GRI Genes Roundtable Summary

September 9, 2021

CureGRIN

Funding Research for GRIN Disorder

CureGRIN Foundation hosted our eighth GRI Genes Roundtable on September 9, 2021. Our goal is to **promote collaboration so that we can accelerate the path to treatments and cures for GRI Disorders.**

We brought together researchers and clinicians studying GRI Disorders, GRIN genes, GRIA genes, GRIK genes, NMDA receptors, and other ionotropic receptors (AMPARs, kainate receptors, and delta receptors) to discuss and exchange ideas. There were 43 participants present for the meeting.

We asked Madison Wentland to share her family story about her son with a variant in GRIN2D. A panel of four researchers presented their work on NMDAR functioning and GRIA3 variants. Additionally, Dr. Dennis Lal presented a demo of the GRIN Portal and Keith McArthur (CureGRIN, CEO/Head of Science) unveiled the new GRI Connect platform. This document summarizes these presentations.

Presentation Summaries: Family Story

- Madison Wentland
  - Mom to son, Jude, with a variant in GRIN2D (c.2043 G-A, p.M681L)
    - Received autism diagnosis at 18 months
    - GRIN2D diagnosis at 22 months
    - Symptoms: global developmental delay, feeding/swallowing difficulties, reflux, fussiness, epilepsy, sleep issues, cortical visual impairment, disordered movements, nonverbal
    - Medications: mirtazapine, Neudexta, baclofen, gabapentin, CBD and THC
    - Ketogenic diet for epilepsy

Presentation Summaries

Katheron Intson, PhD Candidate (Ramsey Lab), University of Toronto, Canada

- NMDA receptors beyond the neuron
  - NMDARs in microglia, endothelial cells, and astrocytes
    - Impaired vasodilation contributes to lower levels of nutrients.
    - NMDARs play diverse roles in the CNS and beyond.

Dr. Vasanthi Jayaraman, University of Texas Health Science Center at Houston, United States

- Glutamate receptors from single molecule to synapses
  - Dr. Jayaraman described her lab's work on single molecule fluorescence in ionotropic glutamate receptors.
    - Dr. Jayaraman discussed how a variant in the agonist binding domain in GRIN1 was LOF at the glutamate binding site.
    - They use fluorescence resonance energy transfer (FRET) as a molecular ruler to study transfer kinetics and dynamics.

Dr. Lonnie Wollmuth, Stony Brook University, United States

- An integrated approach to evaluate the functional effects of disease-associated NMDAR variants
  - Dr. Wollmuth described how his lab is working to characterize NMDAR variants with a limited number of measurements, generate consolidated parameters for LOF and GOF, and normalize parameters with pharmacology.
    - They are currently using assays for ion channel gating, voltage dependence of Mg^{2+} block, and Ca^{2+} influx to normalize with PAMs or NAMs for their measurements.
    - They are currently assessing GRIN1 and GRIN2A variants.

Dr. Yun Stone Shi, Nanjing University, China

- Dysfunction of GLUA3 promotes aggressive behavior in humans
  - GRIA3 is associated with aggressive behaviors in mice
    - Social dominance and impulsive behavior in $Gria3^{Y/-}$ mice
  - Found that variants in GRIA3 (G630R and E787G) are associated with aggressive outbursts and self-injuries.

Presentation Summaries: Demos

Dr. Dennis Lal, Cleveland Clinic, United States

- GRIN Portal
  - The GRIN Portal was developed by an international team of researchers and clinicians including Dr. Johannes Lemke (University of Leipzig, Germany), Dr. Tim Benke (University of Colorado Denver, United States), Dr. Steve Traynelis (Emory University, United States), and Dr. Lal.
  - Dr. Lal described that detailed clinical and variant knowledge are needed to optimize clinical care.
  - The goals of the GRIN Portal are to provide information on GRIN-related disorders, support research, facilitate registry recruitment, provide support for variant classification and analysis, and visualize data.
  - **To learn more about the GRIN Portal visit:** http://grin-portal.broadinstitute.org

Keith McArthur, CureGRIN, CEO/Head of Science

- GRI Connect and forums
  - GRI Connect is a new social network for all members of the GRI Community – families, researchers and clinicians.
  - Families can learn more about their child's disease, find families with the same variant, and connect with people in different languages. Researchers can learn about the latest research as well as grant and collaboration opportunities. Clinicians can learn more about GRI Disorder symptoms and possible treatment options.
  - **Register today at GRIConnect.community!**

GRIN, GRIA, GRIK, and GRID

GRI CONNECT

Online community connecting GRI families, researchers and physicians

Register today at GRIConnect.community!

- Check out our ***Connect to Win* contest** throughout the month of October.
- We will be hosting a special **Ask Me Anything** event in GRI Connect on **Friday, October 22**.
    - If you are a researcher or clinician who would like to participate in answering questions, please email Meagan Collins (Research Coordinator) at meagan@curegrin.org.

At our next meeting, researchers who have recently joined the Roundtable will present their work, and researchers who have previously presented will provide research updates.

Our next GRI Genes Research Roundtable is scheduled for:
Thursday, October 21, 2021

If you are a GRIN, GRIA, GRIK or GRID genes researcher or clinician, please reach out to meagan@curegrin.org to be added to the next meeting invitation.