GRIN Genes Roundtable Summary

September 24, 2020

CureGRIN

Funding Research for GRIN Disorder

CureGRIN Foundation hosted our first GRIN Genes Roundtable on September 24, 2020. 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 **share research updates and exchange new ideas.**

The first GRIN Genes Roundtable was an introductory meeting for all participants. We asked researchers to give three-minute presentations on their work. This document summarizes these presentations.

Total Participants

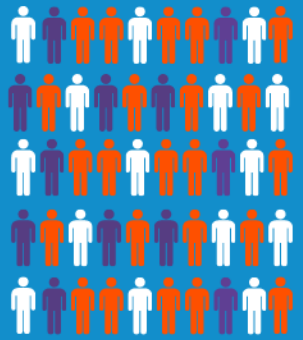
Collaboration

Our goal is to promote collaboration to accelerate the path to therapies and cures for GRIN disorder.

CureGRIN

50

Participants



10

Countries

Presentations from researchers and many more global attendees

19

Researcher and doctor presentations

Next meeting is Thursday, October 29, 2020.

If you are a GRIN / NMDA researcher or clinician, please reach out to keith@curegrin.org to be added.

Presentation Summaries

Dr. Dennis Lal, Cleveland Clinic, United States

- New computational approaches to explore genetic variants on GRIN/NDMA protein structures
    - Dr. Lal's lab is working to build a new software to annotate proteins and create computational/statistical models by mapping and scoring patient variants.

Dr. Karen Avraham, Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University, Israel

- GRIN2D: Updates from Israel
    - Dr. Avraham and Dr. Moran Rubinstein's labs are working to study cell lines in GRIN1 and GRIN2D, perform functional testing, and study a CRISPR genome-edited mouse model.
    - Dr. Avraham and Dr. Rubinstein's labs are also assessing drug identification and repurposing for GRIN2D.
    - Dr. Avraham and Dr. Rubinstein have a new partnership with Dr. Wayne Frankel at Columbia University, funded by the US-Israel Binational Science Foundation.

Dr. Johannes Lemke / Dr. Ilona Krey, University of Leipzig, Germany

- How to Enter the GRIN Online Registry
    - Dr. Lemke's lab is working to develop and conduct patient registries to capture genetic variants, clinical/family history, and epilepsy features.
    - Details regarding the patient registry can be found here: https://www.uniklinikum-leipzig.de/einrichtungen/humangenetik/forschung/grin
    - Dr. Lemke and Dr. Tim Benke are collecting the same data from geographically different regions and will merge data in the end.
    - Dr. Lemke is a member of the CureGRIN Scientific Advisory Board.

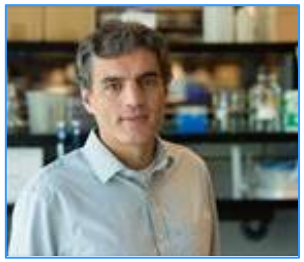
Presentation Summaries

Dr. Maura Ruzhnikov, Director Neurogenomics Clinic, Stanford University, United States

- Stanford Neurogenomics and Epilepsy Genetics Clinics
    - Dr. Ruzhnikov's clinic is working to provide diagnostic and ongoing care, as well as capturing information for natural history studies of rare and ultra-rare disorders.
    - Dr. Ruzhnikov's clinic is also focused on developing collaborations to provide variant interpretation, functional analyses, and customized therapeutics for patients.

Dr. Michael Salter, Hospital for Sick Children, University of Toronto, Canada

- GRIN1 splicing and NMDAR regulation
    - Dr. Salter's lab is working to assess long-term potentiation and learning and memory in GRIN1 mouse models with alternative splicing (GluN1a and GluN1b) and IPSC-derived neurons.



