare Reality’ that has been named as one of Patient Worthy’s top rare disease podcasts. The podcast endeavors to be both Jordan’s Syndrome specific and rare disease broad, allowing our listeners to enjoy a wide variety of topics. The podcast is available on all major platforms, with a video version available on the Jordan’s Guardian Angels website. Listenership and viewership continue to grow week to week.

The foundation connects with families through our weekly newsletter and with stakeholders via a quarterly newsletter. A video blog, “JGA Connection” is also available to families on a quarterly basis. These touchpoints allow the foundation to provide new and ever-changing information, from research to fundraising, to calls to action and everything in between.

Our website traffic is increasing at a substantial rate and our videos have been shared and seen by hundreds of thousands of people all over the world. To date, Jordan’s Guardian Angels team members have given dozens of presentations to thousands of people in various groups that have local, regional, and international reach.

Domestic and international media continue to cover and follow the group and the research efforts. Major media outlets and members of the rare disease community continue to tell our story in print, television, blogs, podcasts and more. Jordan’s Guardian Angels families are also telling their stories for our podcast and blog. Their honest and candid remarks continue to inspire.
Together we can change the world. Words to live by for Jordan's Guardian Angels. The advocacy work the team is accomplishing is truly impacting the world and putting the foundation and Jordan's Syndrome on the map.

Team members attended Rare Disease Week on Capitol Hill spreading the word about Jordan's Guardian Angels, Jordan's Syndrome and advocating for rare disease legislation. There is extremely strong support for rare disease events and advocacy work across multiple states including California, Colorado and in Washington, D.C.

The foundation has partnered or worked with important rare disease groups such as the Rare Epilepsy Network (REN), The Everylife Foundation, Rare Disease Legislative Advocates, Global Genes, Rare Revolution Magazine, Patient Worthy, National Organization of Rare Diseases (NORD), Extra Lucky Moms, and Rare. Jordan's Guardian Angels partnership with Simons Search Light Foundation also continues. The group was also recognized with a Guidestar Gold Transparency Rating.

Jordan's Guardian Angels is also quickly becoming a model for other foundations beginning their rare disease journey, meeting with multiple groups. Team members have met with others who recently received a rare disease diagnosis and are hoping to have the success that Jordan's Guardian Angels is having in finding a treatment or a cure.

The Shine Like Ozzie Scholarship is just one more way Jordan's Guardian Angels is giving back. The foundation provided one lucky recipient with a $1,000 scholarship for a student (undergraduate or postgraduate) studying anything related to Epilepsy. 15 people applied. The scholarship is in loving memory of Ozzie Deason and the other children with Jordan's Syndrome our community has lost.

Jordan's Guardian Angels is proud to be forging partnerships through tremendous collaborative work around the world. The foundation is changing lives through mentoring, paying it forward and leading the way in the rare disease space. Together, with our partners we can change the world.
COMPLETE JGA RESEARCH UPDATE THROUGH MARCH 2022

BACKGROUND

In 2015, it was recognized for the first time that a single point mutation in a subset of genes, encoding a family of proteins called Protein Phosphatase 2A (PP2A), could be the cause of an inborn (neuro)developmental disorder, characterized by a spectrum of symptoms, ranging from developmental delay (delayed motoric development and speech), low muscle tone, to behavioral problems, and sometimes, epilepsy. PP2A proteins are expressed in all human tissues, and act as modifiers/regulators of other proteins (called their ‘substrates’), of which they can remove a small chemical group (called ‘a phosphate’). The presence or the absence of this phosphate group determines the biological activity of these substrates – in other words: it renders these proteins active or inactive. PP2A phosphatases can have positive or negative effects on many different cell and tissue functions. The complexity of the PP2A system mainly derives from their structure, as a functional PP2A in fact consists of three proteins: a catalytic C subunit (which actually removes the phosphate), a regulatory B subunit (which will determine which substrates can be modified), and a scaffolding A subunit (which forms the bridge between the C and the B subunit).

In the PP2A-related neurodevelopmental disorders, either the gene encoding the C subunit (PPP2CA), or the gene encoding the A subunit (PPP2R1A), or two (of all together 15) genes encoding a specific B subunit (PPP2R5D and PPP2R5C) can be affected. So far, the general idea about the effects of the mutations in these PP2A genes, is that the mutation creates a loss-of-function, leading to a dysfunctional subunit that can no longer perform all its functions, including the removal of the phosphate from its substrate(s). However, there is an overall lack of knowledge about which substrate or, more likely, which substrates, a specific PP2A complex modulates and which cell or tissue function or more likely, functions, this modulation affects. In brain, the PPP2R5D- or PPP2R5C-containing PP2A complexes may affect several substrates, and thus several neuronal or brain functions.

