

CureGRIN Research Audit

June 5, 2021



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And many other GRIN families, clinicians and researchers.

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- **Introduction**

In order to better understand the current state of research on the N-methyl-D-aspartate receptors (NMDARs), α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA receptors), and other topics related to the GRI community, we present the following audit, which assesses previous and present research themes and questions that have been published or are currently under investigation. We also highlight the known research laboratories, biotechnology companies, and pharmaceutical companies and demonstrate how their work helps in our search for treatments and therapies.

- **NMDA Receptors**

- **Overview of history of NMDAR research**

- Early studies

- 1960s

- Glutamate and similar acidic amino acids found to excite nerve cells in the vertebrate brain. Synthesis of N-methyl-D-aspartate (NMDA). Used by David Curtis and Jeff Watkins, in Canberra, Australia, to define the NMDA receptor (NMDAR) as a subtype of glutamate receptor. (Watkins, 1962)
 - John Olney showed that glutamate could also be neurotoxic, given rise to the concept of excitotoxicity.

- 1970s

- Jeff Watkins (Bristol, UK) and Hugh McLennan (Vancouver, Canada) synthesized selective NMDAR antagonists, such as D-AP5, and used these to demonstrate with their collaborators that NMDARs contribute to synaptic excitation in the vertebrate central nervous system.
 - Jeff Watkins and Richard Evans discovered that magnesium ions are potent NMDAR antagonist.

- 1980s

- David Lodge (London, UK) discovered that ketamine and phencyclidine are NMDAR antagonists.
 - Graham Collingridge (Vancouver, Canada) showed that NMDARs trigger changes in synapse strength (i.e., long-term potentiation)
 - Richard Morris (St Andrews, UK) showed that NMDARs are important for learning & memory
 - Brain Meldrum (London, UK) discovered that NMDAR could protect against seizures and stroke-induced cell death.
 - Groups in Paris and the USA showed that the magnesium block of NMDARs is highly voltage dependent and that NMDARs have a high permeability to calcium.
 - The glycine co-agonist site was discovered by the Paris team.
 - Activation of NMDARs shown to trigger the formation of nitric oxide in neurons.
 - Single-channel recordings of glutamate receptors (Cull-Candy and Usowicz, 1987; Jahr and Stevens, 1987; Nowak et al., 1984).

- 1990s
 - Between 1989 and 1992, Hollmann and Heineman performed research on the cloning of cDNAs encoding glutamate receptor subunits (Hollmann and Heinemann, 1994).
 - In 1993, Bliss & Collingridge determined that long-term potentiation was generated by activation of NMDARs in the hippocampus (Bliss & Collingridge, 1993).
 - The primary structure and genetics of the NMDAR subunits were identified by cloning, by groups in Japan and Germany.
 - Inhibition of the NMDAR by protons and by Zinc discovered.
 - Ifenprodil found to be a highly selective antagonist for NMDARs containing the GluN2B subunit, heralding the search for subtype selective NMDAR modulators.
 - Endogenous steroids, such as pregnenolone, and endogenous cholesterol found to act as negative and/or positive allosteric modulators (NAMs and PAMs) of the NMDA receptor.
 - Pancreatic islet cells express glutamate receptors which modulate the secretion of insulin (Inagaki et al., 1995; Weaver et al., 1996, 1998).
 - Structural analysis of NMDARs (Armstrong et al., 1998).
- 2000s
 - Memantine (Namenda) licensed for the treatment of Alzheimer's disease. Scientists at Merz (Germany) showed how this low potency NMDA receptor antagonist could slow the decline in cognition in some patients.
 - Discovery of NMDA receptor encephalitis. This autoimmune condition is usually due to antibodies raised against the patient's GluN1 and results in psychosis, memory impairments, seizures and dyskinesias.
- 2010s
 - Structure of the NMDAR determined.
 - (S)-Ketamine licensed for the treatment of depression by Johnson & Johnson

- **GRIN genes**
 - GluN1 is encoded by GRIN1, GluN2A-D are encoded by GRIN2A-D, and GluN3A-B are encoded by GRIN3A-B.
 - NMDARs are heterotetramers comprised of subunits including two GluN1 and typically two GluN2 (or a GluN2 and GluN3 combination) (Monyer et al., 1992; Schorge and Colquhoun, 2003; Ulbrich and Isacoff, 2007, 2008; Traynelis et al., 2010)
 - GluN3 subunits cannot form functional subunits alone. The GluN1/GluN3A and GluN1/GluN3B receptors are activated by agonists binding at the glycine-binding site in the Ligand-Binding-Domain (LBD) (Chatterton et al., 2002; Yao and Mayer, 2006; Traynelis et al., 2010; Kvist et al., 2013; Skrenkova et al., 2019).

