3rd International KAT6A and KAT6B Conference

Baltimore, USA | June 4, 2022

Summary

This report is tailored for scientist, clinicians and families who have a child with KAT6A or KAT6B gene variations. The purpose is to:

- **Provide a summary of the scientific sessions;**
- **Identify gaps and bottlenecks in current projects and the resources needed to overcome them;**
- **Propose a strategy to generate those resources.**

ABSTRACT

The 3rd International KAT6A and KAT6B Conference was a patient-centered, collaborative event organized by the KAT6A Foundation. It was 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. It provided a platform for the KAT6 community to expand its network and for participants to build connections with families and experts in field. More than 140 individuals attended the event, including 42 families and 18 scientists from USA and internationally.

The Conference was a one-day event held at Baltimore, USA, and including a range of topics such as: diagnostic episignatures; personalised medicine; role of iPSC cell lines; neuropsychological assessments; communication; the KAT6A and KAT6B patient registry and the initiatives led by KAT6A Foundation such as KAT6A walk.

The KAT6A 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-related syndromes

Scientific Sessions

Natacha Esber
Director of Science and Research
KAT6A Foundation

Jordan Muller
Chairperson
KAT6A Foundation Board

Dr. Natacha Esber, Director of Science and Research at the KAT6A Foundation opened the scientific session by highlighting the importance of studying KAT6A and KAT6B gene variations and driving therapeutics research to support children and families affected by these disorders.
Mr. Jordan Muller, Chairperson of the Board of the KAT6A Foundation, moderated the scientific presentations.

Scientific Sessions

Jill Fahrner
Assistant Professor of Pediatrics and Genetics and
Director, Epigenetics and Chromatin
John Hopkins University School of Medicine, USA

Dr. Jill A. Fahrner introduced the basic concepts of genetics and epigenetics, before transitioning to more complex science, highlighting the epigenetic consequences, molecular changes and clinical features occurring in response to KAT6A gene variations.

Families who have a child with rare gene variations often come across a range of scientific terminologies such as 'DNA', 'Genes' and 'Genetic codes'. Dr. Fahrner provided an overview of these terms and introduced the KAT6A syndrome, setting a stage for families and other speakers to discuss this rare genetic disorder in detail. Dr. Fahrner mentioned that bodies are made up of billions of cells and each cell contain genetic material in the form of DNA. KAT6A gene is one of the 22,000 genes contained in the DNA. Genes determine traits and each gene holds a set of instructions to make a protein. The KAT6A gene encodes the KAT6A protein that is vitally important to the body.

Dr. Fahrner highlighted that KAT6A protein activates other genes in cells by adding a chemical group called 'acetylation'. By disrupting the acetylation mark and gene expression, mutations in the KAT6A gene causes KAT6A syndrome. Variants or mutations are mistakes in genes that alter the DNA sequence or code. Dr. Fahrner emphasized that "KAT6A syndrome is a genetic disorder with epigenetic consequences". She discussed the various types of KAT6A variations such as 'missense', 'early truncating' and 'late truncating' and how these variations correspond to severity of the phenotypic features. Her presentation fuelled conversation on the possibility of treating KAT6A syndrome by correcting the epigenetic marks. Drugs that can assist in the reversing epigenetic marks or restoring the loss of acetylation may have the potential to treat KAT6A syndrome.

Scientific Sessions

Rowena Ng
Assistant Professor
Psychiatry and Behavioral Sciences

Jacqueline Harris
Assistant Professor
Pediatrics, Neurology and Genetics

Kennedy Krieger Institute and John Hopkins
Unsiversity SChool of Medicine, USA

Dr. Jacqueline Harris navigated the neurologic and neurodevelopmental manifestations of KAT6A syndrome by answering two key questions: 1) What do we know about the KAT6A syndrome, and 2) What should be the next steps to better understand this genetic disorder. Dr. Harris highlighted that KAT6A syndrome has neurodevelopmental attributes that overlap with other, similar epigenetic disorders but also features that are specific and unique. For instance, intellectual disability is a common feature among many mendelian disorders, whereas sleep issues, significant delays in expressive language/speech, oromotor dysfunction, craniosynostosis are features that are distinctive to KAT6A gene variations. Dr. Harris expanded on the sleep dysfunction by presenting data collected using standardized tests which identified sleep issues in a much larger proportion than reported in the literature (30-40%). Multiple or prolonged awakening, restless sleep, enuresis (7+ years), and daytime drowsiness were commonly reported sleep challenges. In addition, more than 60% of families had sought advice or treatment for sleep challenges faced by their child.

