GNAO1 & GNB1 Conference 2026
Researcher Bios and Lay Summaries

Clinical EEG features of GNAO1-related disorders

Erika Axeen, MD
University of Virginia, USA

Bio: Dr. Erika Axeen is a pediatric epileptologist and Associate Professor of Neurology and Epilepsy who specializes in evaluating and managing seizures and epilepsy in children at the University of Virginia. She has a particular interest in the clinical diagnosis and management of genetic epilepsies and rare disease. She has published on defining the epilepsy phenotype in GNAO1 in the 2019 published in Epilepsia (Kelly 2019) and led the GNAO1-related disorders caregiver survey (Axeen 2021). Dr. Axeen is interested in continuing to understand the clinical spectrum of epilepsy within GNAO1-RD.

Lay summary: Published reports on EEGs (electroencephalograms) from 129 individuals with GNAO1-related disorders were to better understand range of brainwave patterns seen in patients. People without seizures usually had normal EEGs, though some showed mild abnormalities. In contrast, people with epilepsy most often had abnormal EEGs, although a small number still had normal results at times. “Epileptiform activity” or “electrical pops” that are associated with seizures was most common abnormal finding, but there was no single EEG pattern unique to this condition. More severely abnormal EEG patterns were only seen in those with epilepsy. Overall, the results suggest EEGs can be helpful but are not definitive for diagnosing or predicting disease features in GNAO1-related disorders, and more standardized research is needed.

Longitudinal phenotypic trajectories in GNAO1-related disorders and plasma cell-free RNA profiling: clinical profiles, disease progression and candidate biomarkers

Juan Darío Ortigoza-Escobar, MD, PhD
Hospital Sant Joan de Déu, Barcelona, Spain

Bio: Juan Darío Ortigoza-Escobar, MD, PhD is a pediatric neurologist specializing in childhood movement disorders and rare neurodevelopmental disorders. He leads the Movement Disorders Unit at Hospital Sant Joan de Déu in Barcelona, Spain. He is a Board Member of the European Paediatric Neurology Society (EPNS). He also serves as Coordinator of the Chorea & Huntington Disease Group within the European Reference Network for Rare Neurological Diseases (ERN-RND). His clinical and research work focuses on genetic movement disorders, including *GNAO1*-, GPCR signaling pathway genes-, and *NKX2-1*-related disorders, natural history studies, biomarkers, deep brain stimulation, and international clinical guidelines.

Lay summary: This presentation explores how *GNAO1*-related disorders evolve over time and how objective biomarkers may improve disease monitoring. Based on longitudinal clinical follow-up, overall disease severity appears largely stable in most patients, arguing against broad neurodegenerative progression. However, severely affected patients may show increasing movement-disorder burden over time, highlighting the need for targeted monitoring. The study also integrates genotype–phenotype relationships and functional molecular data to support better risk stratification. In parallel, plasma

cell-free RNA profiling identified candidate biomarkers that may help distinguish disease-related biological signatures. Together, these findings move the field toward precision medicine by combining clinical trajectories, genotype, and molecular biomarkers.

Constructing a multicenter neuroimaging dataset to unveil structural brain alterations in GNAO1-related disorders

Juan Darío Ortigoza-Escobar, MD, PhD
Hospital Sant Joan de Déu, Barcelona, Spain

Lay summary: This presentation examines whether quantitative MRI volumetry can reveal hidden brain structural alterations in GNAO1-related disorders, even when conventional MRI appears normal. Using age-matched volumetric analysis, the study identified a reproducible structural signature involving the entorhinal cortex, caudate nucleus, amygdala, corpus callosum, and ventricles. The entorhinal cortex showed the most consistent volume deficit, while caudate abnormalities were associated with greater movement-disorder severity. Corpus callosum changes correlated with molecular dysfunction, and ventricular enlargement was linked to overall clinical severity. These findings support a network-level view of GNAO1-related disorders, connecting genetic dysfunction, brain structure, and clinical phenotype. Although not yet ready for clinical use, quantitative MRI may become a valuable tool for patient stratification, longitudinal monitoring, and future therapeutic trials.