Table 1: General Information for GRIN Genes

Symbol	Name	Base Pairs	Protein Name	Amino Acids	Alternate Protein Name	Chromosomal Location
<i>GRIN1</i>	glutamate ionotropic receptor NMDA type subunit 1	4379	GluN1	938	NR1	9q34.3
<i>GRIN2A</i>	glutamate ionotropic receptor NMDA type subunit 2A	14706	GluN2A	1464	NR2A	16p13.2
<i>GRIN2B</i>	glutamate ionotropic receptor NMDA type subunit 2B	30609	GluN2B	1484	NR2B	12p13.1
<i>GRIN2C</i>	glutamate ionotropic receptor NMDA type subunit 2C	4271	GluN2C	1233	NR2C	17q25.1
<i>GRIN2D</i>	glutamate ionotropic receptor NMDA type subunit 2D	5511	GluN2D	1336	NR2D	19q13.33
<i>GRIN3A</i>	glutamate ionotropic receptor NMDA type subunit 3A	7838	GluN3A	1115	NR3A	9q31.1
<i>GRIN3B</i>	glutamate ionotropic receptor NMDA type subunit 3B	3281	GluN3B	1043	NR3B	19p13.3

(Gene group: HUGO Gene Nomenclature Committee. Retrieved October 9, 2020, from <https://www.genenames.org/data/genegroup/>)

- **Identification of Variants**

gnomAD: Approximately 700 variants reported in GRIN genes (absent in healthy population) (Karczewski et al., 2020; Hansen KB, Wollmuth LP, Bowie D, Furukawa H, Menniti FS, Sobolevsky AI, Swanson GT, Swanger SA, Greger IH, Nakagawa T, McBain CJ, Jayaraman V, Low C-M, Dell'Acqua ML, Diamond JS, Perszyk RE, Camp CR, Yuan H, Traynelis SF. Structure, Function, and Pharmacology of Glutamate Receptor Ion Channels. 2020.)

- Types of variants found in GRIN genes reported in gnomAD (Karczewski et al., 2020; Hansen et al., 2020)
 - 76% missense variants
 - 6.9% nonsense variants
 - 8.4% frameshift variants
 - 2.8% splice site variants
 - 6.3% chromosomal translocation, deletion, or inversion variants
- Percentage of variants by gene reported in gnomAD (Karczewski et al., 2020; Hansen et al., 2020)
 - 13% in *GRIN1*
 - 44% in *GRIN2A*
 - 37% in *GRIN2B*
 - 2.8% in *GRIN2C*
 - 3.8% in *GRIN2D*
- **Functional classification of variants**
 - To better understand how disease-associated variants result in a GRIN-disorder phenotype, the function of identified variants have been assessed. This allows for variants to be classified broadly as loss-of-function (LoF) or gain-of-function (GoF).
 - **Center for Functional Evaluation of Rare Variants (CFERV)** (<http://functionalvariants.emory.edu/database/index.html>)
 - Dr. Stephen Traynelis, Emory University
 - Created with support from the National Institute of Neurological Disorders and Stroke (NINDS) and Emory University.
 - Additional support/funding from Simons, CureGRIN, CURE, and Austin's Purpose.
 - Goals:
 - Working to provide functional characterization of all glutamate receptor variants to stratify patients and ultimately understand subgroups for natural history, working closely with a dozen clinical groups to do this.
 - Use this data to correlate specific function and localization with globally accepted HPO clinical terms
 - Working to come up with criteria for formally classifying GRIN variants for the ACMG (the gold standard), as well as create an ontology so that altered ligand gated channel

function can be integrated into NCBI ClinVar as search language fields

- Creating new, free modelling tools for predicting pathogenicity based on structure
- Publishing high quality detailed papers that describe both mechanism underlying phenotype as well as rescue pharmacology
- Creating new mouse models and collaborating with others to use the functional data to decide which mouse models to create
- Provide cDNA tools to investigators world-wide
- **GRIN database (www.grin-database.de)**
 - Dr. Johannes Lemke, University of Leipzig
 - Goal: Provide data on variants and function
- **GRIN variants database (<http://lmc.uab.es/grindb>)**
 - Dr. Mireia Olivella, University of Vic-Central University of Catalonia
 - Dr. Xavier Altafaj, University of Barcelona, Barcelona GRIN Team, Spain
 - Goal: Provide functional annotation/stratification of GRIN variants and compiling all existing annotations of GRIN variants.
- **Descriptive Studies** (classified in research system/tissue where this is assessed):
 - NMDAR studies
 - General biology, Processing, Assembly, Mapping Studies
 - NMDA receptor subunits are encoded by seven genes: the GRIN1 gene encodes GluN1, the GRIN2 genes encode GluN2A-D, and the GRIN3 genes encode GluN3A-B (Traynelis et al., 2010; Hansen et al., 2018).
 - NMDA receptors form a central ion pore by heterotetrameric assemblies of the subunits (Traynelis et al., 2010; Hansen et al., 2018).
 - NMDAR stoichiometry has been shown to consist of two GluN1 subunits which are glycine-binding and two GluN2 subunits which are glutamate-binding (Ulbrich & Isacoff, 2007; Karakas & Furukawa, 2014; Hansen et al., 2018).
 - Excitatory neurotransmission in the central nervous system (CNS) is facilitated mostly through the release of glutamate, resulting in the activation of pre- and postsynaptic G-protein-coupled metabotropic glutamate receptors and ionotropic glutamate receptors (iGluRs) (Traynelis et al., 2010; Hansen et al., 2018).
 - iGluRs are cation channels that are ligand-gated which are comprised of 3 functional classes: the α -amino-3-hydroxy-5-methyl-4-isoxasolepropionic acid (AMPA) receptors, kainate

receptors, and NMDA receptors (Traynelis et al., 2010; Hansen et al., 2018).

