KAT6A & KAT6B Virtual Symposium 2022

KAT6A FOUNDATION

Inside

GOAL

The symposium series aims to drive patient-centered and collaborative research to improve outcomes for individuals with KAT6A and KAT6B-related conditions. The symposium series also aims to spark new collaborations among the KAT6A and KAT6B research groups and healthcare communities. The first KAT6A and KAT6B symposium, conducted in 2021, discussed a range of neurodevelopmental challenges faced by children with KAT6A and KAT6B gene variations. The second symposium expanded on the stakeholder representation to include parents of children with KAT6A and KAT6B gene variations along with health care professionals, clinicians, and researchers. This symposium focused on understanding the impact of KAT6A and KAT6B gene variations on speech and language development, a domain that is most commonly affected in this population of children.

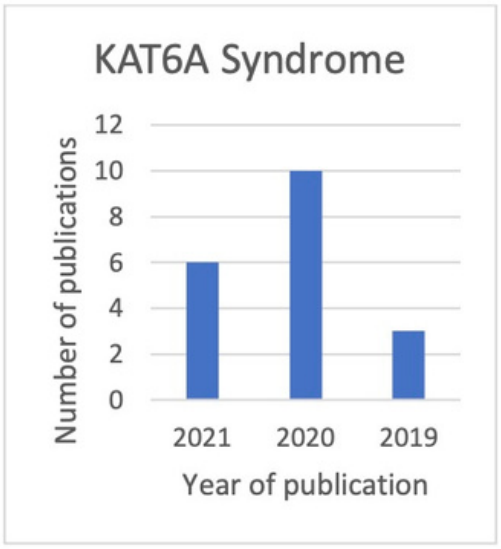
INTRODUCTION

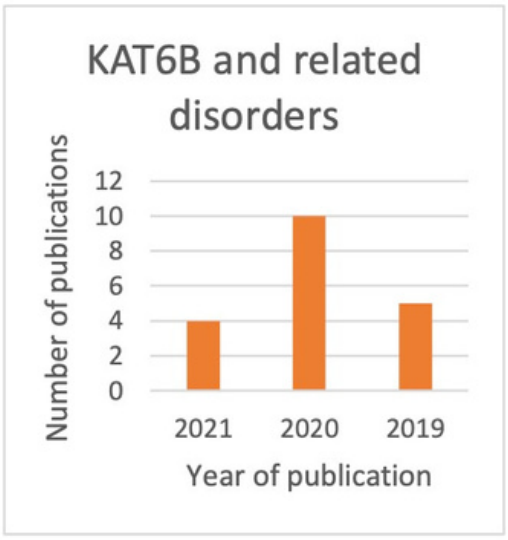
The 2022 KAT6A and KAT6B symposium was the second collaborative research event organized by the KAT6A Foundation. It was designed to solidify the KAT6A and KAT6B research network of clinicians and researchers through identification of research gaps, opportunities and collaborations. More than 100 families registered for the event and on the day of the symposium 34 families and 31 researchers attended the symposium.

The symposium ran for three hours and was organized in two sessions: the first session provided an overview of the KAT6A Foundation's goal to empower patient-centered research, and initiatives led by the Foundation to support research, and the second session focused on understanding the pathophysiology of KAT6A and KAT6B related speech and language disorders.

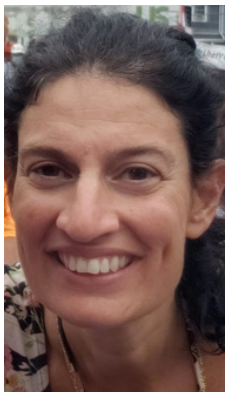
KAT6A $ KAT6B RESEARCH IN NUMBERS

Published research reports



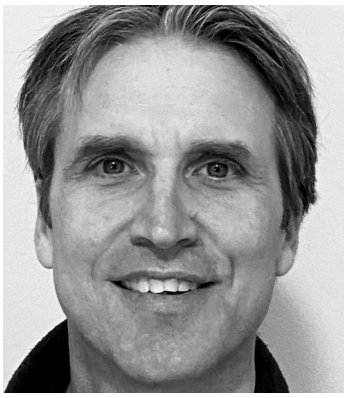


SESSION'S SUMMARY



Natacha Esber

Emile Najm



Jordan Muller

Ying Weng

Session 1: KAT6A Foundation - Empowering Patient-centered research and collaboration

Opening remarks

Dr. Natacha Esber, Director of Science and Research at the KAT6A Foundation opened the session, highlighting the need to understand the manifestations of the KAT6A and KAT6B syndromes and strengthen therapeutics research to support children and families affected by these gene variations.