Outcomes of Bilateral Globus Pallidus Internus Deep Brain Stimulation in GNAO1-Related Movement Disorder: A Multicenter Experience

Katerina Bernardi, MD
Boston Children's Hospital - Harvard Medical School, Massa chusetts, USA

Bio: Dr. Katerina Bernardi is specializing in Movement Disorders at Boston Children's Hospital, Harvard Medical School, where she works under the mentorship of Dr. Darius Ebrahimi-Fakhari. She is also an R25 Scholar in the NIH-funded Rare Disease Clinical Research Training Program. Trained in pediatric neurology in Italy (Sapienza University, Rome) and Germany (University Hospital of Cologne), her research focuses on rare childhood-onset movement disorders, particularly G protein-related neurodevelopmental disorders and deep brain stimulation outcomes in children. She leads the prospective international natural history study for GNB1/GNB2-related disorders.

Lay summary: Children with GNAO1-related disorder can experience sudden, extreme bursts of uncontrollable movement, called dyskinetic crises, that may become life-threatening. Analyzing data from 46 children treated across multiple international centers, we found that deep brain stimulation reduced crises in 95% of patients, cut hospital admissions dramatically, and improved movement scores by over a quarter. Children also experienced less pain, better sleep, and weight gain. Our findings support earlier surgical intervention, before crises become frequent, to protect children from harm and reduce the burden on their families.

GNB1/GNB2-Related Neurodevelopmental Disorders: Preliminary Prospective Natural History Data

Katerina Bernardi, MD
Boston Children's Hospital - Harvard Medical School, Massachusetts, USA

Lay summary: Mutations in the GNB1/GNB2 genes cause a rare condition with developmental delays, movement disorders, and epilepsy. Because so little is known about how this condition evolves over time, we recently launched a prospective natural history study with check-ins every six months. Nearly all patients seen so far (ca. 20) had motor and speech delays from early infancy, most had overlapping movement disorders, and many had swallowing difficulties. This registry will help us understand the disease course, identify the best ways to track progress, and lay the groundwork for future treatment trials.

Genes in the GPCR signalling pathway: GNB1 phenotype, natural history and first-year assessment results

Juan Darío Ortigoza-Escobar, MD, PhD
Hospital Sant Joan de Déu, Barcelona, Spain

Lay summary: This presentation focuses on *GNB1*-related disorder, the most frequently represented condition within a broader cohort of genes involved in the GPCR signaling pathway. It combines international registry data (n=48) with a prospective Spanish first-year assessment cohort to define phenotype, severity, and early natural history. The Spanish cohort includes detailed standardized evaluations of epilepsy, movement disorders, motor function, language, cognition, sleep, nutrition, video-EEG, and brain MRI. Preliminary first-year data from 16 *GNB1* Spanish patients show a heterogeneous phenotype, often beginning early in life with developmental symptoms, epilepsy, movement disorders, and variable motor and language outcomes. By integrating genotype, clinical scales, neurophysiology, imaging, and longitudinal follow-up, the study aims to identify genotype–phenotype correlations and clinically meaningful trajectories. These results will support better diagnosis, patient stratification, anticipatory care, and future trial readiness in *GNB1*-related disorders.

Targeting GNAO1- related disorders with zinc: Findings from the ZINCGNAO1 an open-label, single-arm, monocenter, phase 2 trial

Moritz Thiel, MD
University of Cologne, Germany

Bio: Moritz Thiel, MD, is a paediatrician and paediatric neurologist at the Department of Paediatrics, University Hospital Cologne, Germany. His clinical and scientific work focuses on rare neurogenetic movement disorders, with a particular emphasis on GNAO1-related disorders. He has contributed to genotype–phenotype studies, treatment analyses, GeneReviews, and translational research exploring zinc as a mechanism-based therapeutic approach for GNAO1-related disorders. He is involved in building international clinical research structures for GNAO1, including natural history and treatment registries, and has led the ZINCGNAO1 pilot trial evaluating oral zinc treatment in affected children and young adults. In addition, he serves as Chair of the Young European Paediatric Neurology Society and is a board member of the European Paediatric Neurology Society.

