KAT6 NEWS

Volume 8 | December 2022 | KAT6 Foundation, Inc. | www.kat6foundation.org

New Name/New Logo!

In 2022, the Board of Directors approved changing our name from the KAT6A Foundation to the KAT6 Foundation. The “KAT6” name refers to both the KAT6A and KAT6B genes, which are known as epigenetic regulator genes such that they open our DNA to make the right genes available at the right time for our bodies to function properly. Individuals diagnosed with KAT6 syndromes have many overlapping symptoms and challenges.

Our communities have increased our information sharing and collaboration over the past several years, and we believe we can achieve our goals and leverage our resources more effectively by having one foundation represent both communities. The KAT6 Foundation is devoted to supporting families diagnosed with both KAT6A and KAT6B syndromes.

Inside This Issue

LETTER FROM BOARD CHAIR

Dear KAT6 Community,

It has been a great year for the KAT6 Foundation thanks to the engagement and participation of our family community and the dedication of our volunteers. Thank you to all of the organizers, participants and donors of our annual KATwalk awareness and fundraising event - it was a great success. Thank you as well to all the families, researchers, and clinicians, particularly the Kennedy Krieger Institute, that attended our annual KAT6A & KAT6B conference in June in Baltimore. We look forward to even greater participation in 2023.

I'd also like to recognize some new initiatives at the Foundation. First, we are now directly funding some exciting new research initiatives you can learn about in this newsletter. Second, we have expanded the funding support for the Empowered Grant program to increasingly offset the costs to families for therapies and assistive equipment. Third, we created a family advocacy team to leverage the experience and expertise of parents who have already navigated complex school or regulatory challenges (see page 9 of this newsletter).

Lastly, I have two requests for you. First, I'd ask you to please read the notification on page 11 of this newsletter regarding the critical importance of maintaining vigilance for bowel obstructions within our patient population, given the difficulty in detection and their potentially severe effects. Second, we are always looking for volunteers interested in assisting the Foundation's activities - if you are interested, please reach out to support@kat6a.org.

Sincerely,
Jordan Muller
KAT6 Foundation, Board Chair

Emile Najm (CEO), Dr.Natacha Esber, Kevin Young, Jordan Muller (Board Chair), Marjorie Weintraub, Karen Ginsburg
3rd International KAT6A & KAT6B Conference

EVENTS RECAP

3rd International KAT6A & KAT6B Conference

The 3rd International KAT6A and KAT6B Conference took place on June 4, 2022 in Baltimore, Maryland. It was a patient-centered, collaborative event organized and sponsored by the KAT6 Foundation designed to solidify KAT6A and KAT6B research internationally and enable open dialogue between families, clinicians, and researchers.

The Conference was the first in-person meeting since the COVID-19 pandemic, which provided a platform for the KAT6 community to expand its network and for participants to build connections with families and experts in the field. More than 140 individuals attended the event, including 42 families and 18 scientists from the USA and internationally. The Conference speakers spoke about a range of topics including: diagnostic episignatures, personalized medicine, iPSC cell lines, neuropsychological assessments, speech and language disorders and the patient registry.

The KAT6 Foundation assisted three research groups with data collection at the Conference by providing a space for families to participate in research. The Foundation also organized consultation visits for families to meet Dr. Richard Kelley and Dr. Gabrielle Lemire, who are experts in the fields of KAT6A and KAT6B syndromes.

View presentations from the Conference on our **YouTube channel**, and read a full **recap** of the event on our website.

KATwalk 2022

WALKING FOR A BRIGHTER TOMORROW!

Our 5th annual walk event was another huge success! We had our largest turnout to date, and raised **US$151,400** in donations to support the KAT6 Foundation. In-person walks took place in seven US states and internationally in Australia, Canada, Germany and Spain, and we had more virtual participants than ever before!

We want to extend a massive thank you to everyone who volunteered their time, donated, walked, spread the word, or supported your loved ones in person or from a distance.

We are so fortunate this year to have had a song written especially for us by Australian singer/songwriter Stocker. She writes from first hand experience as her cousin Ginger has KAT6A and performed it at their walk in Brisbane.

KATwalk Highlight video Featuring Stocker

Top 10 Teams

Team Lexi $28,801
Team Hadley $14,398
Team Benjamin $14,263
Will's Warriors $13,383
Chloe's KATwalkers $11,201
Gigi's Guardian Angels $11,179
Team JACKman $5,939
Team Robin 2022 $5,353
Wyatt's Warriors $4,754
The Tom Squad $4,398

2022 Published Research

A KAT6 Foundation Funded Research Project Gets Published!