About the KAT6A Foundation: the power of a collaborative approach

Emile Najm, Chief Executive Officer, and Jordan Muller, Chairperson of the Board of KAT6A Foundation thanked the Chan Zuckerberg initiative for supporting this symposium and reflected on the ongoing initiatives by the KAT6A Foundation that was established in 2017. In the last 5 years, the foundation has grown tremendously with more families, clinicians, and researchers participating in its initiatives. More than 500 families with KAT6A and KAT6B gene variations are part of the Foundation, and more than 230 families are registrants in the KAT6A and KAT6B patient registry. In 2017-18, the Foundation raised a total of $10,000 which has increased to $250,000 in the last year. The KAT6A Foundation continues to work actively on establishing mouse and cell lines, fundraising, and supporting families and researchers. Emile and Jordan emphasized on their and the Foundation's motto of "Alone we are rare, together we are strong". To highlight KAT6A Foundation's research connections, Dr. Ying Weng who is an assistant professor at Tongji University in China presented at the symposium. Her line of research focuses on micro-RNA (miR-143-3p) which plays a crucial role in KAT6A gene expression. She shared data collect from more than 10 children with KAT6A gene variation identified in China.

About the KAT6A Foundation: the power of a collaborative approach

Using a human neuroblastoma cell line as the in vitro cell model, the primary data supports that the inhibition of mRNA is possible using the proposed method. However, the rise in KAT6A expression was not observed. To reinvestigate this research question, Dr. Weng's lab is planning to use a different cellular model i.e., patient-specific iPSC or CRISPR edited iPSC.

SESSION'S SUMMARY

Session 2: Understanding the pathophysiology of KAT6A and KAT6B related speech and language disorders.

Distinguish speech from language. Understand the spectrum of speech, language and communication difficulties in children with KAT6A and KAT6B related disorders

Mia St John
MCRI, Australia

Severe communication difficulties are at the core of the KAT6A gene variation. **Miya St John**, provided a strong start to 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 also 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. Majority of the participants were located in the USA (45%), followed by Australia (19%) and Spain (10%). Most individuals with KAT6A gene variation 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.

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 used by individuals with KAT6A gene variation. 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 exemplary 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 acknowledges that 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 under review for publication.

Neuroimaging in KAT6A and KAT6B related disorders

Frederique Liegeois
University College of London, UK

Marc Seal
Murdoch Children's Research Institute, Australia

Neuroimaging can be a valuable tool to understand the neurobiology of speech and language disorders with a genetic origin. Use of neuroimaging techniques in children with KAT6A and KAT6B gene variations is a novel area of research and the Foundation needed guidance from experts to understand its feasibility.

Dr. Marc Seal reflected on how neuroimaging techniques can be implemented to map speech pathways and region of interest that are relevant for speech and language research. He provided an overview on the basics of MRI for families to understand how the technology works, what are the commonly used MRI parameters, and what types of information can be collected using the MRI. An MRI can be used to study the brain's structure and shape, its function or activity, pathways or white matter tracts and brain chemistry. It is a noninvasive and safe method of studying brain in children.

Dr. Seal shared some important resources that can be used as reference by researchers and clinicians interested in the neurobiology of speech and language development. In collaboration with researchers in Melbourne, Australia, an atlas of white matter tracts, mapped in newborn brain was developed using sophisticated MRI techniques. This resource is freely available on the internet and it provides an enriched set of data for clinicians and researchers. In addition to this, MRI techniques can be incorporated to track the development of the brain in utero. Another resource is from over 100, fetal MRI scans that were undertaken at Kings College London, UK to understand the development of white matter tracts.

Dr. Frederique Liegeois expanded on the use of neuroimaging techniques by sharing 3 case reports of children with childhood apraxia of speech (CAS), two with genetic origin and one with an unknown origin of CAS. Although these children had a similar presentation of CAS some being more severe than the other, the disruptions observed in the structures and pathways were significantly different from each other. Thus, providing a different explanation to the same diagnosis of CAS. Dr. Liegeois highlighted that by linking findings from brain imaging to genetics there is a potential to establish an understanding of the biological basis of communication impairment. This information is crucial to tailor interventions and explain prognosis to families. Both the researchers acknowledged that imaging techniques might not be a practical approach of testing for children with severe intellectual disability. Thus, it is important to keep exploring and creating new methods of assessments.

1.https://osf.io/mnwv9/
2.Wilson, Siân, et al. "Development of human white matter pathways in utero over the second and third trimester." Proceedings of the National Academy of Sciences 118.20 (2021).

Neuropsychological assessment of kids with apraxia

Kate Baker
University of Cambridge, UK

Emma Baker
Murdoch Children's Research Institute, Australia

Neuropsychological profile (emotional, social and quality of life) of individuals with KAT6A or KAT6B gene variants is not well understood, and is a complex domain to investigate and assess. **Dr. Kate Baker** is a clinical geneticist and researcher based in the UK. Her team uses a range of assessment batteries and imaging methods to understand how an individual's genetic diagnosis affects brain development, what specific constraints are impacting brain changes, and how does these constraints affect the dynamics of cognition and mental health. Using semi-structured interviews, documenting lived experiences of individuals with rare genetic variation and incorporating standardized questionnaires, Dr. Baker's research maps cognitive dimensions impacted by the gene variations. Her team developed an iPad-based cognitive tool known as "FarmApp" for children who are not able to participate in traditional IQ tests or structured cognitive tests. To understand, the underlying mechanisms, imaging techniques such as MRI and MEG (magnetoencephalography) are used to understand brain structure, connections, and most importantly study the dynamics of the brain functions. By comparing brain and behavior functions across genetic disorders and understanding the constraints that interfere in the development of complex domains such as cognition, Dr. Baker's research is untangling a complicated yet important domain of development i.e., cognition and intellectual functioning that plays a crucial role in day-to-day functioning.

