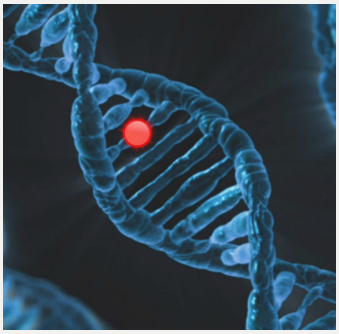
Gastrointestinal Health and Beyond in Children with Rare Genetic Variations

Webinar

September 7th, 2022

KAT6 Foundation

This particular report is tailored for scientists, clinicians, and families who have a child with rare genetic variations. In addition to providing a summary of the scientific presentations that focused on the gastrointestinal system, this report aims to identify resources needed to translate ongoing research on gastrointestinal health in children with complex needs by including KAT6A or KAT6B genetic variants into account.



Introduction

The **Gastrointestinal Health and Beyond in Children with Rare Genetic Variations** was a 2-hour long, patient-centered, collaborative event organized by the KAT6A Foundation. 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. The webinar provided a platform for the KAT6 community to expand its network and build connections with new researchers and experts working on tackling GI and GI related issues. More than 90 individuals registered for this event. On the day of the webinar, 20 families and 35 scientists attended the event. With some international representation, 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.

Scientific presentations

Dr. Sarkis Mazmanian, CalTech, USA

Dr. Sarkis Mazmanian provided a strong start to the scientific presentations by introducing the bi-directional connection between the gut and the brain and how does this relationship impacts behavior. By exploring the gut brain axis. Dr. Mazmanian and his team have developed potential therapies to intervene autism and its implications on behavior. The gut microbiome contains more cells than the human body with a metabolic capacity of a liver and mass similar to adult brain. Dr. Mazmanian highlighted a range of health issues such as autism spectrum disorders, metabolic disorders, obesity, depression, cognitive issues, immune-related disorders, and neurological disorders that have been linked with the microbiome. The gut-brain connection includes various conduits or pathways for communication. This complex relationship results in the production of molecules in the gut under the synchrony of microbiome, hormones and neurotransmitters. These neurotransmitters and hormones are speculated to receive directions by the microbiome and consequentially have an impact on neurological activity or behaviors. Dr. Mazmanian mentioned that the immune system certainly plays a role in the gut brain relationship either as a driver of neurological outcomes, facilitator or bystander as immune dysregulation is observed in many neurological conditions.

The second half of Dr. Mazmanian's presentation focused on autism spectrum disorders. Beside the core features of autism (social challenges, communication issues and repetitive/stereotyped behaviors), a significant proportion of individuals with autism have gastrointestinal symptoms, immune dysfunctions and metabolic abnormalities. Mouse models (maternal immune activation model) have been used to demonstrate that certain infections during pregnancy leads to increased risk of autism in offspring.On investigation if these mice offspring had any GI issues, it was found that the GI challenges were like the ones found in individuals with autism, and a change in the mouse's microbiome was also observed which was again similar to individuals with autism.

In these mouse models, an improvement in the behavioral manifestation was observed with the use of a probiotic (Bacteroides fragilis). The maternal immune activation model identified elevation in a gut metabolite, 4EPS (4-ethylphenylsulfate) in mice with neuro pathologies and behavioral abnormalities consistent with autism. It was interesting a decrease in 4EPS levels in these mice in response to the probiotic treatment. These promising results led to exploration of if these experiments can be validated in humans.

The **CHARGE** (Childhood Autism Risks from Genetics and Environment)1 study was a large, population-based case-control investigation of environmental risk factors, broadly defined, in relation to autism. High throughput metabolomics was performed on fecal samples acquired from participants in the CHARGE study which showed elevated level of 4EPS. Individuals with autism exhibiting challenging social behaviors were found to have a higher level of 4EPS compared to typically developing individuals without any underlying health and behavioral issues. This finding was further correlated with the GI status of individuals with autism where individuals with GI issues had elevated level of 4EPS. These initial findings led to research understanding the biological function or microbial pathway of 4EPS if it could be biomarker associated with behavioral and GI alterations. Mouse models provided confirmatory data linking 4EPS to emotional behaviors and its impact oligodendrocyte maturation, thus giving a molecular insight into pathophysiology. This research has involved into clinical trials (Axial therapeutics) testing therapeutic drugs to ameliorate behavioral challenges in individuals with autism by targeting the gut-bacteria.