Lay summary: In this talk I will talk about zinc as a potential mechanism-based treatment for GNAO1-related disorders. Previous laboratory and animal studies suggested that zinc can improve the

function of altered GNAO1/Gαo proteins. In the ZINCGNAO1 pilot trial, we tested whether daily oral zinc treatment is safe and feasible in children and young adults with GNAO1-RD in a six-month treatment. The results suggest that zinc is safe and feasible and may help improve motor function and daily activities in some patients, but larger studies and long-term follow-up are needed to better understand who benefits most. We are currently in the long term follow up of the trial and will present the first results of this as well. Some variants seem to profit more than others and close clinical observation and regular blood tests are needed in long term follow up.

Building disease in a dish models to study the impact of GNB1 mutations

Robert Rizk, PhD Candidate
McGill University, Canada

Bio: Robert Rizk is a PhD candidate in Pharmacology and Therapeutics at McGill University under the supervision of Terry Hébert. His research focuses on the regulation of Gβγ subunit signaling downstream of GPCRs. He studies how KCTD proteins, acting as Cullin3-based ubiquitin ligase adaptors, control the abundance, composition, and localization of Gβγ complexes across cellular systems. Using an integrative approach that combines molecular pharmacology, proteomics, RNA sequencing, and stem cell–derived models, he investigates how changes in Gβγ regulation influence key signaling pathways such as cAMP/PKA and calcium signaling. His work aims to define fundamental mechanisms governing Gβγ signaling dynamics and identify new strategies to selectively modulate this pathway.

Lay Summary: Mutations in the gene GNB1 affect how brain cells communicate with each other. This gene plays an important role in controlling signals inside cells, and when it does not function properly, it can lead to developmental challenges that impact learning, movement, behavior, and other aspects of brain function. However, the exact way these mutations cause disease is still not fully understood. Our research aims to better understand this using human cell models in the laboratory. We use special stem cells called induced pluripotent stem cells (iPSCs), which can be turned into many different cell types, including brain cells. We have created cell lines where the GNB1 gene is removed, as well as cell lines where patient-like mutations are introduced. This allows us to compare healthy cells, cells missing the gene, and cells carrying disease-causing mutations.

We guide these cells to develop into early brain cells (neural progenitor cells) and more mature brain cells (cortical neurons). This helps us study how changes in GNB1 affect brain development and how brain cells communicate. We will also test whether restoring normal GNB1 can improve cell function. This may help determine whether future treatments could work by increasing healthy GNB1 levels. Overall, this project aims to understand how GNB1 mutations lead to disease and to support the development of targeted therapies for affected individuals and families.

A novel mouse model of GNAO1 disorder for therapeutic development

Gloria Brunori, PhD
University of Miami, USA

Bio: Gloria Brunori, PhD, is an Assistant Scientist in the Martemyanov Lab at the University of Miami. Her research focuses on how G protein signaling regulates brain function and how its disruption leads to neurological disorders. Using genetic tools and animal models, she studies the molecular and circuit-level mechanisms underlying disorders associated with G protein dysfunction, with a particular interest in movement and neurodevelopmental phenotypes. Through this work, she aims to uncover fundamental principles of neuronal signaling and identify potential avenues for therapeutic intervention in neurological conditions.

Lay Summary: GNAO1 disorder causes a range of neurological symptoms, including involuntary movements, developmental delay, and seizures, but it is still not well understood how mutations in the GNAO1 gene affect specific brain circuits to produce these diverse features. In this study, we used an innovative preclinical mouse model carrying the severe GNAO1 G203R mutation to examine its impact on neural circuits, identifying brain regions involved in movement abnormalities and seizures and revealing insight into the circuit-level basis of the disorder. Importantly, we found that caffeine can improve movement-related symptoms in the mouse model. Together, these findings help clarify how GNAO1 dysfunction affects the brain and support the development of more targeted therapies for individuals with GNAO1-related conditions.

Novel insights into the GNAO1-related disorder through hiPSC-based modelling

Harald Mikkers, PhD
Leiden University Medical Center, Netherlands

Bio: Dr. Harald Mikkers is a molecular stem cell biologist at the Leiden University Medical Center, Leiden, the Netherlands, where he holds a position as assistant professor in the department of cell and chemical biology. He received his PhD training at the Netherlands Cancer Institute, Amsterdam, the Netherlands. During his post-doctoral fellow period at the Karolinska Institute, Stockholm, Sweden he got into neurobiology related research. He was one of the first researchers that used the induced pluripotent stem cell (iPSC) technology. He co-founded the human iPSC core facility at the LUMC, which he headed until 2020. His research group has used hiPSCs to model multiple monogenic disorders to understand the disease underlying mechanisms and study therapeutic interventions. Since 2020 his research, supported by different GNAO1-patient organizations, has focused on the GNAO1-related disorder.