For children with significant communication difficulties, most standardised tests of intelligence and cognitive functioning are either inappropriate or holds poor validity. Careful selection of battery of assessment is utmost important as it can be challenging for children with severe ID to engage in these assessments and there is a heavy load on expressive language.

Dr. Emma Baker is an expert on neuropsychological assessment of children with apraxia with specialisation in autism spectrum disorders. Dr. Baker described the importance of neuropsychological assessment to identify child's strengths and weaknesses, inform intervention and treatment planning. She emphasised that "neuropsychological testing is not just about the scores", clinicians and researchers can gather a lot of information during the assessment by observing behaviours such as how does the child approach the test? Or how does the child engage with the examiner? Her research model uses cognitive tools that commensurate with the child's abilities and are developmentally appropriate. In addition to this, Dr. Baker incorporates a range of creative methods to provide a holistic approach to the intellectual development assessment. By using parent reports, reflections of the teachers and observing the child in different settings such as at school and in the community, Dr. Baker's research is creating a phenomenal set of data. Through a case report of child with CAS, Dr. Baker made a point of sharing findings from the intellectual assessment with anyone involved in the child's care and using the child's strength to improve the weaknesses.

Neurological markers of speech and language impairments in rare genetic disorders.

Simon E. Fisher
Radbound University
Netherlands

To continue to explore the relationship between gene, brain and speech and language behavior, **Dr. Simon E. Fisher**, a world-renowned geneticist was invited to discuss molecular windows into speech/language impairment in monogenic disorders. Dr. Fisher's lab focuses on identifying DNA variations which affect speech, language and social skills, in relevant disorders and in the general population. His research aims to bridge gaps between genes and language by understanding the impact of the gene variation at the protein, cellular, neurological and behavioral levels. Dr. Fisher presented the role of FOXP2 gene in speech and language production by delineating its molecular network, functions and its role in defining neurobiological pathways. His lab is currently working on a range of genes relevant to speech and language. By developing brain organoids using iPSCs, his team aims to use sophisticated research models that can mimic early fetal human brain development.

Animal models in speech and language research.

Anne Voss
WEHI, Australia

Dr. Anne Voss studies the role of KAT6A and KAT6B in neuronal differentiation and function through behavioral animal models. Her team is assessing the KAT6A and KAT6B gene role in behavior, learning and memory.
Dr. Voss's lab generates patient-specific variant in cells to determine if variant causes a loss or gain of function variant, followed by modelling in mice to assess pathology, cellular defects, molecular chromatin/biochemical and behavioral dysfunctions. Findings from these objectives will assist in assessing the efficacy of HDAC inhibitors and acetyl-donors to improve biochemical and behavioral function that is currently being studied in Dr. Voss's lab using mice models.

Dr. Voss is one of the few experts in the world who studies vocalizations in mice models to support speech and language research in KAT6A and KAT6B gene variations. By investigating ultrasonic vocalization in mice under two situations, pups calling out to their mother when separated and male singing to a female during mating behavior, it is possible to study the neurobiology of speech and language in rare genetic variations using animal models. At the symposium, Dr. Voss also presented data collected on mice with KAT6B gene variation using the vocalization model.

Parent perspective on navigating speech, language and communication challenges in children with rare genetic variation.

Patricia Wilson
Otto Specht School, USA

Typhaine Lejuene
Board Member, KAT6A Foundation

To understand the perspective of parents and therapist with lived experience of addressing speech, language and communication needs of children with KAT6A and KAT6B gene variations, **Patricia Wilson**, a speech-language pathologist based in the USA and **Typhaine Lejuene** , parent of child with KAT6B gene variation based in Canada were invited to present at the symposium. Patricia discussed a range of communication methods based on PROMPT techniques and AAC to support speech and language outcomes. Typhaine shared the story of her son, Robin who was diagnosed with KAT6B gene variation at 3 years of age. The depth and breadth of knowledge presented by Typhaine at the symposium was inspiring and empowering for many who attended the symposium. She discussed various communication strategies and alternative methods, Robin and his family have adapted over the years. She also simultaneously highlighted the challenges of each method. For instance, fine motor skills got in the way of learning some sign language but Typhaine's family used their creative hats and adapted new ways.

Typahine highlighted that learning how to use an AAC is difficult with delayed motor skills and intellectual deficiency. Thus, a combination of support and team work is required. AAC with OT and Speech therapy is important as oral motor skills are complex and a multidomain approach may provide the best support, She emphasized on intensity by including speech exercises in the child's everyday, home routine. Most importantly, families should practice patience and resilience and find what motivates their child as each child is unique.

NEXT SYMPOSIUM

The next symposium is tentatively scheduled in September 2022. This symposium will focus on unraveling the range of gastrointestinal difficulties faced by individuals with KAT6A and KAT6B gene variations.