References

1. https://beincharge.ucdavis.edu/
2. https://www.theautismstudy.com/study
3. https://www.axialtx.com/newsfeed/nature-medicine-publishes-full-results-from-axial-therapeutics%E2%80%99-phase-1b%2F2a-clinical-trial-in-autism-spectrum-disorder-(asd)

Scientific presentations

Dr. Gustavo Mostolvasky, Boston University, USA

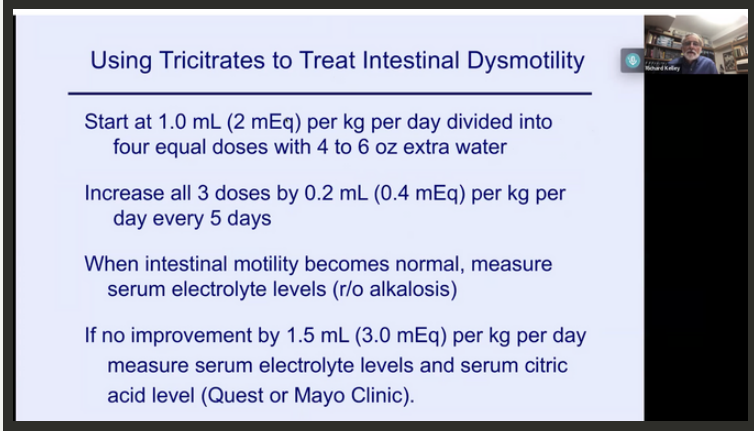
Dr. Gustavo Mostoslavsky's presentation strengthened one of KAT6 foundation's current research themes that aims at supporting iPSC models and corresponding data bank to support KAT6A and KAT6B researcher internationally. His lab primarily focuses on iPSC cells and has successfully made hepatic cells, immunomodulatory cells, intestinal organoids and have developed brain organoids modelling Creutzfeldt-Jacob Disease. After testing multiple protocols, Dr. Mostoslvasky lab has built robust models to develop intestinal organoids as confirmed by upregulation and downregulation of genes using RT PCR that are responsible for gut cells differentiation. This research model was further expanded by the ability to create regional characterization to simulate small and large intestine. This step holds a huge clinical relevance as several diseases affect either the large intestine or small intestine or both. Detailed characterization to map secretion of critical intestinal substrates supported the concept of programming iPSCs to create functional organoids. Dr. Mostoslavsky's lab have created mesenchymal free intestinal organoids which are important to study cellular applications. During the pandemic, his lab used the iPSC derived intestinal organoids to study the impact of SARS CoV-2 infection on the gut and understand pathophysiology of SARS CoV 2 infection. At Center for Regenerative Medicine in Boston, with the use of intestinal organoids derived from human iPSCs, Dr. Mostoslavsky lab was able to replicate SARS CoV-2 infection and associated structural changes in the intestine. Dr. Mostoslavsky's lab will be dedicating a year on developing protocols to create iPSCs modelling KAT6A or KAT6B gene mutations.