- NMDA receptors are different from other glutamate receptors because they involve extracellular Mg^{2+} voltage-dependent blocking, are highly permeable to Ca^{2+} , and require both glutamate and glycine (or d-serine) to bind for the channel to activate (Johnson & Ascher, 1987; Kleckner & Dingledine, 1988; Benveniste & Mayer, 1991; Clements & Westbrook, 1991, 1994; Traynelis et al., 2010; Hansen et al., 2018).
 - NMDAR activation mediates a current which activates with a time course lasting for tens to hundreds of milliseconds (Hestrin et al., 1990; Sah et al., 1990; Trussell et al., 1993; Geiger et al., 1997; Hansen et al., 2018).
 - NMDA receptor current is dependent on membrane potential and synaptic release frequency (Bourne & Nicoll, 1993; Seeburg et al., 1995; Nevian & Sakmann, 2004; Hansen et al., 2018).
 - This results in an increase of intracellular Ca^{2+} which acts as a signal resulting in changes at the postsynaptic neuron, including different alterations in synaptic strength (Lau & Zukin, 2007; Holtmaat & Svoboda, 2009; Traynelis et al., 2010; Higley & Sabatini, 2012; Zorumski & Izumi, 2012; Paoletti et al., 2013; Volianskis et al., 2015; Hansen et al., 2018).
 - NMDARs are upregulated on the cerebrovascular endothelium through oxidative stress which increases the potential for disruption to the blood brain barrier by glutamate (Betzen et al., 2009).
 - GRIN2A KO mice are susceptible to abnormally regulated redox as sub-threshold oxidative stress (Cardis et al., 2018).
 - Activation of extrasynaptic NMDARs results in apoptosis, yet the activity of synaptic NMDARs promotes cell survival (Hardingham and Bading, 2010).
 - NR1 C-terminal domains modulate coupling to downstream signaling pathways (Bradley et al., 2006)
 - In primary hippocampal neurons, downstream of NMDA receptors, MARK/Par1 is activated (Bernard and Zhang, 2015).
- **General Interactome Studies**
 - Protein-protein interactions
 - GRIN1 (The UniProt Consortium UniProt: a worldwide hub of protein knowledge Nucleic Acids Res. 47:D506-515 (2019))
 - Heterotetramer: Forms heterotetrameric channels composed of two zeta subunits (GRIN1), and two epsilon subunits (GRIN2A, GRIN2B, GRIN2C or GRIN2D) (*in vitro*) (Planells-Cases et al., 1993; Volgraf et al., 2016; Hackos et al., 2016; Chen et al., 2017; UniProt, 2019)

- Can form channels with zeta subunit (GRIN1), an epsilon subunit, plus GRIN3A or GRIN3B (*in vitro*).
- *In vivo* subunit composition and expression levels may vary (UniProt, 2019).
- Complex with GRIN2A or GRIN2B, GRIN3A and PPP2CB (By similarity) (UniProt, 2019).
- Complex with GRIN2A or GRIN2B and GRIN3B (By similarity).
- Interacts with SNX27 (via PDZ domain); the interaction is needed for recycling to the plasma membrane when endocytosed and stopping degradation in lysosomes (By similarity) (UniProt, 2019).
- Interacts with DLG4 and MPDZ (UniProt, 2019).
- Interacts with LRFN1 and LRFN2 (By similarity) (UniProt, 2019).
- Interacts with MYZAP (Roginski et al., 2008; UniProt, 2019).
- Complex with DLG4 and PRR7 (By similarity) (UniProt, 2019).
- Complex with GRIN2B and PRR7 (Kravchick et al., 2016; UniProt, 2019).
- GRIN2A (The UniProt Consortium UniProt: a worldwide hub of protein knowledge Nucleic Acids Res. 47:D506-515 (2019))
 - Complex with GRIN1, GRIN3A and PPP2CB (By similarity) (UniProt, 2019).
 - Complex with GRIN1 and GRIN3B (By similarity) (UniProt, 2019).
 - Interacts with AIP1 (By similarity) (UniProt, 2019).
 - Interacts with HIP1 and NETO1 (UniProt, 2019).
 - Interacts with SNX27 (via PDZ domain); the interaction is required for recycling to the plasma membrane when endocytosed and prevent degradation in lysosomes (By similarity) (UniProt, 2019).
 - Interacts with PDZ domains of PATJ and DLG4 (UniProt, 2019).
 - Interacts with LRFN2 (By similarity) (UniProt, 2019).
 - Interacts with RPH3A and DLG4; this ternary complex regulates NMDA receptor composition at postsynaptic membranes (By similarity) (UniProt, 2019).
 - Interacts with SORCS2 (By similarity).
 - Interacts with ARC; preventing oligomerization (By similarity) (UniProt, 2019).
- GRIN2B (The UniProt Consortium UniProt: a worldwide hub of protein knowledge Nucleic Acids Res. 47:D506-515 (2019))
 - Complex with GRIN1 and GRIN3B (UniProt, 2019).

