KAT6A and KAT6B Research in Canada

Key Researchers in KAT6 network

DR. PHILIPPE CAMPEAU
Medical Geneticist at CHU Sainte-Justine Research Center, Montreal
Assistant Clinical Professor, Department of Pediatrics, Université de Montréal

Dr. Campeau and his team used exome sequencing to discover that a variant in the KAT6B gene causes genitopatellar syndrome (GPS), a finding published in 2012. Today, his lab focuses on epilepsy, epigenetic, and skeletal diseases, identifying disease-causing genes, understanding disease mechanisms, and improving care for affected children. Their work has uncovered genetic causes for several conditions, including GPS (KAT6B), a form of osteopetrosis (SLC29A3), osteogenesis imperfecta and early-onset osteoporosis (WNT1), Yunis-Varon syndrome (FIG4), and DOORS syndrome (TBC1D24). They are currently using murine models to further explore the functions of these genes.

Top Publications on KAT6A/KAT6B

1. DNA methylation episignatures are sensitive and specific biomarkers for detection of patients with KAT6A/KAT6B variants.
2. Further delineation of the clinical spectrum of KAT6B disorders and allelic series of pathogenic variants.
3. Deficient histone H3 propionylation by BRPF1-KAT6 complexes in neurodevelopmental disorders and cancer.
4. KAT6B disorders.
5. Mutations in KAT6B, encoding a histone acetyltransferase, cause Genitopatellar syndrome.

KAT6 Foundation

Research Summary

Role of KAT6B and KAT6A in Histone Modification

Dr. Campeau's research explores how KAT6A and KAT6B, in collaboration with the protein BRPF1, add chemical tags to histone proteins, specifically at lysine 23 (H3K23). These tags include both acetylation and propionylation.

Association with Active Chromatin and Impact of BRPF1 Deletion

Using advanced imaging techniques, Dr. Campeau showed that H3K23 propionylation occurs in active regions of the genome. He found that removing BRPF1 in mice completely stops this tagging process, emphasizing BRPF1's crucial role.

Identification of BRPF1 Variants and Their Effects

Dr. Campeau identified new mutations in BRPF1 in 12 patients with intellectual disabilities. These mutations, along with known ones, disrupt H3K23 propionylation and can also cause heart problems. He also discovered that cancer-related BRPF1 mutations impact this process.

Potential Therapeutic Approaches

The research investigated how various drugs and compounds affect H3K23 acylation. Medications like valproate and vorinostat, as well as compounds such as propionate and butyrate, were found to enhance this modification, suggesting potential treatments for disorders caused by faulty histone tagging.

Conclusion

Dr. Campeau has significantly advanced our understanding of histone modification by studying KAT6B and BRPF1. His work shows how these proteins modify histone H3 at lysine 23, reveals the essential role of BRPF1, and identifies new mutations linked to intellectual disabilities and cancer. His research also points to new treatment possibilities by enhancing H3K23 acylation.

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DR. XIANG-JIO YANG
Medical Geneticist at Rosalind and Morris Goodman Cancer Research Center, McGill University
Professor at Department of Medicine, McGill University

Dr. Yang has been an independent investigator at McGill University since 1997 and a full professor since 2009. His research focuses on post-translational modifications, gene regulation, chromatin, cell signaling, and their roles in mouse development and human diseases. Dr. Yang's team has extensively studied the critical role of histone and lysine acetyltransferases in brain development, particularly the BRPF protein, which is vital for forming key brain structures like the hippocampus, gyri, and sulci. Dr. Yang's research aims to understand de novo mutations in the BRPF1 gene which are essential for improving molecular diagnosis and developing targeted treatments.

Top Publications on KAT6A/KAT6B

1. Analysis of lysine acetylation and acetylation-like acylation in vitro and in vivo.
2. Further delineation of the clinical spectrum of KAT6B disorders and allelic series of pathogenic variants.
3. Deficient histone H3 propionylation by BRPF1-KAT6 complexes in neurodevelopmental disorders and cancer.
4. Mutations in KAT6B, encoding a histone acetyltransferase, cause Genitopatellar syndrome.

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Research Summary

Genetic Basis of Genitopatellar Syndrome (GPS)

Dr. Yang's research focuses on the genetic and molecular causes of neurodevelopmental disorders, particularly mutations in the KAT6B gene, which encodes a histone acetyltransferase. A key study identified de novo truncating mutations in KAT6B as the cause of GPS. These mutations affect the C-terminal region, leaving the acetyltransferase domain intact but disrupting the transcriptional activation domain, leading to dominant-negative or gain-of-function effects. Expression studies in mice revealed that Myst4, the mouse ortholog of KAT6B, is expressed in tissues affected in GPS. This study also compared GPS phenotypes with other syndromes caused by mutations in KAT6B, showing how these truncated proteins dysregulate key developmental programs.