We are proud to report that research led by Dr. José A. Sánchez-Alcázar and his team was published on November 15, 2022 in a journal article titled, **Pantothenate and L-carnitine Supplementation Corrects Pathological Alterations in Cellular Models of KAT6A Syndrome**. The article is available on the Preprints Platform as it is waiting peer review. This is an important milestone for our Foundation as it is the first research project that we directly funded to reach publication, and is an important step forward on the path to finding a treatment for KAT6 individuals.

Three individuals with KAT6A gene variation participated in the study conducted at Universidad Pablo de Olavide in Spain. An initial series of experiments generated evidence supporting the use of patient-derived fibroblast to study KAT6A gene variation.

The team identified four critical pathophysiological processes altered by KAT6A gene variation: 1) Coenzyme A (CoA) metabolism, 2) Iron metabolism, 3) Enzymatic antioxidant system and 4) Mitochondrial function. Two compounds were identified to have a positive impact on the altered physiological pathways. These compounds are: 1) Pantothenate and 2) L-carnitine. Pantothenate is a CoA metabolism activator and L-carnitine is a mitochondrial boosting agent. Supplementation with pantothenate and L-carnitine supported the survival of the KAT6A fibroblast in a stress inducing medium. The concentration of pantothenate and L-carnitine varied in all three KAT6A cell lines suggesting that different type of mutations respond differently to these positive compounds. The KAT6A gene plays a significant role in histone acetylation which is a key process involved in cell progression and differentiation. Supplementation with pantothenate and L-carnitine resulted in significant increase in histone acetylation, recovery of gene expression patterns and expression levels of proteins affected due to the KAT6A gene variation.

We want to extend our sincere thanks to Dr. José A. Sánchez-Alcázar and his entire team for their professionalism and commitment to rare disease research and the KAT6 community. We look forward to building upon this partnership in the future.

Journal Articles Published in 2022

A Case of Ophthalmoplegia, Hypotonia, and Developmental Delay in the Setting of Corpus Callosum Hypoplasia

Epilepsy in KAT6A Syndrome: Description of Two Individuals and Revision of the Literature

Identification of a Novel KAT6A Variant in an Infant Presenting with Facial Dysmorphism and Developmental Delay: A Case Report and Literature Review

Speech and Language Development and Genotype–Phenotype Correlation in 49 Individuals with KAT6A Syndrome

The Role of Histone Modifications: From Neurodevelopment to Neurodiseases

New Research Projects Funded by KAT6 in 2022

Assaraf Research Lab at Technion Institute

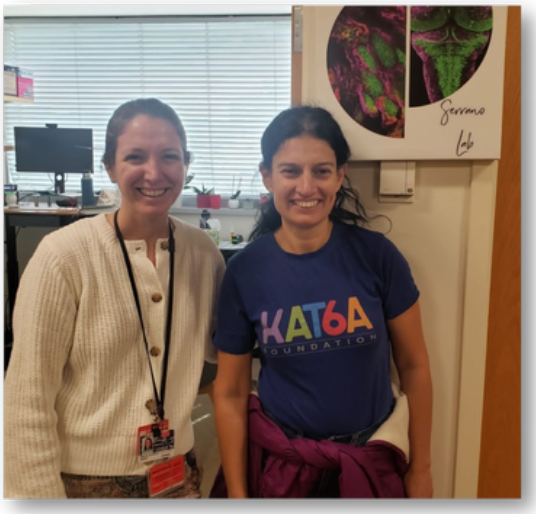
Dr. Yehuda Assaraf of Technion Institute in Israel has been studying KAT6A gene mutations since 2017. In June, 2022 the KAT6 Foundation began funding new research at the Assaraf Research Lab. The current research aims to characterize the molecular loss of function of the KAT6A and KAT6B genes in dermal fibroblasts obtained from the mutation of the KAT6A and KAT6B gene when compared to healthy counterparts, using state-of- the-art metabolomics analysis, including cutting edge seahorse technology. Quantitative and qualitative alterations in metabolites from mutant KAT6A and KAT6B fibroblasts could uncover the metabolic pathways that may be dysregulated or impaired in KAT6A and KAT6B patients. Upon cross-verification with the complementary omics, analyses which the team previously performed with a single KAT6A patient, paired with relevant literature, this information could be used for the selection of the most appropriate nutrients for personal supplementation of KAT6A and KAT6B individuals, as well as for possible therapeutic interventions.

iPSC Bank at Boston University

Also this year, the KAT6 Foundation and collaborators established the first patient-derived induced Pluripotent Stem Cells (iPSC) bank for KAT6A and KAT6B variants. The foundation's Science Advisor, Dr. Angie Serrano, will store and maintain biospecimens, such as skin and blood samples of KAT6A and KAT6B patients at Boston University. This bank will broadly share iPSC to the whole research community and industry to spark collaboration and advance research in KAT6 syndromes.

