GRI Genes Roundtable Summary

July 8, 2021

CureGRIN

Funding Research for GRIN Disorder

CureGRIN Foundation hosted our seventh GRI Genes Roundtable on July 8. 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 on GRIN, GRIA, and GRIK variants. There were 50 participants present for the meeting.

Keith McArthur (CureGRIN, CEO/Head of Science) unveiled the new name of the meeting, the GRI Genes Roundtable. We asked Heather Cartwright to share her family story about her son with a variant in GRIA4. Additionally, a panel of seven researchers presented on their work on GRIN, GRIA, and GRIK gene variants. Following the presentations, we also had time for a few questions for the panelists. This document summarizes these presentations.

Presentation Summaries: Family Story

- Heather Cartwright
  - Mom to son, Maximillian, with a variant in GRIA4
    - Family currently lives in Germany.
    - Received epilepsy diagnosis in 2013.
    - GRIA4 variant (p.A644V) GOF found in 2016.
    - Symptoms: epilepsy (last seizure in 2016), intellectual disability, balance and coordination issues, mostly non-verbal, behavioral issues, requires assistance with daily tasks
    - Currently taking sodium valproate for seizures, tried perampanel for 8 months (no change in Bayley test plus behavioral issues at a higher dose). In the process of reducing perampanel to eventually stop taking it.

Presentation Summaries

Dr. Shai Berlin, Technion-Israel Institute of Technology, Israel

- Two de novo GluN2B mutations affect multiple NMDAR-functions and instigate severe pediatric encephalopathy
    - Dr. Berlin discussed his lab's new publication on two novel LoF GRIN2B variants (p.G689C/S) in patients
        - These variants are located in the ligand binding domain.
        - The receptors were expressed in oocytes, and they found large shifts in affinity.
        - There was no potentiation response to spermine or D-serine.

Dr. Allan Bayat, Filadelfia Epilepsy Hospital, Denmark

- X-linked neonatal-onset epileptic encephalopathy associated with a gain-of-function variant p.R660T in GRIA3
    - Dr. Bayat discussed their group's new publication on a GRIA3 variant.
        - He noted how most disease-causing GRIA3 variants have been reported in males with X-linked ID and epilepsy. He noted that there have been two de novo variants found in females although their functional properties were never explored. Their case is the third affected female to be reported and also the first case to show that GRIA3 variants can cause a gain-of-function in AMPAR receptors.
        - The patient is currently 4 years old, has daily myoclonic jerks, bilateral tonic clonic seizures several times per week, and is treatment resistant.
        - The variant identified is located in the linker between the third transmembrane domain (M3) and the S2 extracellular domain.
        - Functional patchclamp testing showed that the GRIA3 variant detected in the subject caused a gain-of-function in AMPAR receptors.

Dr. Andrew Penn, University of Sussex, United Kingdom

- Synapse dysfunction arising from GRIN2 mutations
    - Dr. Penn described how his lab is working to evaluate GRIN mutations effects by molecular replacement in CA1 neurons.
        - They found that GOF and LOF mutants cause similar defects in synaptic transmission, but mutations in GRIN2A and GRIN2B have opposite effects.
        - They also found that the changes in synaptic transmission by GRIN2 mutations are sufficient to modify neuronal firing during bursts of synaptic activity.

Presentation Summaries

Dr. Ian Coombs, University College London, United Kingdom

- GRIA disorder: Gain-of-function mutations at the Lurcher site
  - Dr. Coombs discussed his lab's latest work on GRIA2 A643V
    - They applied glutamate to outside-out patches from HEK293 cells transfected with GluA2(Q) A643V homomers.
    - They found that this variant has gain-of-function properties.
    - The NAM perampanel inhibited GRIA2 A643V, however they found that it is less effective on the variant than GRIA2.
    - Future work will focus on other potential inhibitors of GRIA2 A643V.

Dr. Geoffrey T. Swanson, Department of Pharmacology, Feinberg School of Medicine, Northwestern University, United States

- Clustered mutations in the GRIK2 kainate receptor subunit gene underlie diverse neurodevelopmental disorders
  - Dr. Swanson described his lab's work on GRIK2 variants
    - They have identified six patients with a p.A657T variant, three patients with a p.T660K variant, two patients with a p.T660R variant, and one patient with a p.I668T variant.
    - These variants alter residues in critical functional domains and affect KAR gating.
    - Dr. Swanson contrasted the shared features of patients with different variants.
      - For the patients with the p.A657T variant, they share features of intellectual disability, developmental delay, and do not have seizures, visual, or sensory abnormalities.
      - For the patients with the p.T660K/R variants, they share features of intellectual disability, epilepsy, white matter abnormalities, and are non-verbal.
      - The patient with the p.I668T variant has autism spectrum disorder.

Presentation Summaries

Dr. Tim Benke, University of Colorado, United States

- An Update on disease-associated GRIA variants
    - Dr. Benke discussed new data from Dr. Hongjie Yuan (Emory University) and Dr. Steve Traynelis (Emory University)
        - Dr. Benke highlighted that GRIA variants are associated with intellectual disability, epilepsy, speech/language issues, autism spectrum disorders, and movement disorders.
        - Dr. Yuan and Dr. Traynelis have prepared a manuscript characterizing 52 disease-associated GRIA variants (5 GRIA1, 7 GRIA2, 33 GRIA3, and 7 GRIA4)
            - They found that the GRIA4 variant p.N641D and the GRIA3 variant p.G803E showed enhanced agonist potency. The GRIA4 variant p.R697P and the GRIA3 variant p.F553S showed reduced agonist potency.

Megan Sullivan, PhD student (Lab of Dr. Amy Ramsey), University of Toronto, Canada

- Characterization of the GRIN1 Y647S+/- patient variant mouse model
    - Megan Sullivan described the location of the Y647S+/- variant in the M3 helix of the transmembrane domain of the GluN1 subunit, the patient's phenotype, and the mouse phenotype.
        - The patient is a 30-year-old female who presented with infantile spasms, profound intellectual disability, and limited speech/communication.
        - The mice display seizure activity, travel further, have a hyper-social phenotype, and display less-anxiety-like behavior.

Presentations: Discussion Summary

- A researcher had a question about loss-of-function variants in the GRIA genes.
  - A clinician responded that GRIA loss-of-function variants have been characterized in patients with intellectual disability and developmental delay. He noted that panels and exomes have not been as widely implemented for diagnostics in patients without epilepsy.
  - A researcher noted that the patient with the GRIK2 p.I668T variant has autism spectrum disorder. The researcher mentioned that the GRIK genes are not included on most panels, so more diagnoses may occur in the future.
- A researcher asked about how to promote the inclusion of GRI genes on panels.
  - A clinician noted that the companies that create the gene panels respond well to publications. He also mentioned that there is an access/health care policy issue in the United States.
- A researcher discussed the GRIK variant kinetics.

At our next meeting, a researcher will present on non-neuronal NMDARs, new researchers will present their work, and previous presenters will provide recent updates.

Our next GRIN Genes Research Roundtable is scheduled for:
Thursday, September 9, 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.