Lay Summary: Our GNAO1-related disorder research exp patient-derived induced pluripotent stem cells (iPSCs) to study the (variant)-specific mechanisms underlying the disorder These pluripotent stem cells, which were derived from the skin cells from the patients, can be matured into the cell types that we think lie at the root of the disorder. In this way we try to mimic parts of the clinical phenotype in a Petri dish. We have generated iPSCs from patients with the GNAO1 p.R209H variant, which predominantly leads to a movement disorder, and p.K278del and p.S229R variants, which are associated with early onset seizures as well as involuntary movements. From these iPSCs we generated neurons of the outer part of the brain, that drive high-level cognitive functions and regulate behavioral responses. The neurons with a pathogenic GNAO1 variant have a different morphology, and their activity (communication with other neurons) is also aberrant. Neurons from movement disorder patients have a different activity when compared to neurons from patients with early onset epilepsy. In addition, anti-epileptic drugs restore the defective communication of p.K278del neurons indicating the feasibility of drug screening for the GNAO1-related disorder using these iPSC-derived neurons.

Mapping Signaling Network Dysregulation in Clinical GNAO1 Mutations

William Grant Ludlam, PhD
University of Miami, USA

Bio: William Grant Ludlam received his PhD in Biochemistry from Brigham Young University. He worked with Dr. Barry Willardson to study the synthesis and folding mechanisms of G proteins variants. He is currently working as a postdoctoral researcher with Dr. Kirill Martemyanov at the University of Miami. His research has focused on understanding the pathogenic signaling mechanisms of GNAO1 variants.

Lay Summary: The gene GNAO1 encodes for the G Protein Gαo subunit. Mutations in this protein cause developmental and epileptic encephalopathy 17 (OMIM#615473) and neurodevelopmental disorder with involuntary movements (OMIM#617493), diseases characterized by developmental motor delay, intellectual disability, and epilepsy. Although Gαo is the most abundant Gα subunit expressed in the brain, there is very little consensus as to what physiological function it actually performs. To better understand the roles Gαo plays, we biochemically analyzed the ability of several Gαo mutations to perform a variety of cellular functions. Surprisingly we found that of the functions measured, the ability of the mutations to form stable G protein heterotrimers under unstimulated conditions was the most correlated with clinically severe cases. This suggests that sequestering free Gβγ is the most clinically relevant function of Gαo and that future therapies could aim to reduce this pool of free Gβγ.

Altered Dendritic Structure and Function in a Mouse Model of GNB1 Encephalopathy

Dr. Samuel Gritz, PhD
Rutgers University, USA

Bio: Sam Gritz is a neurophysiologist specializing in neurodevelopmental disorders. He holds a B.S. in Neuroscience and recently earned his Ph.D. from Rutgers University. Sam's research uniquely combines advanced computational modeling—specifically studying the specialized brain cells that encode our sense of space and memory—with hands-on experimental techniques to investigate the root causes of *GNB1* encephalopathy. By understanding how genetic changes alter both individual brain cells and overall behavior, his goal is to bridge the gap between basic bench research and clear, viable therapeutic targets for patients.

Lay Summary: *GNB1* encephalopathy (*GNB1*-E) causes epilepsy and developmental challenges, but standard seizure medications often fall short because they don't target the root of the disease. By studying mice with the specific *GNB1* I80T mutation, we discovered that this genetic change physically alters brain cells—leaving them with fewer "receiving branches" (dendrites) that are dangerously overactive. We found that this hyperexcitability occurs because a crucial internal cellular "brake"— the GIRK potassium channel—fails to engage properly. Excitingly, when we applied a specific drug (ML297) designed to manually activate these GIRK channels, we successfully calmed the hyperactive brain cells back to normal levels. This research directly links the physical symptoms of *GNB1*-E to a specific cellular breakdown, offering hope by identifying a clear, druggable target for future precision therapies.