The second half of Dr. Harris's presentation focused on future research. Dr. Harris's team is working on understanding more about non-verbal cognitive profile of children with KAT6A gene variation to build a bigger study and design outcome measures using cognitive tests and sleep measures. Dr. Harris proposed that by learning about the non-verbal cognitive profile a better therapy/treatment plan can be developed, and this can provide anticipatory guidance to families, clinicians and researchers.

Scientific Sessions

Neuropsychological profile (emotional, social and quality of life) of individuals with KAT6A or KAT6B gene variations is not well understood. **Dr. Rowena Ng** brought this understudied area in to spotlight by discussing the various types of neuropsychological assessments in KAT6A syndrome and its implications for understanding brain function. Dr. Ng said that “We are all born with great potential. Shouldn’t we all have the chance to achieve it?” A range of domains such as intellectual functioning, language skills, visual processing, non-verbal reasoning, motor skills, attention, executive functioning, memory and learning, academic skills, social cognition, emotional and behavioural functioning and adaptive functioning can be assessed using neuropsychological assessments. Dr. Ng discussed the type of referrals that a neuropsychologist may receive in the clinic. Persistence or emergence of cognitive concerns such as developmental delays, decline in cognitive function following an acquired injury (seizures, viral infection, etc), unexplained regression, Attention Deficit /LD ?and autism are common referrals needing neuropsychological assessment. These assessments play a significant role in patient care by listing the strengths and weakness of the child and can support access to services and determine dosage and type of care. Neuropsychological assessments are substantial tools for monitoring cognitive functions in the context of new medical diagnosis and treatments or monitoring progress in response to behaviour or academic interventions. Dr. Ng touched base on seldomly discussed topics such as providing support to children transitioning from adolescence to adulthood, and helping families navigate questions of guardianship, residential living and vocational help.

Scientific Sessions

Dr. Ng outlined that neuropsychological evaluations can be implemented in the form of interviews, behavioural observations and informal assessments. These evaluations also make a note of the testing environment and other internal factors such as fatigue, motivation, emotion/behaviour functioning, compliance, sensory and physical impairments, medication, sleep and more. Additionally setting (school or home) plays an important role in defining the context of the scores. Neuropsychological assessments can contribute to the development of a roadmap featuring patient-focused outcomes in clinical trials. Through these assessments clinicians can conceptualize treatment benefits by identifying concepts of interest for meaningful treatment benefit.

Scientific Sessions

Gabriel Lemire
Research Fellow
Broad Institute of MIT and Harvard, USA

Dr. Gabrielle Lemire, Research Fellow at Boston Children's Hospital provided an overview of her research on KAT6B disorders. Dr. Lemire's work delineating the clinical spectrum of KAT6B disorders has served as a useful resource for clinicians to develop a clinical management plan. The KAT6B gene is associated with two clinical conditions: Say-Barber-Biesecker-Young-Simpson syndrome (SBBYSS) and Genitopatellar syndrome (GPS). The KAT6B gene was identified as the causative gene for these syndromes in 2011-2012. Similar to KAT6A, the KAT6B protein works in a complex with other proteins as an epigenetic regulator. Dr. Lemire outlined the clinical features of the KAT6B related disorders. Major features of GPS are genital anomalies, patellar hypoplasia, contractures at the hips, knees and/or clubfoot, agenesis of the corpus callosum and renal anomalies. Dr. Lemire also presented the clinical profile of SBBYSS individuals, characterised by long thumbs/great toes, immobile mask-like face, ptosis, lacrimal duct anomalies and patellar hypoplasia are some common features. Dr. Lemire discussed the management of affected individuals, including evaluation for genital and anal anomalies, evaluation of contractures, echocardiogram, renal ultrasound, ophthalmological evaluation, neurological evaluation including cerebral MRI and clinical surveillance for seizures, and periodic hearing and thyroid function tests. Dr. Lemire suggested that ongoing research to understand the underlying mechanisms and delineate the natural history and clinical spectrum is needed to optimize care for affected individuals.

Scientific Sessions

Miya St John
Doctoral Candidate
Department of Audiology and Speech Pathology,
MCRI, Australia

Severe communication difficulties are at the core of the KAT6A gene variation. **Ms. Miya St John**, opened the speech and language session by discussing the speech, language and communication profile of individuals with KAT6A gene variation and describing methods to study these domains in detail. Speech and language in KAT6A syndrome are commonly described as “speech delay” or “absent speech”. However, what these terms mean in the context of speech and language diagnosis is not clear.