Furthermore, the biospecimens can be used by multiple researchers for multipurpose research studies. In 2022, the KAT6 Foundation is responsible for the cost of the reprogramming services for the generation of 5 patient-specific iPSC lines and will continue to fund more cell lines in 2023 if funding is available.

Email support@kat6a.org to provide samples for the KAT6A and KAT6B (iPSC) Bank.



Dr. Serrano and KAT6 Foundation co-founder, Natacha Esber at Serrano Lab in October.

KAT6A & KAT6B Fly Models

The KAT6 Foundation in collaboration with the Rare Diseases: Models & Mechanisms Network (RDMM) is proud to co-fund the first study involving fly models to investigate the neurological implications of KAT6A and KAT6B gene variants.

In June 2022, Paul Marcogliese, PhD, Assistant Professor of Biochemistry & Medical Genetics at Rady College of Medicine began using CRISPR-Cas9 gene-editing technology to modify the fruit fly genes in a study called, "KAT6A and KAT6B Models in Flies: Expanding Tools, Determining Post-Developmental Roles & Variant Assessment." Dr. Marcogliese will generate flies in order to test the KAT6A and KAT6B variant function, determine KAT6A and KAT6B expression in the nervous system, examine fly lifespan and phenotype, conduct neurobehavioral analysis, as well as treat the flies with a drug that increases KAT6A and KAT6B expression. Marcogliese's drug studies and post-developmental analysis will shed light on KAT6A and KAT6B function in neurons.

These results could identify key conserved signaling pathways that may be candidates for future drug targeting. The fly models will be deposited in a public bank and will be available for free for any other researcher to access.

Pilot Study of Cognition and Neurobehavior in KAT6A Syndrome

The KAT6 Foundation has teamed up with Jacqueline Harris, MD, MS and Rowena Ng, PhD of the Kennedy Krieger Institute in Baltimore, Maryland to fund a pilot study entitled, "Characterizing the Cognitive Profile of KAT6A Syndrome."

KAT6A syndrome is known to cause cognitive impairment with expressive language being most severely impacted. However, little is known about the cognitive profile outside of the speech and language issues. KAT6A syndrome, like many disorders of histone machinery may prove to be at least partially correctable in postnatal life. However, before truly robust and effective trials can be constructed to test potential treatments for cognitive impairment in these syndromes, disease-specific and quantifiable outcome measures and biomarkers must be developed using data about specific cognitive strengths and weaknesses. This pilot study will investigate 20 patients with KAT6A syndrome between the ages of 3 and 18 years old with a specifically designed outline of neuropsychological tests. We aim to expand this research to include KAT6B and will do so if the funding is available in 2023.

Updates to the Patient Registry

- The KAT6A Patient Registry was renamed as KAT6A/KAT6B patient registry. This change acknowledges the presence of KAT6B families in the patient registry and reflects the Foundation's aim to support all KAT6 families.
- The format changed from 5 longer surveys to 12 short, digestible, easier to fill out surveys

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Join the Registry

KAT6A/KAT6B Symposium Series

The foundation held two virtual symposiums in 2022. These events expanded upon the first symposium, which took place in 2021, to include parents of children with KAT6A and KAT6B gene variations along with health care professionals, clinicians, and researchers.

The first symposium held on March 24th focused on understanding the impact of KAT6A and KAT6B gene variations on speech and language development, since this is the most commonly affected area of development in KAT6 individuals.

The three hour event was divided into two sessions. The first session provided an overview of the KAT6 Foundation's goal to empower patient-centered research and initiatives led by the Foundation to support research. The second session focused on understanding the pathophysiology of KAT6A and KAT6B related speech and language disorders by experts in the field.

Read full recaps of the presentations that took place during our symposium events.