- Complex with GRIN1, GRIN3A and PPP2CB (UniProt, 2019).
- Interacts with PDZ domains of PATJ, DLG3 and DLG4 (UniProt, 2019).
- Interacts with HIP1 and NETO1 (By similarity) (UniProt, 2019).
- Interacts with MAGI3 (Wu et al., 2000; UniProt, 2019).
- Interacts with DAPK1 (By similarity) (UniProt, 2019).
- Complex with GRIN1 and PRR7 (Kravchick et al., 2016; UniProt, 2019).
- Interacts with CAMK2A (Stephenson et al., 2017; UniProt, 2019).
- Interacts with ARC; avoiding ARC oligomerization (By similarity) (UniProt, 2019).
- Interacts with TMEM25 (By similarity) (UniProt, 2019).
- GRIN2C (The UniProt Consortium UniProt: a worldwide hub of protein knowledge Nucleic Acids Res. 47:D506-515 (2019))
 - Interacts with PDZ domains of PATJ and DLG4 (By similarity) (UniProt, 2019).
 - Interacts (via PDZ-binding motif) with SNX27 (via PDZ domain); essential for recycling to the plasma membrane when endocytosed and stopping degradation by lysosomes (Cai et al., 2011; UniProt, 2019).
- GRIN2D (The UniProt Consortium UniProt: a worldwide hub of protein knowledge Nucleic Acids Res. 47:D506-515 (2019))
 - Interacts with PDZ domains of PATJ and DLG4 (By similarity) (UniProt, 2019).
- GRIN3A (The UniProt Consortium UniProt: a worldwide hub of protein knowledge Nucleic Acids Res. 47:D506-515 (2019))
 - Forms channel of a zeta subunit (GRIN1), a epsilon subunit (GRIN2A, GRIN2B, GRIN2C or GRIN2D) and a third subunit (GRIN3A or GRIN3B). Does not establish homomeric channels that are functional (UniProt, 2019).
 - Complex with GRIN1, GRIN2A or GRIN2B and PPP2CB. Possibly interacts with PPP2CB. (By similarity) (UniProt, 2019).
- GRIN3B (The UniProt Consortium UniProt: a worldwide hub of protein knowledge Nucleic Acids Res. 47:D506-515 (2019))
 - Forms channel of a zeta subunit (GRIN1), an epsilon subunit (GRIN2A, GRIN2B, GRIN2C or GRIN2D) and a third subunit (GRIN3A or GRIN3B). Does not establish homomeric channels that are functional (UniProt, 2019).
 - Complex containing GRIN1 and GRIN2A (By similarity) (UniProt, 2019).
- Human Reference Protein Interactome Mapping Project (<http://www.interactome-atlas.org/about/>)

- Luck, K., Kim, DK., Lambourne, L. et al. A reference map of the human binary protein interactome. Nature 580, 402–408 (2020). <https://doi.org/10.1038/s41586-020-2188-x>

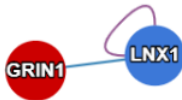
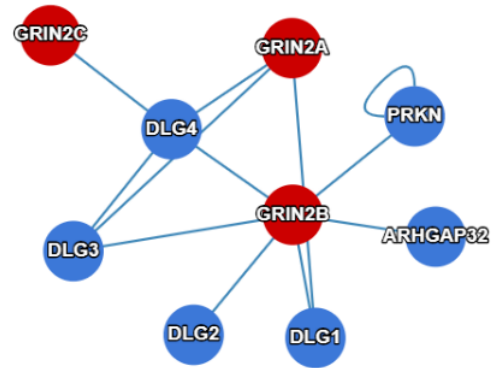


Figure 1: Interactome Map
Generated with Human Reference Protein Interactome Mapping Project
(<http://www.interactome-atlas.org/about/>)

- **Promoters/Enhancers** (Retrieved from Eukaryotic Promoter Database (EPDNew) (Dreos et al., 2014))
 - A promoter region is a DNA sequence which initiates transcription, whereas an enhancer is a DNA sequence that increases the rate of transcription.
 - GRIN1
 - Promoter ID: GRIN1_1 (EPDNew (Dreos et al., 2014))
 - GeneHancer (GH) Identifier: GH09J137139
 - Genomic Location: chr9:137139000-137139231 (GRCh38/hg38); chr9:140033452-140033683 (GRCh37/hg19)
 - Sequence: ggaccggaaccagegccgtccgaggagccgccgccgccggcc CTTTCCAAGCC
 - Promoter ID: TRAF2_2/TRAF2_1 (Gene: *TRAF2*) (EPDNew (Dreos et al., 2014))
 - GeneHancer (GH) Identifier: GH09J136881
 - Genomic Location: chr9:136881316-136888001 (GRCh38/hg38); chr9:139775768-139782453 (GRCh37/hg19)
 - Sequence (TRAF2_2):
ggggactctgccccggagctgcggctgccttctggaacactctgtcAGATGACT
GCA
 - Sequence (TRAF2_1):