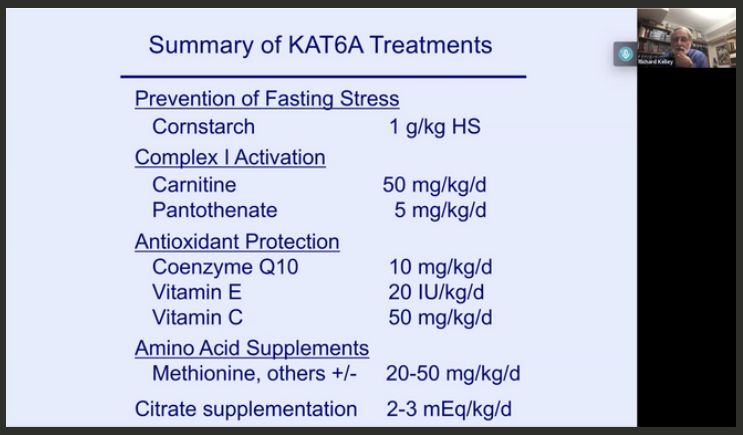
Scientific presentations

Dr. Richard I Kelley, Boston's Children Hospital, USA

Dr. Richard I Kelley biochemical basis of intestinal dysmotility in KAT6A. Dr. Kelley's research focuses on identifying metabolic abnormalities in health conditions that are not identified as metabolic disorders. Dr. Kelley mentioned that it is important to delineate the metabolic pathways as that provides an understanding of drug discovery and treatment. Dr. Kelley provided a brief overview of the KAT6A and KAT6B protein complex, amino acids profile derived from plasma of KAT6A individuals and mitochondrial treatment developed to address the biochemical abnormalities. Dr. Kelley has also analysed the plasma amino acid levels of individuals with autism where some significant metabolites such as alanine and glycine were increased in children with autism. These changes in levels of metabolites indicate a mitochondrial deficiency in individuals affected by autism. By comparing the amino acid profile of individuals with KAT6A gene mutations (N=28) with a healthy cohort, deviations in a range of metabolites (alanine, glycine, asparagine, citrulline, and proline) thus indicating mitochondrial deficiency. Dr. Kelley introduced the citric cycle to families and researchers to highlight why the study of amino acids is important to identify mitochondrial dysfunctions. Any blocks in the citric cycle will result in an increase or decrease in the levels of specific amino acids which can be identified by studying their ratio in plasma. A thorough study of the citric cycle identified that carnitine and acetate play significant roles in driving mitochondrial metabolism by maintaining Acetyl CoA reserves. Also, intra-nuclear pyruvate dehydrogenase is an enzyme that works in conjunction with carnitine which further supports the citric cycle. These basic investigations have led to the identification of supplements that can support mitochondrial functions in individuals with KAT6A gene variations.

Dr. Kelley highlighted that another way of boosting Acetyl CoA values is through tricitrates which are used mostly in kidney disease. Intestinal dysmotility is a severe form of GI issue in children with KAT6A gene variation. Tricitrates drive Acetyl CoA production which aids in the making of fat that further acts as a primary neurotransmitter for gut motility. By linking the biochemistry of gut motility with plasma amnio acids profile, Dr. Kelley found that an increase in asparagine value indicates a block at point where citrate is produced in the citric acid cycle. Thus, by addressing this block intestinal dysmotility can be addressed in individuals. Dr. Kelley brought to our attention the role of myenteric and meissner's plexus in supporting intestinal dysmotility. The nerve innervations are cholinergic which means that Acetyl CoA acts as a neurotransmitter to signal the contraction of intestinal muscles. These mechanisms support the hypothesis that citrate deficit is expressed as a deficit of Acetyl CoA which further impacts intestinal motility. Through citrate supplementation episodes of severe intestinal dysmotility can be addressed in children with KAT6A gene mutation. Dr. Kelley advised that tricitrates have the potential to treat intestinal dysmotility. Tricitrates are prescription medications and the dose recommended for children with KAT6A gene mutation is to start at 1.0 mL per kg per day divided into four equal doses with 4 to 6 oz extra water. Increase all 3 doses by 0.2 mL per kg per day every 5 days. When intestinal motility becomes normal, measure serum electrolyte levels. If no improvement, increase the dose by 1.5 mL per kg per day measure serum electrolyte levels and serum citric acid level.





Another compound Dr. Kelley discussed was propionate which is speculated to regulate a group of genes that lower lipogenesis, serum cholesterol levels, and carcinogenesis in other tissues. Propionate is usually found in gut bacteria and is also present in dietary fiber. By increasing the proporionylation of histones by using isoleucine has some clinical benefits. Towards the end Dr. Kelley summarized some potential treatment options derived from metabolic supplements.

Thank you!