Thus, if we aim to therapeutically intervene in order to reverse the effects of the PP2A gene mutations, we need to understand which substrates and pathways are regulated by the affected PP2A complexes. A great amount of progress has been made in this area since the project began.

UPDATES

Clinical Data & Basic Understanding

Dr. Wendy Chung and her team at Columbia University in New York have continued to enroll individuals with PPP2R5D mutations from around the world in natural history studies. Dr. Chung has confirmed eligibility by reviewing genetic test reports, and collected parent reported information about their child. Parents provide baseline information during a medical history interview and provide an assessment of their child’s adaptive development through the standardized Vineland Adaptive Behavioral Scale conducted by telephone with a genetic counselor or research assistant. Data was also collected on behaviors with the Child Behavior Checklist (CBCL) and Social Communication Questionnaire (SCQ).
Clinically, the team continues to find the most common features across the PPP2R5D individuals include developmental delay, autism, ADHD, behavioral challenges, hypotonia, macrocephaly, difficulty with coordination, seizures, visual impairment, scoliosis, gastroesophageal reflux, constipation, and diarrhea. Team members have developed a heuristic clinical severity score. Some correlations are now also able to be made between the biochemical activity and the clinical severity.

At Seattle Children's Hospital, the Mirzaa lab studies brain overgrowth or Megalencephaly (MEG), a developmental disorder often associated with multiple comorbidities, including epilepsy, intellectual disability (ID), and Autism Spectrum Disorders (ASD). Dr. Mirzaa and her team have successfully established a repository of patient-derived brain overgrowth (MEG) cell lines including PI3K-AKT-MTOR mutant cell lines, as well as PPP2R5D mutant fibroblast derived cell line. These cell lines are critical for the proposed experiments in this project and their availability in hand strongly facilitates completion of the proposed aims.

At the Janssens Lab at KU Leuven, Dr. Janssens and her team have developed a novel biochemical assay to help characterizing the pathogenicity or non-pathogenicity of novel PPP2R5D variants. This data allowed the team to define at least three different molecular subgroups amongst currently known PPP2R5D variants.

The University of South Alabama is home to the Honkanen Lab where the team performed unbiased quantitative global proteomic, phosphoproteomic, transcriptional and metabolic analyses of wild-type and variant cell lines, comparing the E198K, E200K and E420K variants.

Quantum mechanical modeling is also being performed by the Honkanen team to help the overall effort to understand the regulation of PPP2R5D function in wild type cells and determine how the normal function is altered by the variants at a molecular level.

**Induced Pluripotent Stem Cell (iPSCs) Work**

The Chung Lab at Columbia University is making iPSCs from 6 more individuals covering several different PPP2R5D variants.

Concurrently, the Fink Lab at the University of California Davis Institute for Regenerative Cures have differentiated these cells into any type of cell, including neurons.

The Stem Cell Core has created five patient specific lines harboring four of the common Jordan’s Syndrome Mutations. All of these cell lines have passed rigorous quality control for measures of potency in addition to karyotypic stability. The Fink Lab has created and is expanding and differentiating four isogenic or “corrected” iPSC lines with the remaining mutations still in process. These control cells are critical for understanding the impact of PPP2R5D mutations in neurons, the most affected cell type.
The Fink Lab also launched an Allelic Series of iPSC in collaboration with Synthego where they have created 11 unique mutations in a parent iPSC line. This allele series have been received, genotyped and are currently being expanded and banked within the stem cell core at UC Davis. The Fink Lab has shared these cells with other members of the consortium and have planned experiments underway to perform RNA-sequencing and proteomics.

The Honkanen Lab in this cycle modified the CRISPR_PRIME method developed to generate the E198K lines reported in the last cycle and used the new method to generate the E200K variant lines. In addition, the CRISPR-PRIME editing methods were modified to enable the repair of the pathogenetic variants. In the last cycle the team was successful in repairing the E420K variant HEK-293 cell lines and E420K human fibroblasts. This team has now initiated the development of methods to repair the E198K variant.

At Seattle Children’s Hospital the Mirzaa Lab has generated iPSCs, NPCs, cortical neurons, and cerebral organoids from several PI3K-AKT-MTOR mutant cell lines, as well as controls, using established in-house protocols. The team has successfully performed genome editing on these cell lines to generate isogenic controls using CRISPR-Cas9. These cell lines will be further used in downstream experiments comparing them to mutant PPP2R5D cell lines.