Expanding the Spectrum of KAT6B Disorders

Dr. Yang also expanded the clinical and molecular spectrum of KAT6B disorders by analyzing data from 32 new patients and 89 previously reported cases. The study described 23 new pathogenic KAT6B variants, mostly in exons 16-18, and showed that proximal exon 18 mutations are more likely to cause GPS, while variants across the gene can result in SBBYSS or intermediate phenotypes. The authors proposed a classification system based on clinical features, improving diagnosis and evaluation.

Protocols for Analyzing Protein Acetylation

Dr. Yang developed protocols for analyzing protein lysine acetylation and other acylations, such as propionylation and crotonylation, using antibody-based detection methods. These protocols, applicable both in vitro and in vivo, use specific antibodies to differentiate between various acylations at lysine residues, offering insights into the role of these modifications in epigenetics, development, and disease.

Conclusion

Dr. Yang's work has significantly enhanced our understanding of KAT6B-related disorders and provides valuable tools for studying protein acetylation, highlighting the epigenetic mechanisms involved in these conditions.

Research Summary

Genet Med. 2020 August ; 22(8): 1338–1347. doi:10.1038/s41436-020-0811-8.

Further Delineation of the Clinical Spectrum of *KAT6B* Disorders and Allelic Series of Pathogenic Variants

This paper is one of the collaborative efforts between Dr. Campeau and Dr. Yang, focusing on a group of rare genetic disorders caused by mutations in the KAT6B gene. These mutations result in a spectrum of conditions, primarily characterized by developmental delays, intellectual disabilities, and various physical abnormalities. The paper highlights two key disorders: Genitopatellar Syndrome (GPS) and Say-Barber-Biesecker-Young-Simpson Syndrome (SBBYSS), both of which fall under the broader category of KAT6B-related disorders.

Genitopatellar Syndrome (GPS) is associated with a set of distinct physical and developmental characteristics. Patients typically present with genital abnormalities, such as cryptorchidism (undescended testes) in males or abnormalities of the external genitalia. Additionally, patellar hypoplasia (underdeveloped kneecaps) or even aplasia (absence of kneecaps) is commonly observed. Other skeletal anomalies, such as joint contractures and spinal abnormalities, are also frequently reported. Neurologically, GPS is marked by severe intellectual disability, hypotonia (reduced muscle tone), and often, a lack of speech development. These patients may also have distinctive facial features, such as a broad nasal bridge, a prominent forehead, and a short nose.

Say-Barber-Biesecker-Young-Simpson Syndrome (SBBYSS), on the other hand, shares some overlapping features with GPS but also presents with its own unique set of symptoms. Individuals with SBBYSS often exhibit a milder form of intellectual disability compared to GPS. They typically have distinctive craniofacial features, including blepharophimosis (narrowing of the eye opening), ptosis (drooping of the upper eyelid), a broad nasal tip, and a thin upper lip. Other common features include hearing loss, heart defects, and hypothyroidism. Limb abnormalities, such as brachydactyly (short fingers or toes) and cutaneous syndactyly (fusion of the skin between fingers or toes), are also frequently observed.

The study presented in the article significantly advances the understanding of KAT6B-related disorders by examining 32 new patients, many of whom exhibit novel mutations in the KAT6B gene.

Research Summary

Genet Med. 2020 August ; 22(8): 1338–1347. doi:10.1038/s41436-020-0811-8.

Further Delineation of the Clinical Spectrum of *KAT6B* Disorders and Allelic Series of Pathogenic Variants

The researchers identified 24 previously unreported genetic variants, thereby expanding the known spectrum of mutations that can lead to these conditions. By analyzing these new cases alongside previously documented ones, the study underscores the considerable variability in symptoms among individuals with KAT6B mutations. This variability, known as phenotypic heterogeneity, complicates the diagnosis of KAT6B-related disorders based solely on clinical features. However, genetic testing for KAT6B mutations remains essential for confirming the diagnosis and understanding the underlying cause of the symptoms.

The article also delves into the molecular mechanisms by which KAT6B mutations lead to disease. The KAT6B gene encodes a protein that functions as a histone acetyltransferase, an enzyme involved in regulating gene expression by modifying the structure of chromatin (the complex of DNA and proteins in the nucleus of cells). Mutations in KAT6B disrupt this process, leading to abnormal gene expression during development, which contributes to the wide range of physical and intellectual disabilities observed in affected individuals.