Speech & Language Related Disorders in KAT6

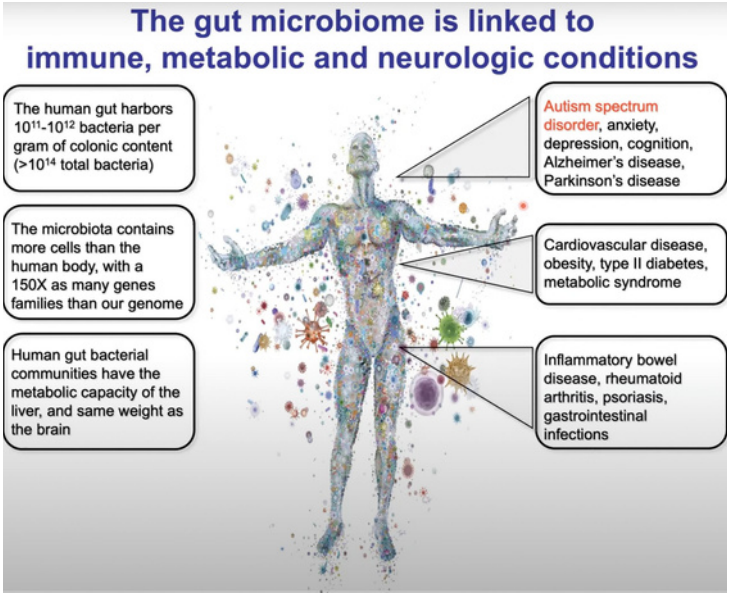
Gastrointestinal Health and Beyond in Children with Rare Diseases

Please contact us at support@kat6a.org if you are a researcher interested in joining our network, or if you are a parent and want to enroll your child in a study.

The second virtual event took place on September 7th and focused on gastrointestinal health in children with rare diseases. It was designed to fuel conversation about the gastrointestinal challenges faced by children with KAT6A and KAT6B gene variations and enable open dialogue between families, clinicians, and researchers.

20 families and 35 scientists attended the event. With some international representation, the majority of the families and researchers were based in the USA. Dr. Tanya Tripathi, research coordinator of the KAT6 Foundation moderated three scientific presentations by renowned scientists – Dr. Sarkis Mazmanian, Dr. Gustavo Mostoslavsky and Dr. Richard I Kelley.

View select presentations from the event on our Youtube channel.



ASSISTING FAMILIES

Empowered Grants

Thus far In 2022, we have awarded **20** grants to KAT6 individuals living in **8** different countries. Caregivers have received awards to help pay for a wide range of therapies and assistive equipment including: hippotherapy, hydrotherapy, physical therapy, tablets with communication software, eye glasses, and a wheelchair ramp.

In 2023, the KAT6 Foundation looks to support even more families.
See https://kat6a.org/empowered-grant/ for a full set of guidelines. Applications will be reviewed in order of receipt and granted based on full completion.

"Wilder has done so well with the therapies she has received with the help of the Empowered Grant! Her therapies help her work on things from toileting, eating, to playing games and even writing her name! We're so grateful for the help, and the opportunity to provide her with more support." -Lindsay

KAT6 Advocacy

In 2022, the KAT6 Foundation established our advocacy team to help caregivers navigate the educational and medical systems to make informed decisions and obtain optimal services and care for their child.
The team is a great resource for families transitioning from education to adult services. They assist families in understanding the process and rights of students with Individual Education Plans and help parents interpret evaluative reports and their implications.

The Foundation distributed the first ever KAT6A/KAT6B Handbook in September, 2022. The handbook was developed to help caregivers better understand the common characteristics and symptoms that many KAT6 individuals experience. Families are encouraged to share this resource with their child's medical doctors, therapists, teachers and family members.

SUPPORT KAT6

We are incredibly grateful for all of the support throughout 2022. As we look forward to 2023, we are eager to continue supporting families, and driving research to better inform our patient community. With the funding ending at year end from the grant we received from CZI's Rare as One Network, it is critical that we increase our fundraising capacity to continue progressing as a Foundation.

How you can help us continue our work?

1. **Donate to our End-of-Year Annual Appeal via our website HERE**
2. **Select the KAT6 Foundation, Inc as your charity to support when you shop on Amazon via smile.amazon.com this holiday season. (Our name has not been updated on Amazon yet.)**
3. **Spread the word about #GivingTuesday, which takes place on November 29, 2022.**