**Mice Studies**

The Strack Lab at the University of Iowa is looking forward to leveraging the E198K constitutive knock-in mouse model to test FDA-approved and experimental drugs as therapeutic interventions. These “preclinical trials” are a precondition for human safety and efficacy clinical trials.

The Strack team has uncovered that the brains of E198K mice are characterized by a general hypophosphorylation state of multiple proteins involved in synaptic transmission. Decreased phosphorylation in E198K-mutant brains is predominantly at cAMP-dependent protein kinase (PKA) sites; RxxS. This is encouraging, as it suggests that Jordan’s Syndrome mutations may be gain-of-function and also justifies the team’s focus on elevating PKA activity with PDE4 inhibitors as a therapeutic strategy.

The team immediately set up new breeder pairs to expand our E198K mouse colony for the proposed “preclinical trials”. With small cohorts of available mice, the Strack Lab is currently evaluating several assay of cognitive function that can be carried out longitudinally and with minimal or no habituation phases. The team is presently favoring the Y maze assay of spatial memory because of its low inter-animal variability. While waiting for sufficient numbers of
E198K mice for testing, the team is currently determining optimal route, dose, and timing of administration of rolipram to elicit memory improvements in wild-type mice.

Meanwhile, the Xia Lab at the University of Rochester has revisited I/O curve for E198K hippocampal Sch-CA1 synapses and found that there is indeed an increase of synaptic transmission in E198K mouse, consistent with E/I ratio studies in E420K mouse, suggesting that Jordan variants enhance excitatory synaptic transmission.

**Nanobodies and Structure Development**

At the Wadzinski Lab at Vanderbilt University, the team has developed a plethora of alpaca-derived antibodies and nanobodies pertinent to the study of Jordan’s Syndrome. Several of these antibodies/nanobodies have been sent to the JGA team colleagues for ongoing studies in their labs. These tools are being utilized to further understanding of the molecular biology of wild type and variant forms of PPP2R5D.

In addition to the development of multiple antibodies/nanobodies, the team has also been actively involved in studies of the regulation and stability of PPP2R5D holoenzymes.

The Xing Lab at the University of Wisconsin-Madison has further examined the cryo-EM datasets for the wild type, E197K, E198K, E200K, and E420K disease variants of the PPP2R5D holoenzyme. Careful 3D classification allowed the team to calculate the percentage of open active forms of the holoenzyme at basal conditions for all variants. The knowledge learned from this analysis is consistent with many observations from biochemical characterization of the variants and observations on cellular substrate interactions from the Janssens Lab at KU Leuven.

The cryo-EM structure for the close form of the E197K holoenzyme was determined by the Xing team. The high-resolution structure reveals critical structural mechanisms. Such structural features provide coherent explanations for the effects of ID mutations and the mechanisms of how activation phosphorylation modulates the holoenzyme functions. Furthermore, the high-resolution structure provides an important basis for structure-guided investigation of disease mutations and structure-guided drug discovery for targeting mutant holoenzymes.

**Road to a Treatment**

Because the Strack Lab and other team members data strongly indicates that Jordan's Syndrome mutations uniformly activate the enzymatic function of PP2A (dephosphorylation of substrates), the team is also proposing to develop high-throughput screens (HTS) for selective inhibitors of the PP2A/R5D enzyme. These screens of chemically diverse and natural products libraries will be conducted at the University of Iowa High Throughput Screening facility in the College of Pharmacy.
The Strack team developed a novel Regenerating Activity Sensor of PP2A (RASP) assay to selectively monitor the activity of the PP2A/R5D enzyme in cells. This assay interrogates the phosphorylation state of a high-affinity, PPP2R5-selective artificial substrate that regenerates itself by autophosphorylation via cyclin-dependent kinase 5 (CDK5) fused to its C-terminus. Using the RASP assay, the team showed that all Jordan's Syndrome mutations increase the enzymatic activity of the PP2A holoenzyme.

At the University of South Alabama, the Honkanen Lab determined the data is starting to indicate that there may not be one cure for all symptoms, i.e., the team will need to determine if they need to change the actions of PPP2R5D in the same way in all cells and if the neurons are indeed the critical target cells.

Importantly, the team found that existing drugs that may not be able to cross the blood brain barrier and therefore will have little or no actions in neurons may still be useful to manage intestinal issues, hypotonia or other clinical symptoms occurring outside the brain.

The team also combined quantitative proteomics and quantitative phosphoproteomics to further explore the biological roles of PPP2R5D and determine if two different pathologic variants alter the same or different normal functions, building upon our observations made by studying wild-type and the E420K variant in HEK-293 cells provided in the previous progress reports.