Importantly, the study underscores the need for a multidisciplinary approach to managing KAT6B-related disorders. Given the broad range of symptoms, patients often require care from a team of specialists, including neurologists, endocrinologists, orthopedic surgeons, and speech therapists. Early diagnosis and intervention are crucial for improving the quality of life for individuals with these conditions.

In conclusion, the article significantly contributes to the understanding of KAT6B-related disorders by expanding the known spectrum of mutations and associated clinical features. The findings highlight the complexity and variability of these conditions, emphasizing the importance of genetic testing and a comprehensive, individualized approach to patient care.

KAT6A and KAT6B Research in Canada

Key Researchers in KAT6 network

Dr. Paul Marcogliese
Assistant Professor, Max Rady College of Medicine, Biochemistry and Medical Genetics
Research Scientist, Children's Hospital Research Institute of Manitoba

Dr. Paul Marcogliese's research focuses on unraveling the molecular and cellular mechanisms underlying neurological diseases. Using *Drosophila melanogaster* (fruit flies) as a model organism, his team investigates the effects of patient-derived genetic variants in vivo. By rapidly generating *Drosophila* with strong loss-of-function mutations, they create an effective platform for detailed phenotypic analysis, exploring biological mechanisms, and testing potential drug therapies. Recently, Dr. Marcogliese's research has centered on developing mutant fruit fly models to study variants in the KAT6A and KAT6B genes. This work aims to understand the roles of these genes in fly development and adult brain function, while also screening drugs that may reverse the phenotypic defects caused by these mutations.

Top Publications on Preclinical Modelling

1. Cdk8/CDK19 promotes mitochondrial fission through Drp1 phosphorylation and can phenotypically suppress pink1 deficiency in Drosophila.
2. Variant functional assessment in Drosophila by overexpression: what can we learn?
3. Drosophila functional screening of de novo variants in autism uncovers damaging variants and facilitates discovery of rare neurodevelopmental diseases.
4. Loss of the endoplasmic reticulum protein Tmem208 affects cell polarity, development, and viability.

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Research Summary

Dr. Paul Marcogliese's research focuses on using fruit flies (Drosophila melanogaster) to study the functional impact of KAT6A and KAT6B gene variants, model disease symptoms, and screen potential therapeutic drugs. This summary is based on his presentation at the 5th Annual KAT6A and KAT6B Meeting in Baltimore, USA, on June 8, 2024.

Background and Importance

Fruit flies have been instrumental in genetic research for over a century, serving as models for understanding fundamental genetics, signaling pathways, and neurobiology. Recent advancements in gene editing, such as CRISPR, have enhanced their utility in precision medicine.

Research Goals

The research aimed to develop mutant fruit flies to model KAT6A and KAT6B gene variants, assess these genes' roles in fly development and adult brain function, and screen for drugs that can rescue phenotypic defects caused by gene mutations.

Findings

Key findings from mutant flies included the discovery that the fly homolog of KAT6A and KAT6B, called enoki mushroom (enok), is essential for viability. Homozygous loss of enok resulted in embryonic lethality, and knocking down enok in neurons during development or in adult flies led to severe phenotypic defects, including impaired climbing ability and reduced lifespan.

Drug Screening

Dr. Marcogliese reported on drug screening efforts, including testing miltefosine, which showed potential in increasing KAT6A and KAT6B expression in mouse models but failed to rescue the fly phenotypes. Future plans include testing other drugs, such as luteolin and N-acetylcysteine, in adult-specific phenotypes and seizure assays.