A silence & repair gene therapy strategy to treat a hybrid mouse model of GNB1 Encephalopathy

Anna Behr, MEng, PhD Candidate
Vall d'Hebron Institute of Research (VHIR)/ Universitat Autònoma de Barcelona, Spain

Bio: Anna Behr, MEng, is a predoctoral researcher working at the Vall d'Hebron Research Institute (VHIR) and the Autonomous University of Barcelona (UAB), Spain, within the Gene Therapy for the Central Nervous System (GT4CNS) research group, led by Dr. Miguel Chillón Rodriguez.

After graduating in 2023 with an engineering degree in biotechnology and a master's degree in synthetic biology from the University of Strasbourg, France, Anna specialised in gene therapy for the central nervous system. She first worked at the Bertarelli Gene Therapy Platform of the Swiss Federal Institute of Technology in Lausanne (EPFL), Switzerland, where she conducted a study under the supervision of Dr. Bernard Schneider on the development of a gene therapy for ALS targeting the

neuroinflammation. Aside, she also contributed to the design of another gene therapy for the rare neurodevelopmental disease SLC6A1.

In 2024, she joined Dr. Chillon's team to pursue her career with a PhD, focusing entirely on developing a gene therapy strategy for GNB1 Encephalopathy. There, she developed and characterized both an in vivo mouse model and an in vitro iPSCs-derived model for the disease, using these to test the efficacy and safety of the strategy. Collaborating with researchers worldwide, particularly with Dr. Nathan Dascal who also works on GNB1, she actively participates in the scientific meetings of the GNB1 Advocacy Group, Asociación GNB1 España y Fundación Gen Rebelde.

Lay summary: This talk will outline the gene therapy strategy developed and currently being tested by the GT4CNS research group led by Dr. Miguel Chillón in Barcelona. It will first detail the design of the strategy, including the key components and the validation tests that led to our therapeutic candidate. Next, it will introduce on a new mouse model that recapitulates both the epileptic and behavioural phenotypes observed in patients with GNB1 Encephalopathy, such as cognitive impairments and visual deficits. Finally, the talk will present the latest biosafety results for our therapeutic candidate in this mouse model.

2nd generation AAV gene therapy for GNAO1 deficiency

Miguel Sena-Esteves, PhD
UMass Chan Medical School, USA

Bio: Miguel Sena-Esteves, PhD, is a Principal Investigator at the University of Massachusetts Chan Medical School, where he leads a laboratory in the Department of Genetics and Genome Sciences focused on developing AAV gene therapies for rare neurological diseases in children. Broadly, Dr. Sena-Esteves develops and translates gene therapy approaches from preclinical studies through IND-enabling work and into clinical trials. He also leads the UMass Chan Translational Institute for Molecular Therapeutics (TiMT), which aims to reduce the cost and complexity of gene therapy development so that treatments can reach children with rare diseases more quickly. His laboratory collaborates closely with patient advocacy communities, recognizing families as essential partners in advancing therapies from bench to bedside.

Abstract: GNAO1 mutations cause severe childhood epilepsy and movement disorders, and no curative treatment currently exists. Because these mutations act dominantly and complete loss of the GNAO1 protein is harmful, our gene therapy strategy must both silence the mutant gene and restore normal protein expression. To achieve potent gene delivery to the brain, we are using a next-generation AAV capsid—AAV-CapX—that crosses the blood-brain barrier 40–50 times more efficiently than the AAV9 vectors used in currently approved neurological gene therapies. We have engineered a series of AAV-CapX-GNAO1 vectors with distinct regulatory elements to drive safe and appropriate levels of GNAO1 expression in the brain, and we are testing them in a mouse model. Our initial results show that the choice of regulatory element profoundly affects safety outcomes, with some configurations causing adverse effects and others enabling survival to the study endpoint, guiding us toward a lead candidate vector.