Dr. Jorge J. Palop, University of California, San Francisco, United States

- Targeting Oscillations by Enhancing GluN2A-containing NMDA Receptor Activity Improves Network and Cognitive Functions in Dravet Syndrome and Alzheimer’s Disease Models
    - Dr. Palop's lab is working to assess the pathophysiology of neuronal circuits in neurological disorders with increased hypersynchrony (*in vivo*).

Presentation Summaries

Dr. Shujia Zhu, Institute of Neuroscience, Chinese Academy of Sciences, China

- To reveal the structure-and-function relationship of distinct NMDA receptor subtypes.
  - Dr. Zhu's lab is working to educidate high-resolution structures of human NMDA receptors using cryo-EM.
  - Dr. Zhu's lab is also screening subtype-specific pharmacology and working on the autoimmune encephalitis.

Dr. Tim Benke, Children's Hospital of Colorado, University of Colorado, United States

- GRIN Registry Updates
  - Dr. Benke's lab is working on collecting information on patients with variants in GRIN, GRIK, GRID and other related proteins in their ongoing patient registry (The GRIN Registry).
  - Dr. Benke is a member of the CureGRIN Scientific Advisory Board.

Dr. Lonnie P. Wollmuth, Stony Brook University, United States

- Zebrafish as a model organism to studying NMDA receptor disease associated variants
  - Dr. Wollmuth's lab is working in partnership with Dr. Howard Sirotkin's lab to humanize NMDAR signaling in zebrafish and to express NMDAR variants to characterize their effect on development, as well as perform small molecule screenings to reverse deficits.

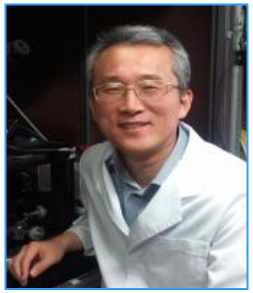
Presentation Summaries

Dr. Katherine Roche, National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), United States

- Synaptic dysfunction in neurodevelopmental disorders: insights from rare variants
  - Dr. Roche's lab is working on GRIN disorders (including rare variants in GRIN2A and GRIN2B) and neuroligins.
  - Dr. Roche's lab is also studying the functional regulation of c-terminal variants which are exclusively LoF.
  - Dr. Roche is a member of the CureGRIN Scientific Advisory Board.

Dr. Amy Ramsey, University of Toronto, Canada

- GRIN1 mouse models to identify biomarkers and therapies
  - Dr. Ramsey's lab is working to characterize 3 mouse models ($GRIN1^{KD}$, $GRIN1^{Y647S}$, $GRIN1^{Q536R}$).
  - Dr. Ramsey's lab is studying biomarkers, physiology, simple behaviors, drug therapies, and gene therapies in the mouse lines.
  - Dr. Ramsey is a member of the CureGRIN Scientific Advisory Board.



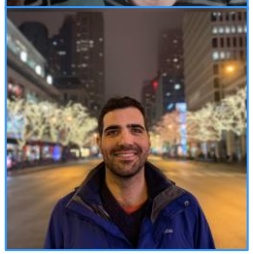
Dr. Eunjoon Kim (presented by Dr. Wangyong Shin), Center for Synaptic Brain Dysfunctions, Institute for Basic Science, Korea

- Improvement of abnormal phenotypes of $GluN2B^{-C456Y}$ mutant mice by early correction
  - Dr. Kim's lab is working to assess and characterize GRIN2B mouse mutants with abnormal fear and sensory hypersensitivity behaviors.

Presentation Summaries

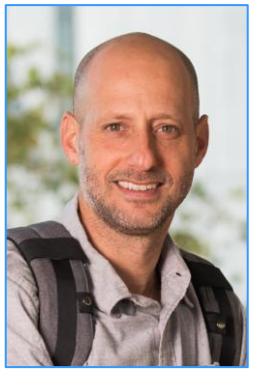
Dr. Derek Bowie, McGill University, Canada

- Are GRIN disorders and Fragile X syndrome linked?
  - Dr. Bowie's lab is working to study Fragile X syndrome in mouse models.
  - Dr. Bowie's lab studied chemical transmission of stellate cells in the cerebellum and observed a hypofunction of the NMDA receptors, with a disruption of circuit homeostasis, and was able to rescue the circuit and behavior in a mouse model with a drug.