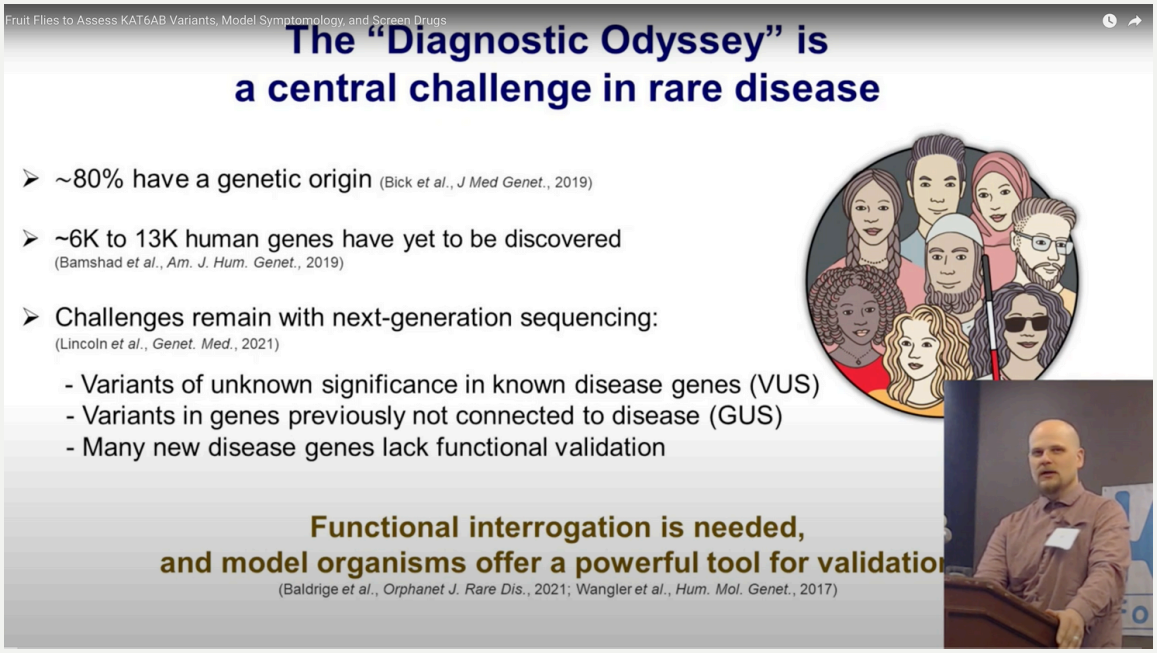
Variant Assessment

The team created transgenic flies overexpressing human KAT6A and KAT6B variants. Overexpression of wild-type KAT6A or KAT6B often resulted in lethality, indicating the genes' dosage sensitivity. Different truncating and missense variants exhibited varying effects on viability and wing morphology, suggesting distinct functional impacts.

Research Summary

Future Directions

Preliminary data suggested a connection between KAT6A and Wnt signaling pathways. Future research will explore this relationship further, develop humanized fly models, and identify potential drugs for repurposing. Dr. Marcogliese highlighted the potential of using fruit flies as a cost-effective and efficient model for studying gene function, understanding disease mechanisms, and screening for therapeutic compounds.



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Dr. Bekim Sadikovic
Professor and Program Head, Molecular Diagnostics Program,
Department of Pathology and Laboratory Medicine
Schulich School of Medicine & Dentistry

Dr. Bekim Sadikovic's research centers on clinical epigenomics, particularly the identification of DNA methylation patterns to characterize and study genetic conditions. DNA methylation, the addition of methyl groups to cytosine, plays an important role in regulating gene expression. This regulation is essential for precise protein production, which is central to normal cellular function. Imbalances in protein levels can disrupt normal cellular processes, contributing to disease.

Dr. Sadikovic's work has shown that genetic mutations in certain genes, such as KAT6A and KAT6B, lead to specific DNA methylation patterns, or episignatures. These condition-specific patterns have significant diagnostic utility. For example, if a patient has a genetic variant of unknown significance in the KAT6B gene, comparing the patient's DNA methylation data to the KAT6B episignature can help determine the variant's pathogenicity and confirm or refute a KAT6B related diagnosis.

Dr. Sadikovic has commercialized his analysis pipeline called EpiSign, which covers 90 conditions. His recent publications have focused on demonstrating the clinical utility of EpiSign and identifying additional condition-specific patterns. Beyond diagnostics, his approach has the potential to offer insights into disease mechanisms by comparing methylation signatures and phenotypic features across different conditions.

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KAT6A and KAT6B Research in Canada

Top Publications on Clinical Epigenomics

1. DNA methylation episignatures are sensitive and specific biomarkers for detection of patients with KAT6A/KAT6B variants.
2. What Have We Learned from Patients Who Have Arboleda-Tham Syndrome Due to a De Novo KAT6A Pathogenic Variant with Impaired Histone Acetyltransferase Function? A Precise Clinical Description May Be Critical for Genetic Testing Approach and Final Diagnosis.
3. Novel diagnostic DNA methylation episignatures expand and refine the epigenetic landscapes of Mendelian disorders.
4. Clinical epigenomics: genome-wide DNA methylation analysis for the diagnosis of Mendelian disorders.
5. Evaluation of DNA Methylation Episignatures for Diagnosis and Phenotype Correlations in 42 Mendelian Neurodevelopmental Disorders.

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