Pre-clinical development of a CRISPR-mediated gene therapy for GNAO1 Encephalopathy using patient stem cells and a mouse model

Pardis Kazemian, PhD Candidate
University of British Columbia, Canada

Bio: Pardis Kazemian, is a PhD candidate in the laboratory of Dr. Blair R. Leavitt at the University of British Columbia. Her research focuses on developing CRISPR-based gene therapies for neurological disorders, including GNAO1. The Leavitt Lab is dedicated to studying neurological disorders and advancing treatments through translational research. The lab works closely with patients, families, academic collaborators, and industry partners to accelerate therapeutic development.

Lay Summary: GNAO1 encephalopathy is a rare neurological disorder caused by disease-causing mutations in the GNAO1 gene. It can result in a range of symptoms, including involuntary movements, developmental delay, epilepsy, and other neurological challenges. Currently, there is no cure for this disorder.

Our research team is developing a personalized gene therapy for a common GNAO1 mutation known as R209H. This approach uses CRISPR, a gene-editing technology designed to precisely correct the underlying genetic change. We are using lipid nanoparticles (LNPs) to deliver CRISPR into cells. Similar LNP-based technologies have already been successfully used in approved genetic therapies and vaccines. We are testing our gene therapy strategy in several study models, including patient stem cells made into neurons and neurons from a mouse model carrying the R209H mutation. So far, we have successfully corrected the mutation in early neural cells. We have also identified changes in how R209H-affected neurons grow, providing an important way to measure whether gene correction improves cell function. At the same time, we are improving our editing efficiency in neurons and investigating additional ways in which R209H affects these cells, which we will use to measure the effects of our gene therapy.

The final phase of our research will evaluate the therapy in the R209H mouse model through direct delivery to the brain. Through close collaboration with patient families, patient-led organizations, academic researchers, and industry partners, we aim to establish the foundation for a future personalized treatment for individuals living with GNAO1 encephalopathy.

Non-Viral Delivery of CRISPR Gene Therapy for Brain Diseases

Dr. Blair R. Leavitt MDCM, FRCPC (Neurology)
University of British Columbia and Incisive Genetics Inc, Canada

Bio: Dr. Blair R. Leavitt is a neurologist, clinician-scientist, and professor at the University of British Columbia. His research focuses on understanding neurodevelopmental and neurodegenerative disorders, as well as translating innovative discoveries and gene therapies into treatments for patients. He is actively involved in clinical trials evaluating new treatments and helping bring promising therapies from the lab into patient care. Dr. Leavitt is also the Founder and Chief Executive Officer of Incisive Genetics Inc., where he leads the development of gene therapies and lipid nanoparticle delivery technologies for targeting neurological diseases in the brain.

Lay Summary: The team at Incisive Genetics (IG) have developed a delivery system that can carry CRISPR gene editing treatments into brain cells allowing precise correction of faulty genes. This delivery system will be combined with a neurosurgical delivery, the Neurochase infusion system, which enables less invasive delivery to the brain and allows gene editing to be administered in several doses to increase the safety and tolerability of these therapies.

I will present data from IG's Huntington disease program to demonstrate how a similar approach might work for other brain diseases such as GNAO1 Encephalopathy. IG uses lipid nanoparticle (LNP) formulations that efficiently deliver active CRISPR complexes to brain cells. We show that LNP-based genome editing enables rapid, transient and safe correction of gene mutations that is highly efficient in human patient stem cell derived brain cells in a dish. I will also show the results of studies in mice, non-human primates and sheep.
In combination with the work presented by my colleague, Pardis Kasemian, this approach will enable the delivery of CRISPR gene editing treatments that may potentially correct the disease-causing gene mutations that cause GNAO1 Encephalopathy.

Beyond Canonical Gi/o Signalling: New Mechanisms in GNAO1-Related Neurological Disease

Taanisha Gupta, PhD Candidate
Charité – Universitätsmedizin Berlin, Germany

Bio: Taanisha Gupta is a PhD candidate at Charité – Universitätsmedizin Berlin under the supervision of Sarah Shoichet, with a background in neuroscience. Her research focuses on understanding how genetic changes shape brain function, with a particular interest in rare genetic disorders and the development of improved treatments. Outside of research, she is an avid reader and enjoys traveling to explore new cultures and perspectives, experiences that continue to inspire her work and scientific curiosity.

