GRIN Genes Roundtable Summary

January 21, 2021

CureGRIN

Funding Research for GRIN Disorder

CureGRIN Foundation hosted our fourth GRIN Genes Roundtable on January 21, 2021. Our goal is to **promote collaboration so that we can accelerate the path to treatments and cures for GRIN Disorder.**

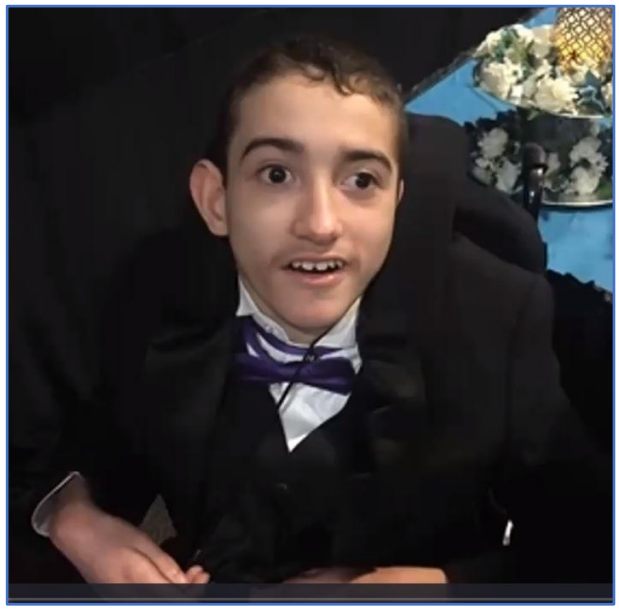
We brought together researchers and clinicians studying GRIN Disorder, GRIN genes, NMDA receptors, and other ionotropic receptors to discuss and exchange ideas on **clinical trials**. There were 55 participants present for the meeting.

We asked Paul Wasielewski to share his family story regarding his son Austin. Additionally, a panel of five researchers and clinicians presented on their work related to GRIN treatments and clinical trials. Following the presentations, we also had an open discussion on this topic. This document summarizes these presentations and the group discussion.

Presentation Summaries: Family Story

Paul Wasielewski (USA)

- Parent to son Austin with a variant in GRIN2A
  - Born May 2003
  - Around 3 months noticed startle behavior
  - First seizure in November 2003
  - Received GRIN2A diagnosis through the Undiagnosed Disease Network at the National Institutes of Health
  - Prescribed Namenda (Memantine)
    - Reduced awake-state seizures, improved sight tracking



Presentation Summaries: Clinical Trials Panel

Dr. Johannes Lemke, University of Leipzig, Germany

- Targeted Treatment Options
  - Dr. Lemke summarized numerous NMDAR drug treatment studies for GRIN2A, GRIN2B, and GRIN2D. Dr. Lemke noted that the replication of beneficial effects of NMDAR drugs is still pending.
  - Dr. Lemke cautioned that when considering possible NMDAR drug treatments, clinicians must make sure that the patient's variant is pathogenic, determine if the variant is GoF/LoF, ensure that there are parameters established to objectively measure the effectiveness of the treatment, and make sure that these treatments are documented and shared with researchers.

Dr. Jurriaan Peters / Dr. Annapurna Poduri, Harvard University, Boston Children's Hospital, United States

- Treatment for a patient with a GRIN2A variant (c.1930A>G, p.Ser644Gly)
  - Dr. Peters follows the patient with a variant in GRIN2A
    - The patient presented at 4 months with delayed development, not tracking, and was hypotonic.
    - Myoclonic seizures developed at 7 months which evolved into infantile spasms.
    - Developmental and epileptic encephalopathy (DEE)
    - Patient is still prescribed memantine treatment.

  - Dr. Poduri stressed the importance of communication across the GRIN community for two very important reasons:
    - Being able to assess the functional consequences of an individual patient's specific variant (which they were able to do through Emory/CFERV).
    - Being able to work together with physicians from the GRIN network (BCH, Colorado, Penn, Emory) to come up with a treatment and monitoring plan that made sense to the group.
  - Dr. Poduri discussed the N=1 treatment of memantine and dextromethorphan offered for this patient.
    - The medications reduced the number of seizures per month.
  - Dr. Poduri mentioned the need for a standard for offering N=1 treatments to patients as well as the importance of establishing a platform.

Presentation Summaries: Clinical Trials Panel

Dr. Xavier Altafaj / Dr. Àngels García-Cazorla , University of Barcelona, Hospital Sant Joan de Déu, Barcelona GRIN Team, Spain

- L-Serine Therapeutic Benefit for GRIN Associated with Hypofunctional NMDARs
  - Dr. Altafaj discussed the pre-clinical studies.
    - Bioinformatic *In silico* studies (in collaboration with Dr. Mireia Olivella) and *in vitro* studies in mammalian cell lines and primary neuronal cultures determined LoF.
    - L-Serine
      - Precursor of D-Serine
      - D-Serine potentiates NMDAR mediated currents
      - L-Serine for GRIN LoF
        - Metabolomics and Lipidomics
        - Pilot study showed that L-Serine nutraceutical treatment improved behavior, motor, and sleep clinical manifestations (epileptiform alterations without seizures persisted on EEG).