Other Ways To Support Fundraising

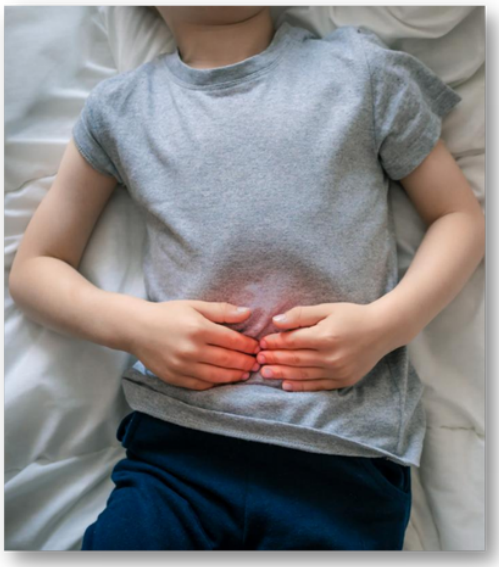
- **Purchase rare disease and KAT6 awareness clothing and other merchandise on our shop**
- **Ask your company if they would consider donating to the KAT6 Foundation or enquire about a matching program**
- **Spread awareness on social media by sharing our stories and fundraising posts**
- **Join the KAT6 Foundation: KAT6A and KAT6B Research and Raising Awareness Group on Facebook**
- **Support our "I Care for Rare" ongoing campaign by starting your own fundraiser.**
- **Join the KATwalk in 2023!**

Facebook Giving

Thank you to all of the individuals who showed their support via Facebook fundraisers this year.
2022 Facebook Donations Total: **US$7,007.17**

Look for our **#GivingTuedsay Fundraiser** on our Facebook page and share it with your friends and family. You can also create your own fundraiser when you login to Facebook on November 29th. Please choose us as your nonprofit organization to support!

Bowel Obstructions in the KAT6 Population



Caregivers, please remain vigilant about monitoring and managing your child's bowel habits. A **volvulus**, an abnormal twisting of the small or large intestine, is a rare occurrence in the general population, but among the KAT6 population it seems common enough to be of serious concern. Although we are still studying the matter and don't have statistics, it appears that untreated bowel obstructions are the leading cause of death among children affected by KAT6 syndromes. It is not our intention to alarm families, but we feel it is important to inform our community of the complications that can result from the chronic constipation that the majority of KAT6 individuals experience.

Parents of a child with a KAT6A or KAT6B syndrome are the first to recognize when the one they care for is in distress and needs medical care. However, people with KAT6 syndromes may quietly tolerate increasing pain until it has become severe and MAY show no signs of a bowel obstruction until it has progressed to a serious degree and even medical emergency. By educating ourselves, paying close attention to the signs our child gives us, and making sure we communicate consistently and accurately with medical providers, we can be our child's best advocates.

Please read David A. Woodbury's recent KAT6 Foundation **blog** post about his personal experience navigating many GI issues with his son, Sam, through infancy into adulthood.

The following resources are available on our website to help you start a conversation with your child's medical team.

- Bowel Obstructions in the KAT6 Population
- GI Health and Beyond in Children with Rare Genetic Variations
- Biochemical Basis of Intestinal Dysmotility in KAT6A by Richard I. Kelley, MD, PhD
- Gut Microbial Metabolites in Human and Animal Behavior by Dr. Sarkis Mazmanian
- KAT6A/KAT6B Handbook 2022/2023
- KAT6A Syndrome: Genotype–Phenotype Correlation in 76 Patients with Pathogenic KAT6A Variants
- Novel Variants in KAT6B Spectrum of Disorders Expand Our Knowledge of Clinical Manifestations and Molecular Mechanisms

Our Team

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Kevin Young, Chair of Finance

Director of Science and Research
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Director of Fundraising
Marjorie Weintraub

Registry Coordinator
Dr. Bhawika Lamicchane

Research Coordinator
Dr. Tanya Tripathi

Science Advisor
Dr. Angie Serrano

Dear KAT6 community:

We need YOU!

Did you know that our foundation is run by a very small group of committed parents? We have only part-time professional support for scientific research and fundraising.

The Board of the KAT6 Foundation is actively seeking new board members from the USA and internationally. They could be from within our support community or from without. Please think about whether you might be interested or might know someone who would be interested. We are especially seeking folks with experience with:

Pharmaceuticals
Scientific Research
Medicine
Marketing
Accounting
Fundraising
Media and PR
Graphic/Web Design
Communications

KAT6 Foundation
3 Louise Drive
West Nyack, NY 10994
Email: support@kat6a.org
www.kat6a.org
EIN # 82-3118535

The Board meets every other month. If you are unable to participate on the board, there are a number of committees members can join. Please contact us at support@kat6a.org to join our team.

Lastly, a huge thank you to Meg Salisbury and Aimee Reitzen for your hardwork and commitment to the KAT6 community as Foundation board members since 2017. Meg represented all of our families in Australia and established the critical connections with researchers at Murdoch Children's Research Institute. Aimee served in so many ways - including, but not limited to, developing the KATwalk fundraising event, managing the Empowered grant program, creating our great website, and writing our newsletters. Thank you, Meg and Aimee! We wish you all the best!