Miya presented her research on phenotyping the communication profile of individuals with KAT6A gene variation in an international cohort. Her research focused on understanding communication and adaptive behavior in the context of the global medical and neurodevelopment profile. Miya highlighted that communication delays are significant in individuals with KAT6A syndrome; however, this statement in itself does not provide enough information to families to understand best therapy options for their child. Miya recruited 49 participants, from 6 months to adulthood, with a confirmed genetic diagnosis of KAT6A gene variation, through national and international support groups. Most participants were located in the USA (45%), followed by Australia (19%) and Spain (10%). Most individuals who participated in this study had a truncating variation. A combination of online surveys and zoom assessments were used to administer verbal and non-verbal assessment battery. The assessment battery captured a range of domains such as adaptive behavior, feeding/oromotor, speech and language.

Scientific Sessions

Miya discussed the link between feeding and communication impairments, and mapped the communicative behaviors used by individuals with KAT6A gene variation who could not use verbal communication. Through this, Miya broadened our lens of understanding communication by highlighting communicative behaviors such as body/limb movement, vocalization, face/eye movement, sign language and AAC (augmentative and alternative communication) devices. Miya's research also refined specific speech features, such as childhood apraxia of speech, dysarthria, and articulation errors in the verbal participants and how these features often overlap and intersect with each other. A link between location of genetic variation and adaptive behavior was established as individuals with late truncating gene variation had significant delays in some adaptive behaviors such as communication, daily living skills and socialization.

Miya's research has brought the KAT6A Foundation a step closer towards advocating for clinical trials focused on improving communication outcomes in children with KAT6A gene variants. Targeted treatment programs to address communication challenges in KAT6A syndrome can only be developed with a thorough assessment of the communication impairment as an underlying motor deficit, linguist impairment in the context of intellectual disability or both can interfere with communication. Miya acknowledged it is not easy to make this differentiation but it is necessary to refine the speech and language diagnosis in children with KAT6A gene variation to improve their outcomes. This research is now published at https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.62899.

Scientific Sessions

Angie Serrano
Assistant Professor
Whitaker Cardiovascular Institute and the Vascular Biology Department
Boston University, USA

The conference provided an excellent platform to discuss the evolving field of induced pluripotent stem cells (iPSCs) and the development of KAT6A syndrome-specific models. Under the leadership of Dr. Angie Serrano at the Center for Regenerative Medicine (CReM) at Boston University, the KAT6A Foundation aims to support iPSC models and the corresponding data bank to support KAT6A and KAT6B researcher internationally. iPSCs are specific type of stem cells produced from somatic cells collected using skin biopsy or blood draw. Patient derived iPSC cells can be differentiated into disease-relevant cell types. By reprogramming these cells, researchers can develop cells with embryo like characteristics and differentiate these to neural progenitor, cardiomyocytes and Schwann cells. Such cellular models can be used for genetic engineering, drug screening, disease modelling and study repair mechanisms and regeneration. Dr Serrano and the KAT6A Foundation share a vision to create data banks with open data sharing policies. Building a cell line is a cost-effective process; data banks with open data sharing policy have the potential to make such research efficient for many institutions and research labs. iPSC cells show extensive self-renewal abilities and have the capacity to become any cell type in the body, proving an inexhaustible source of cells for in vitro disease modelling studies. Dr. Serrano mentioned that iPSC cells stored in the CREM catalogue will have de-identified medical records, thus protecting patient privacy. The KAT6A, iPSC biobank is under development and many families who attended the conference participated in this initiative.

Scientific Sessions

David Heery
Head of Gene Regulation & RNA Biology Group
University of Nottingham, UK

Dr. David Heery is based in the University of Nottingham and he has been working on KAT6A gene regulations for over 20 years. Dr. Heery took us back to the basics of KAT6A and KAT6B genes by discussing their structure, machinery and change in functions due to gene variations. Dr. Heery uses a range of standard molecular, cell biology techniques such as CRISPR editing, RNA sequencing, and confocal microscopy on cell lines (e.g. H293 and K562 cells) to identify proteins that interact directly with KAT6A.