agcggcggcggcggcggcggcgttggggcggttagctgggcgggcccttAGTTCC
GGGCG

- Promoter ID: LRRC26_3/LRRC26_2 (Gene *LRRC26*) (EPDNew (Dreos et al., 2014))
 - GeneHancer (GH) Identifier: GH09J137166
 - Genomic Location: chr9:137167600-137170024 (GRCh38/hg38); chr9:140062052-140064476 (GRCh37/hg19)
 - Sequence (LRRC26_3):
gccgcctgcccgtctagacgcgctgcacctgcgcggcaaccctggggCTGCGGGT
GCG
 - Sequence (LRRC26_2):
accgcgtccgtgcgctgccgccaggtgccttcgcgggagcgggcgcgctACAGCGC
CTGG
- Promoter ID: ENTPD2_1 (Gene *ENTPD2*) (EPDNew (Dreos et al., 2014))
 - GeneHancer (GH) Identifier: GH09J137051
 - Genomic Location: chr9:137053400-137056498 (GRCh38/hg38); chr9:139947852-139950950 (GRCh37/hg19)
 - Sequence:
ctcgtcccggggggcccctaccccgggtcccgggccccgcccgcCTCCGCC
TCCG
- GRIN2A
 - Promoter ID: GRIN2A_3, GRIN2A_2, GRIN2A_4, GRIN2A_1 (EPDNew (Dreos et al., 2014))
 - GeneHancer (GH) Identifier: GH16J010180
 - Genomic Location: chr16:10180601-10183401 (GRCh38/hg38); chr16:10274458-10277258 (GRCh37/hg19)
 - Sequence GRIN2A_3:
agccaggggagcgcgctggggccgcagcatgcgggaaccgctaaccGGTGGC
TGCTG
 - Sequence GRIN2A_2:
gttacctctctttctccctacctccctcgcagcagctcccggtcGCACAACTCC
C
 - Sequence GRIN2A_4:
atgggaccgggtgagcgtgagaatcgcgggccgcagccatcagccctggAGATGAC
CAGG
 - Sequence GRIN2A_1:
gccacacgcgagcgcgctcccactcacacacactcgcctcaaacACACCAG
CCCG
- GRIN2B
 - Promoter ID: EMP1_1 (Gene: *EMPI*)
 - GeneHancer (GH) Identifier: GH12J013193
 - Genomic Location: Genomic Location: chr12:13193348-13212836 (GRCh38/hg38); chr12:13346282-13365770 (GRCh37/hg19)
 - Sequence:
tacaccagcagaggaaactataacctcgggagcaggtcctcccctcAGTGCGGT
CAC

- Promoter ID: GRIN2B_3
 - GeneHancer (GH) Identifier: GH12J013967
 - Genomic Location: chr12:13967777-13967836 (GRCh38/hg38); chr12:14120711-14120770 (GRCh37/hg19)
 - Sequence:


```
cacctcccctcatgcctgcaagtttcagctcagggatcctcagctccagGTCTTCCTGT  
C
```
- GRIN2C
 - Promoter ID: GRIN2C_1
 - GeneHancer (GH) Identifier: GH17J074859
 - Genomic Location: chr17:74859800-74860000 (GRCh38/hg38); chr17:72855923-72856123 (GRCh37/hg19)
 - Sequence:


```
gcgtggtgctcagcttggccgccaggaggcgtggcgcggtccccgccGGAGCCG  
CCGC
```
 - Promoter ID: GRIN2C_3
 - GeneHancer (GH) Identifier: GH17J074861
 - Genomic Location: chr17:74861400-74861801 (GRCh38/hg38); chr17:72857523-72857924 (GRCh37/hg19)
 - Sequence:


```
cggagctgagactgagcgcgccagccctccggggccgaggctctgggacAGACACC  
GCGA
```
- GRIN2D
 - Promoter ID: KDEL1_1 (Gene: KDEL1)
 - GeneHancer (GH) Identifier: GH19J048389
 - Genomic Location: chr19:48389414-48394001 (GRCh38/hg38); chr19:48892671-48897258 (GRCh37/hg19)
 - Sequence:

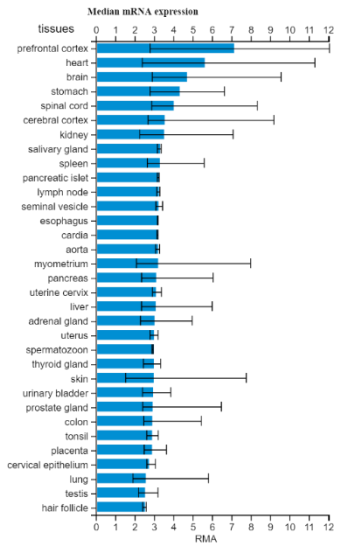
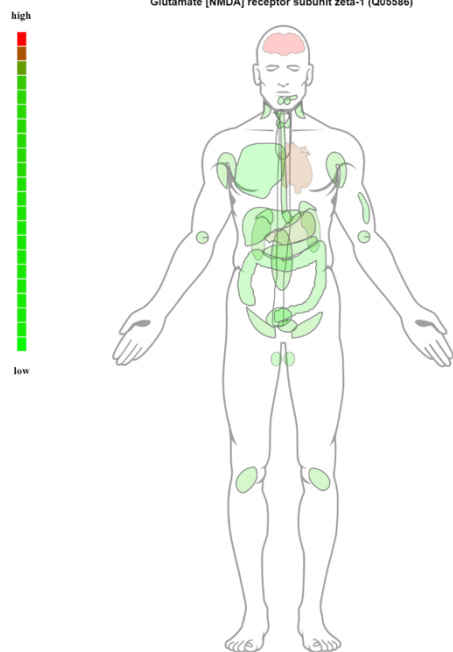
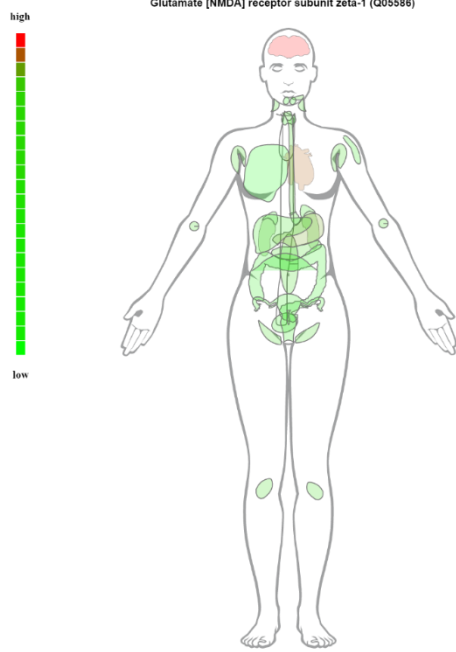

```
ggggcggagcctctctcccggactcctccccctctcgtctctcctCTTCCCGGC  
TC
```
- GRIN3A
 - Promoter ID: GRIN3A_2, GRIN3A_1
 - GeneHancer (GH) Identifier: GH09J101739
 - Genomic Location: chr9:101737807-101738869 (GRCh38/hg38); chr9:104500089-104501151 (GRCh37/hg19)
 - Sequence GRIN3A_2:


```
accgggcgggcagaggatgccaggcggaggacctgggagcgggatctgAGACTG  
CCGGA
```
 - Sequence GRIN3A_1:

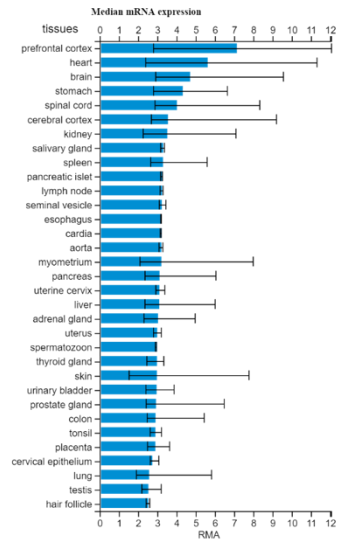

```
gaggcggggagaacttggcgctcggagcagagccacccttctgctggccAGTCGCGT  
TGC
```
- GRIN3B
 - Promoter ID: GPX4_1 (Gene: *GPX4*)
 - GeneHancer (GH) Identifier: GH19J001097
 - Genomic Location: chr19:1097400-1108200 (GRCh38/hg38); chr19:1097399-1108199 (GRCh37/hg19)

- Sequence:
gaggagccgctggctcccagccccgccgcatgagcctcggccgctttGCCGCCTA
CTG
 - Promoter ID: KLF16_1 (Gene: *KLF16*)
 - GeneHancer (GH) Identifier: GH19J001851
 - Genomic Location: chr19:1850200-1866001 (GRCh38/hg38);
chr19:1850199-1866000 (GRCh37/hg19)
 - Sequence:
cggcgccggcgcgcgccggcctcctcctcctcctcctccgctcccgcACTCGAGC
AGC
 - Promoter ID: CSNK1G2_2, CSNK1G2_1 (Gene: *CSNK1G2*)
 - GeneHancer (GH) Identifier: GH19J001939
 - Genomic Location: chr19:1939000-1944801 (GRCh38/hg38);
chr19:1938999-1944800 (GRCh37/hg19)
 - Sequence CSNK1G2_2:
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TCC
 - Sequence CSNK1G2_1:
gcagtggggcgcgctatggctgccgcccccgctggcagacgctggcgccGTAAGGC
GCGC
- **Spatiotemporal expression**
 - GluN1 subunit is ubiquitously expressed (Paoletti et al., 2013; Strehlow et al., 2019).
 - GluN2B and GluN2D subunits are mainly expressed prenatally (Paoletti et al., 2013; Strehlow et al., 2019).
 - GluN2A and GluN2C subunits have low expression prenatally. However, the expression of GluN2A and GluN2C increases postnatally (Bar-Shira et al., 2015; Strehlow et al., 2019).
- **GRIN expression in other tissues (beyond the nervous system)**
 - The genes that are transcribed in an organism are called the transcriptome. The transcriptome connects the genome, the proteome, and the phenotype at the cellular level. Transcriptomics describes the RNA molecules within a cell.
 - Many transcriptomics studies focus on messenger RNA (mRNA), which indicate the genes that are actively being expressed (as protein products) in a cell or a type of tissue at a particular time. In transcriptomics, microarrays are used to determine the level of mRNA expression (Singh & Nagaraj, 2006). The ProteomicsDB uses transcriptomics to describe mRNA expression levels across various tissues (Schmidt et al., ProteomicsDB, 2017).