Lay Summary: Pathogenic variants in GNAO1, encoding the Gαo subunit of heterotrimeric Go proteins, cause a severe neurodevelopmental disorder characterized by early-onset epilepsy and/or hyperkinetic movement disorders. We recently identified a biochemical interaction between wild-type GNAO1 and the small GTPase HRas, and we have demonstrated that GNAO1 can enhance Ras–MAPK signalling in a cell-based assay. Defective Ras-MAPK signaling has been linked – via human genetic studies – to severe neurodevelopmental seizure disorders; Ras signaling is also recognized for its importance in the regulation of synaptic transmission and plasticity. This previously unrecognized convergence of signaling cascades suggests that GNAO1 may link GPCR activity to Ras-dependent pathways that regulate neuronal excitability and network development, thereby providing potential mechanistic data that is relevant for patients with GNAO1 defects.

Receptor internalization dynamics are influenced by mutations in G alpha o

Jacob B. Rowe, PhD
University of Miami Miller School of Medicine, USA

Bio: Jacob B. Rowe is a Postdoctoral Fellow in the Department of Physiology & Biophysics at the University of Miami Miller School of Medicine. His primary research focuses on identifying genetic regulatory mechanisms that influence GPCR neuropharmacology. Prior to this appointment, Dr. Rowe performed research in several different areas, including biophysical chemistry, pharmacology, genetics, and synthetic biology. He hopes to use this diverse background in the near future to start his own interdisciplinary research lab further exploring GPCR biology.

Lay summary: The brain operates as a cellular team, where individual teammates, or brain cells, perform defined tasks and work together to accomplish broader goals. To achieve such physiological teamwork, special cellular proteins are used for individual task completion and cell-to-cell communication. One important protein involved is Gao, as small mutational changes in this single protein cause larger deficits

in brain development and function. However, for medical treatment, a better understanding of the cellular changes resulting from these mutations is needed. Towards this goal, some research efforts have characterized processes downstream of Gao – the tasks of individual cells. Here, we take an alternate "communication is key" approach and investigate how Gao mutations influence cellular communication machinery. We focus on a specific protein class, G protein-coupled receptors (GPCRs), that reside at the cell periphery and receive inputs from neighbors. Once a message has been received, cells regulate communication by removing GPCRs from the surface. This regulated communication is critical for proper brain function. Using a diverse panel of clinical variants, we investigate how changes in Gao influence the regulated localization of GPCRs. Our results reveal a broad range of effects, where some mutations prevent removal of GPCRs from the surface while others enhance it. Furthermore, we explore the discrete Gao properties that guide these receptor localization decisions. Our results suggest that mutations in Gao may be disrupting the larger cellular communication network by altering GPCR localization dynamics.

GNAO1 Disorder and Regulators of G-protein Signaling

Henrik G. Dohlman, PhD
University of North Carolina at Chapel Hill, USA

Bio: Henrik Dohlman is a Professor and Chair of Pharmacology at the University of North Carolina, where he conducts discovery driven research on G proteins. Dohlman earned his PhD with Nobel laureate Robert Lefkowitz, and contributed to the first sequencing of a G protein-coupled neurotransmitter receptor. He has advanced understanding of G protein signaling and desensitization, with discoveries that have opened new avenues for drug development, including the identification of RGS proteins. While neurotransmitter receptors activate G proteins, RGS proteins act as molecular brakes, inactivating G proteins by accelerating their catalytic activity. This established a new paradigm for how cells desensitize to persistent stimuli, with direct implications for understanding drug tolerance and addiction. His current research investigates how genetic variants linked to epileptic encephalopathies alter the cell's response to neurotransmitters and drugs.

Lay Summary: Heterotrimeric G proteins are transducers for a variety of neurotransmitter receptors. In a screen of disease-linked mutations in Gnao1, we identified a subset that had no obvious biochemical defects, warranting further investigation. By structural modeling, protein-protein binding experiments in vitro and in cells, as well as measures of downstream ion channel electrophysiology, we identified a subset that impair interactions with Regulator of G protein Signaling (RGS) proteins. RGS proteins accelerate G protein GTPase activity and are therefore critical for proper neurotransmitter signaling. Synthesis of clinical data revealed that patients harboring these variants have comparatively mild symptoms. Our analysis demonstrates the importance of RGS regulation in G protein function, cell signaling, and human neurobiology.