Dr. Heery's research uses in vitro models to study KAT6A protein and consequences of the variance. He discussed some challenges of working on the KAT6A and KAT6B genes. The protein products of these genes work in groups with other proteins, which means similarities can be found with other genetic syndromes. Dr. Heery emphasized that the more we understand about protein structures the closer we will get to studying drug therapies and discover pathways to drug discovery. Dr. Heery discussed the functional domains of the KAT6A protein and supported the role of patient iPSCs in driving patient-centered research.

Scientific Sessions

Bekim Sadikovic
Professor
Wester University, Canada

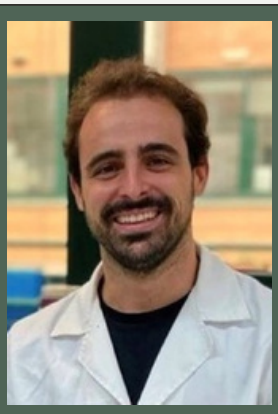
Dr. Bekim Sadikovic provided an overview of his work on diagnostic episignatures in patients with neurodevelopmental disorders and its applications to KAT6A and KAT6B. It was interesting to hear Dr. Sadikovic referring the term “rare” as a misnomer. To this, he added that cumulatively mendelian disorders comprise ~5% of the population affected by one of ~4000 rare disorders. Dr. Sadikovic’s team is working on cataloguing genome patterns in big data by applying machine learning and human intelligence. Through this his team is helping families shorten the diagnosis odyssey and better understand their child’s neurodevelopmental status.

Dr. Sadikovic discussed some epigenetic markers relevant to KAT6A and KAT6B gene mutations and the role played by episignatures in defining new syndromes. Episignatures can be defined as a recurring epigenetic pattern associated with a common genetic or environmental etiology in a particular patient population. By studying epigenetic profiles of a range of chromatin disorders, common DNA methylation profiles can be identified which can further be used to reclassify unresolved cases. Dr. Sadikovic shared data from a study where of the 67 patients with variance of unknown significance, 31% were reclassified following identification of a specific DNA methylation episignatures. Thus, episignatures can be extremely helpful for diagnosis, especially when diagnosis could not be achieved through genome sequencing and exome sequencing.

Scientific Sessions

KAT6A and KAT6B patients have overlapping phenotype and DNA methylation signatures. Dr. Sadikovic proposed Improving KAT6A and KAT6B signatures specificity for better prediction of the severity of the neurodevelopmental manifestations. He discussed the “EpiSign” research network where more than 100 institutions over 20 countries have collaborated and currently recruiting for >500 syndromes. Dr. Sadikovic talked about the next steps which are to continue to study association with phenotype severity, penetrance, progression, treatment response and DNA methylation as potential treatment targets.

Scientific Sessions



Manuel Munuera Cabeza
Investigator
Universidad Pablo de Oliavide-CABD, Spain

The KAT6A Foundation has always placed treatment discovery as one of its top research initiatives. Mr. Manuel Munuera Cabeza addressed this key area of research by presenting his work on personalized medicine in KAT6A syndrome. Mr. Cabeza's research utilizes patient derived fibroblasts to analyze the KAT6A protein, characterize pathophysiological pathways and combine this information to test treatment options. Along with his supervisor, Dr. Jose Antonio Sanchez Alcazar, Mr. Cabeza's research has characterised four pathophysiological pathways: 1) Mitochondrial proteins, 2) Coenzyme A metabolism, 3) Iron metabolism and 4) Antioxidant enzymes. Mr. Cabeza mentioned that after understanding the pathophysiology, the next step is to identify potential treatments. Preliminary data suggest recovery of some of the proteins that were lost due to the gene variation. In addition, he will be focusing on assessing what part(s) of the genome are changed physiologically when KAT6A fibroblasts are under treatment. Personalize medicine approach is needed for treatment discovery in KAT6A research.

Scientific Sessions

Richard I Kelley
Pediatrician and Biochemical Geneticist
USA

Dr. Richard I Kelley touched base on different aspects of treatment discovery that begins with identification of key mitochondrial metabolites and amino acids deficient in individuals with KAT6A and KAT6B mutations. A series of plausible treatment options were discussed where he highlighted the importance of treatment monitoring to further understand cellular biochemistry of individuals with KAT6A and KAT6B gene mutations. Efficiency of these treatment options to improve outcomes in individuals with KAT6A and KAT6B syndrome is under investigation. Dr. Kelley discussed the role of carnitine in KAT6A where he underscored the positive clinical effects of carnitine on children with KAT6A gene variations. Dr. Kelley's presentation stirred conversation on ameliorating the GI challenges. He discussed the role of citrate and tricitrate metabolism in KAT6A as potential metabolites of interest to address GI problems. Dr. Kelley will be discussing these metabolites in detail in a webinar conducted by the KAT6A Foundation focusing on GI challenges. This webinar is tentatively scheduled on September 7th, 2022 at 4 pm (PT).