GRIN1 mRNA Expression



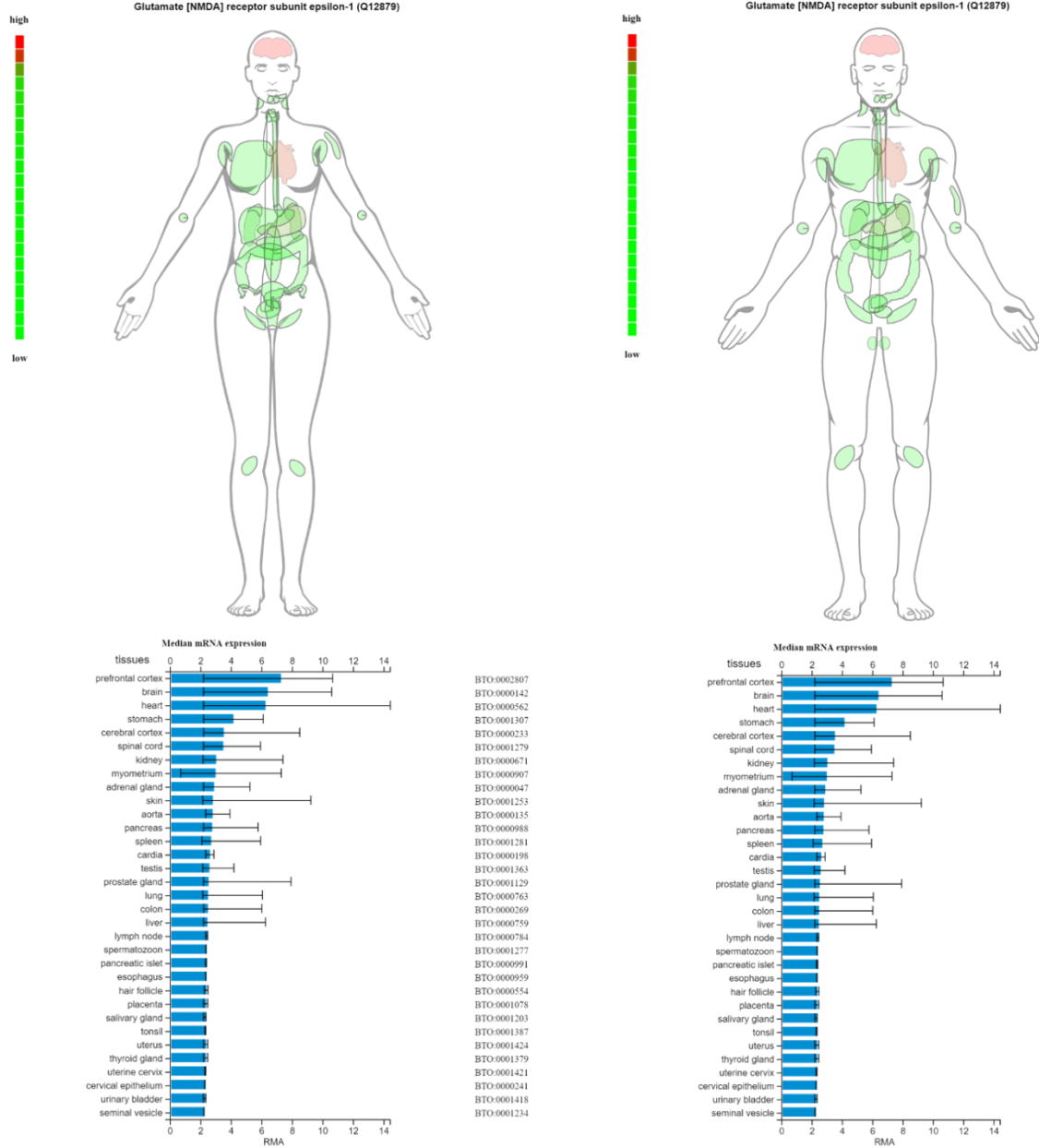
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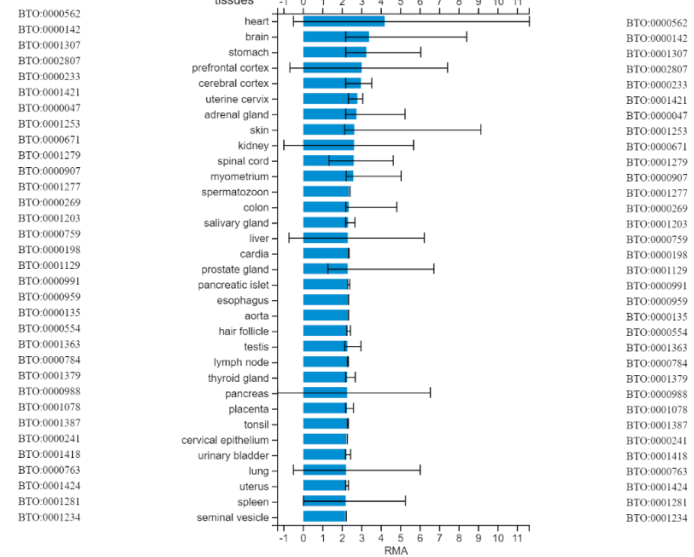
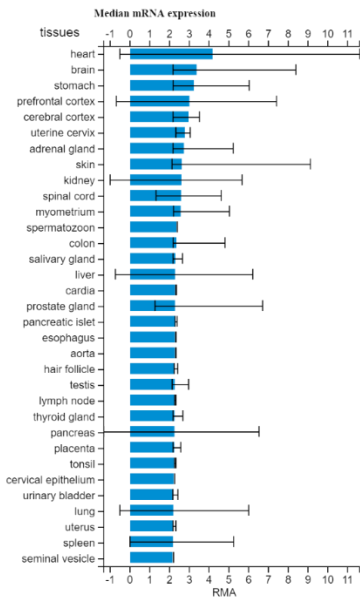
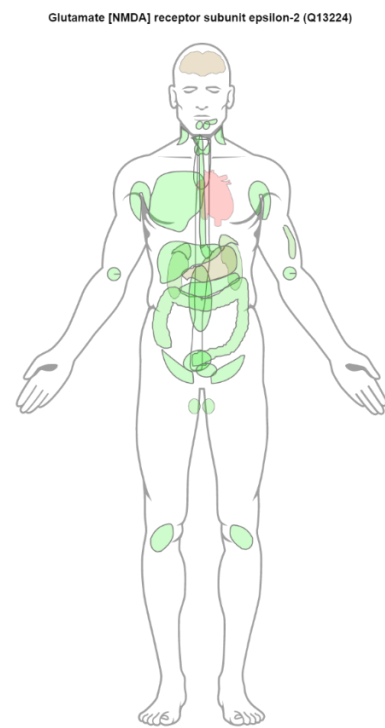
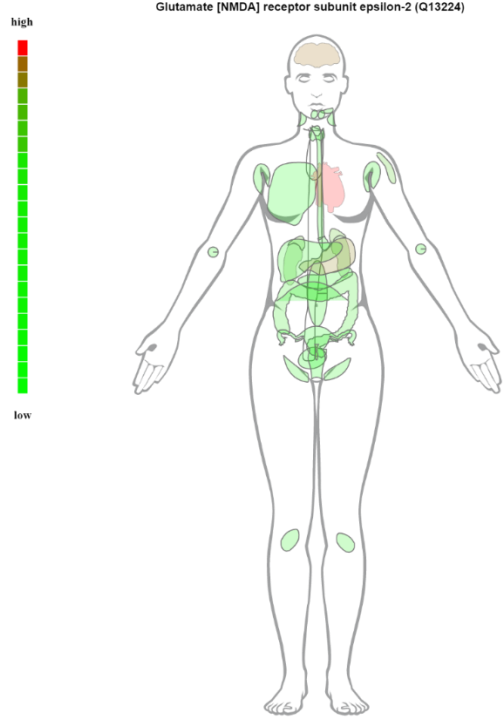
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GRIN2A mRNA Expression