The Mirzaa Lab's preliminary studies have shown that PPP2R5D regulates critical cell growth pathways including the PI3K-AKT-MTOR pathway. Activating mutations of core components of this pathway (PIK3CA, AKT3, MTOR, PTEN) are known to cause similar MEG, ID and ASD in children, a critical observation as many inhibitors of this pathway are known to have been used to treat body overgrowth and dysplasia phenotypes as well as cancer. This raises the exciting possibility of using these molecularly targeted therapies for PPP2R5D related disorders.

The Seattle Children's team has successfully performed several functional assays on the PI3K-AKT-MTOR mutant lines that revealed distinct developmental differences between key nodes in the PI3K-AKT-MTOR pathway (PIK3CA and MTOR). The team therefore expects that similar developmental differences will be seen between these PI3K-AKT-MTOR mutants and PPP2R5D lines suggesting distinct pathomechanisms for their respective neurodevelopmental syndromes. These data points would provide important insights for future therapeutic considerations using MTOR pathway inhibitors.

**Road to a Cure (Genetic Intervention)**

The second project underway in the Fink Lab at the Institute for Regenerative Cures is to develop novel therapeutic interventions targeted at the underlying genetic cause of the syndrome. For the team's work with Jordan's Syndrome specifically, the lab has focused on an approach targeted the gene directly at the DNA level to modify expression of the variant or healthy allele, the RNA using an interference strategy to reduce expression of PPP2R5D selectively, or to “correct” the RNA transcript using a novel CRISPR system.

To date the team has completed preliminary studies of each approach in patient-derived skin cells and determined that correction at the RNA-level holds the most promise. The Fink Lab
recently also designed and acquired the constructs for PRIME editing in the mouse genome for all the Exon 5 and Exon 12 mutations.

Preliminary data from the Fink team suggests that targeted correction of the E198K transcript is possible in patient-iPSC derived neuronal stem cells isolated from a patient harboring this mutation.

**PPP2R1A & PPP2R5C**

The Janssens Lab at KU Leuven finalized a comprehensive set of behavior assays in Ppp2r1a M180T KI mice, specifically at neonatal age. These assays showed a developmental delay at various levels (weight and length gain, developmental milestone development, development of certain reflexes, and neuromotoric development).

The team initiated the collection of epilepsy surveys in PPP2R1A affected individuals. Additional phenotypic characterization of the Ppp2r1a M180T KI mice has been achieved, with the aim of identifying strong and penetrant phenotypes that could be used as a read-out in mouse preclinical studies. The data so far is very encouraging to confirm that these mice indeed mimic the disorder well and would thus be useful for preclinical trials. For the Ppp2r1a R182W KI mice, the occurrence of spontaneous seizures would so far be the ‘best’ readout to use in preclinical trials. Further studies would have to reveal the best phenotypic readouts for the Ppp2r5d E198K mice as well.

The cohort of PPP2R5C affected patients was significantly extended from 9 cases to 17 cases. The Janssens Lab found here as well, all variants were characterized for A/C subunit binding and/or liprin-α1 binding impairments. Of note, there are many striking resemblances between PPP2R5D and PPP2R5C affected cases, both in terms of clinical features of the patients i.e., ID/DD, hypotonia, tendency for macrocephaly, occurrence of seizures, and in terms of biochemical impairments of the genetic variants. Moreover, the new PPP2R5C variants often affect the same amino acids as those affected in PPP2R5D variants.

**RESOURCES**

On the Jordan's Guardian Angels website you'll find helpful resources provided by JGA to help you and your family in your journey with Jordan's Syndrome. To view all of these resources online, scan the QR code to the right or visit [www.jordansguardianangels.org/resource-center/](http://www.jordansguardianangels.org/resource-center/).
Jordan’s Guardian Angels is a Sacramento based non-profit foundation working to unlock some of the world’s greatest medical mysteries. We are leading groundbreaking international research into a mutation on the genes PPP2R5D, PPP2R5C, and PPP2R1A known as Jordan’s Syndrome. It causes global developmental delays among other symptoms and is linked to Autism, Epilepsy, Alzheimer’s, cancer, Parkinson’s and other conditions.

We’ve united families around the world. In partnership with major research institutions, we’re on a mission to make a better future for our children, and potentially millions more, through research that world-renowned medical experts believe will change the world.

Our mission: To conduct research seeking answers to rare genetic mutations affecting children and adults, and assist and improve the quality of life for children and families.