Scientific Sessions

KAT6A Foundation Leadership Presentations

Bhawika Sharma Lamichhane
Postdoctoral Scholar
University of Utah, USA

Dr. Bhawika Sharma Lamichhane is a research member of the KAT6A Foundation and a postdoctoral scholar at University of Utah. Dr. Sharma L. presented about the KAT6A and KAT6B Patient Registry, which is a secure cloud-based platform developed to manage health information shared by families who have a child with KAT6A or KAT6B related syndromes. The purpose of the Registry is to allow participants store and organize their KAT6 medical data in one place. The Registry also serves as a database to enhance understanding of the full range of KAT6 related disorders and enable researchers to identify trends that can generate new insights and areas of additional study. With the Registry, the KAT6A Foundation aims to guide development of standards of care by disseminating information quickly and securely to researchers and clinicians. Of the 334 individuals known to have KAT6A variants, 207 are registered in the KAT6A patient registry. KAT6B-associated disorders were added in the Registry in 2021. Dr. Sharma L. provided a brief overview of the Registry's layout that captures health information classified under multiple domains such as diagnosis, birth and family history, medical history, treatment, and quality of life. Dr. Sharma L. advised families to keep all the information handy before filling out the Registry to make the process less time consuming. The KAT6A Foundation actively practices patient engagement measures to encourage participation in the Registry. Personalized emails and follow ups on social media have increased patient participation. Families can participate in the Registry using this link Kat6a.iamrare.org. Researchers can access the de-identified data collected using the Registry, by submitting a request to the KAT6A Foundation.

Scientific Sessions

KAT6A Foundation Leadership Presentations

Karen Ginsburg
Chair, Fundraising Committee
KAT6A Foundation

Marjorie Weintraub
Fundraising professional
KAT6A Foundation

The KAT6A Foundation dedicates significant time and effort in raising funds to support families and research. Ms. Karen Ginsburg, chair of the fundraising committee, and Ms. Marjorie Weintraub, a fundraising professional, presented the fundraising initiatives led by the KAT6A Foundation. Currently, the foundation hosts two major events each year – KATwalk in spring or fall and Annual appeal in December. The 2022 KATwalk is going to be the 3rd KATwalk since the foundation's establishment in the year 2017 and its goal is to raise $200,000. Last year's KATwalk was one of the most profitable fundraisers in which the. Karen and Marjorie's message to the families was "KAT6 Foundation is your foundation and we need help in developing a donor network, writing grants, and organize annual events." Fundraising work happens all year around and the Fundraising committee need volunteers to accelerate their efforts. The KATwalk can be hosted in a virtual or in-person format and the Foundation supports both the formats. KAT6A Foundation creates regional captains across the world (Easter, Mid-West and Western USA, Australia, Netherlands, UK, Germany, Israel, Canada) to support families who are interested in hosting a KATWalk event. The Foundation manages detailed reporting of registrants and donations. Karen highlighted that both formats are powerful, and families can host these walks in a format that seems easiest and fun.

Scientific Sessions

KAT6A Foundation Leadership Presentations

Amy Young
Parent of a child with KAT6A gene variation
Volunteer, KAT6A Foundation

Aimee Retizen
Board member, KAT6A Foundation

The 'Empowered' grant is another initiative led by the KAT6A Foundation that assists families by providing funds to purchase assistive equipment, technology and supports a variety of therapies. Each grant reward is for $600. Ms. Amy Young, member of the KAT6A Foundation, presented about the Empowered grant (presentation prepared by Ms. Aimee Retizen, Board member) at the conference. The Empowered grant supports a range of assistive equipment such as iPad, AAC software, gait trainers, adaptive bikes and feeding tools. In addition to this, the grant provides reimbursement for private therapies, not covered by health insurance. The Empower grant also allows caregivers to try out an alternative therapy to see if it is a right fit for their child. Since 2020, the KAT6A Foundation has funded over 50 Empowered grants and from 2022 onwards, the grant will support private therapies. The KAT6A Foundation along with its fundraising committee continues to evaluate areas of need with the goal to expand granting capacities in the future. Families can download the application from the Foundation's website at https://kat6a.org/empowered-grant/.

KAT6A

FOUNDATION

Thank you!