Dr. Natalia Colettis / Dr. Luciano Fiore, University of Buenos Aires, *CONICET*, Argentina

- Understanding GRIN2B-Related Neurodevelopmental Disorder from a human brain organoid perspective. Use of flavonoids as a therapeutic approach.
  - Dr. Colettis and Dr. Fiore's labs are working to develop human ES cells with GRIN2B variants to understand their role during development of brain organoids, treat them with flavonoids to modulate GRIN2B related cellular pathways, and perform molecular, cellular, and anatomical analyses by RT-PCR, ISH, and IHQ.



Dr. Gad Vatine, Ben-Gurion University of the Negev, Israel

- Using patient-specific iPSCs to develop disease-in-a-dish models for GRIN-encephalopathies
  - Dr. Vatine's lab is working to develop GRIN1, GRIN2B, and GRIN2D patient-specific iPSC lines, generate brain organoids, assess blood brain barrier (BBB) drug therapies, and study the role of NMDARs in the BBB with BBB-on-chip.

Presentation Summaries

Dr. Graham Collingridge (presented by Dr. John Georgiou), University of Toronto, Canada

- Synapse function in a mouse model of GRIN1^{G620R}
  - Dr. Collingridge's lab is working on studying synaptic plasticity of NMDARs and has developed a GRIN1^{G620R} mouse line which has a reduction in LTP.
  - Dr. Collingridge is a member of the CureGRIN Scientific Advisory Board.

Prof. Alessandra Renieri (presented by Dr. Sara Mannucci), University of Siena, Italy

- Genetic diagnosis and personalized therapy in a GRIN1 mutated patient
  - Prof. Renieri and collaborators followed an 8-year-old patient with psychomotor delay, performed WES and found a variant in GRIN1 assumed to be GoF.
  - Based on this result, Prof. Renieri suggested to the clinician who took charge of the patient to add memantine to anti-epileptic drugs and saw decreased seizure frequency and improved awareness.

Presentation Summaries

Dr. Xavier Altafaj, University of Barcelona, Barcelona GRIN Team, Spain

- From GRIN variants functional stratification to precision therapies
  - Dr. Altafaj's lab has recruited more than 100 GRIN cases, mostly from European families / clinicians.
  - Dr. Altafaj's lab is working on functional annotation/stratification of GRIN variants (upcoming GRINdb webserver, compiling all existing annotations of GRIN variants; in collaboration with Dr. Mireia Olivella), developing animal models, screening natural compounds (nutraceuticals) and FDA drugs' efficacy for the rescue of gain- and loss-of-function GRIN variants.
  - In collaboration with Dr. Àngels García-Cazorla and Dr. Natalia Juliá (Hospital Sant Joan de Déu, Barcelona's Children Hospital), conducting the first clinical trial for individuals harbouring GRIN loss of function variants: recruitment of 30 individuals and evaluation of the therapeutic benefit of a dietary supplementation with L-serine.
  - Dr. Altafaj is a member of the CureGRIN Scientific Advisory Board and, together with Dr. Mireia Olivella, member of the GRIN Variants Curation Expert Panel.

Dr. Maggie Kalev-Zylinska, University of Auckland, New Zealand

- GRIN Effects Beyond the Brain
  - Dr. Kalev's lab is working on NMDAR modulation and characterization of NMDAR effects in platelets and megakaryocytes in the Pf4-driven GRIN1 KO mouse.
  - Dr. Kalev's lab is also studying NMDAR activity in human platelets and megakaryocytes from healthy people and patients with platelet precursor cancers.

Our next GRIN Genes Research Roundtable is scheduled for:

Thursday, October 29, 2020

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