- Dr. Àngels García-Cazorla and her team are conducting the first clinical trial for individuals harboring GRIN loss of function variant:
  - Tolerability and Efficacy of L-Serine in Patients With GRIN-related Encephalopathy (https://clinicaltrials.gov/ct2/show/NCT04646447?term=l-serine&draw=2&rank=1)
    - Recruiting 20 patients with a confirmed pathogenic GRIN variant between 2-18 years of age located in Spain and evaluating the therapeutic benefit of dietary supplementation with L-Serine.
    - The primary objectives for the clinical trial are to assess dose tolerability and efficacy of L-Serine treatment.
    - Dosage: start with dose of 250mg/kg/day, increase dose to 500mg/kg/day (if well tolerated)
    - Period of treatment: 12 months
    - Assessments used: Vineland test, Bayley III, Wechsler, Wechsler subscales, Achenbach System of Empirically Based Assessment, Social Communication Questionnaire, Gross Motor Function Measure-66
    - Estimated completion date: May 2022

Clinical Trials Discussion Overview

- Capturing appropriate outcome measures for treatments
  - Neurological assessments, sleep questionnaires, quality of life assessments, etc.
    - Consider floor effects for some patients (i.e., harder to decipher specific measurable improvements)
  - Continuous monitoring systems
  - Follow patients uniformly
    - Registries and natural history studies
- Biomarker profiling
  - Olink Proteomics panels
  - Clinical biomarkers: multi-channel EEG, proteomics, metabolomics, myelination
- Prioritizing NMDAR target medications
  - PAMs
  - NAMs
  - Radiprodil
- Pathway approaches
- Requirements for gold standard clinical trial design
  - 10+ centers
  - 60+ patients
  - Consideration of budgets, variants chosen, parameters studied, etc.

Clinical Trials Discussion Summary

- A parent raised a question about important measures to assess for clinical trials and if there are markers that we have tested in mice that could be tested in GRIN patients.
  - A researcher responded by discussing her lab's exploration of biomarker panels, particularly with panels from Olink Proteomics, and she suggested that researchers and clinicians could possibly assess NMDARs on platelets.
  - A physician-scientist pointed out that her group is starting to do proteomics and metabolomics studies on the CSF of patients. She also highlighted the importance of multi-channel EEGs to assess the patterns of activation of the brain.
  - A parent mentioned that researchers could also assess myelination, and a physician-scientist mentioned that metabolomics oligodendrocyte biomarkers could be helpful in better understanding the effects on myelination.

Clinical Trials Discussion Summary

- A physician-scientist highlighted the main concerns of GRIN Disorder families and discussed that families are interested in treatments to address multiple symptoms. He noted the importance of determining the appropriate outcome measures for treatments. He added that we should also assess sleep and quality of life measures, and he mentioned the need for considering floor effects for some patients as well.
  - Another physician-scientist commented that patients and families may sometimes experience improvements that might not be measurable by the parameters of a particular test.
  - A parent noted that we need to assess long-term effects of treatments as well. She also mentioned the need for GRIN Disorder to be grouped more so by phenotype (instead of by mutation or function) and the need to perform pathway studies.

Clinical Trials Discussion Summary

- A researcher noted that we may need to pursue treatments to address NMDAR function specifically (i.e., PAMs/NAMs).
  - A researcher suggested that Radiprodil could be a potential compound, and he discussed the importance of natural history studies and registries to follow GRIN patients uniformly.
- A researcher asked the group if anyone has experience with continuous monitoring systems to assess seizure activity.
  - A parent pointed out that she will be meeting with a company in Spain that has developed a continuous monitoring device to detect seizures.

Clinical Trials Discussion Summary

- Researchers discussed what would be necessary to establish a gold-standard clinical trial.
  - A physician-scientist said that at least 10 centers would be needed to gather enough patients (at least 60+) to achieve statistical meaning for a clinical trial. He also discussed the importance of managing expectations based on real-world and budgetary concerns. He suggested that we may need to narrow our study population to a particular subset in order to see a statistical signal first.
  - Another physician-scientist noted that a multicentered approach and different trial designs may be necessary.
  - A parent discussed alternative ideas and suggestions for trial designs.

At our next meeting, we will have an open discussion on the topic of GRIN Research Priorities.

Our next GRIN Genes Research Roundtable is scheduled for:
Thursday, March 4, 2021

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