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GRIN2B mRNA Expression

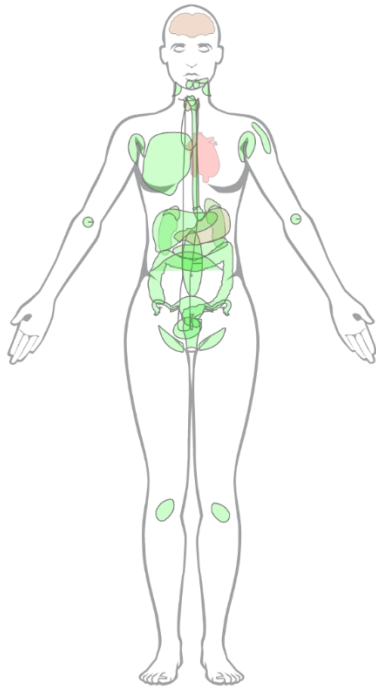


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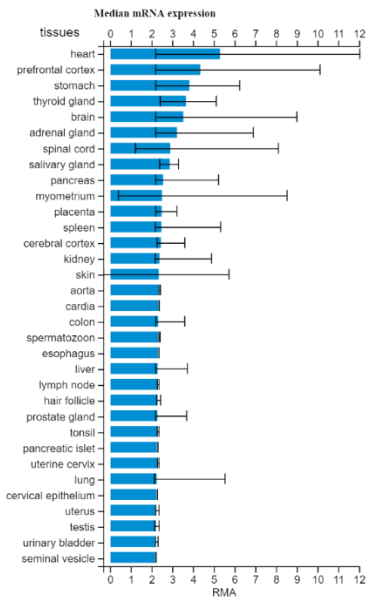
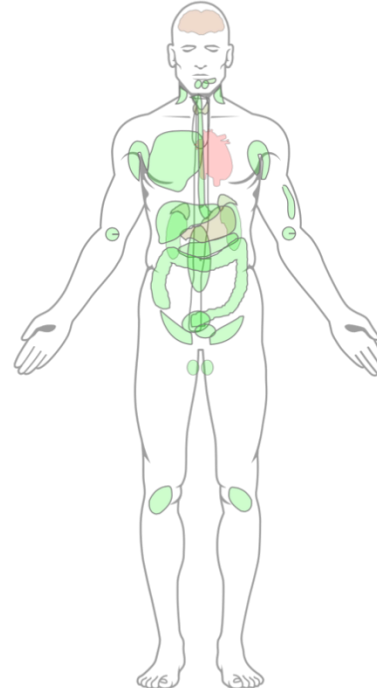
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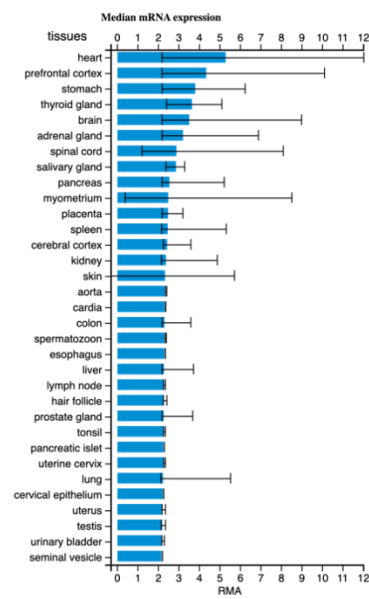
Glutamate [NMDA] receptor subunit epsilon-3 (Q14957)



Glutamate [NMDA] receptor subunit epsilon-3 (Q14957)



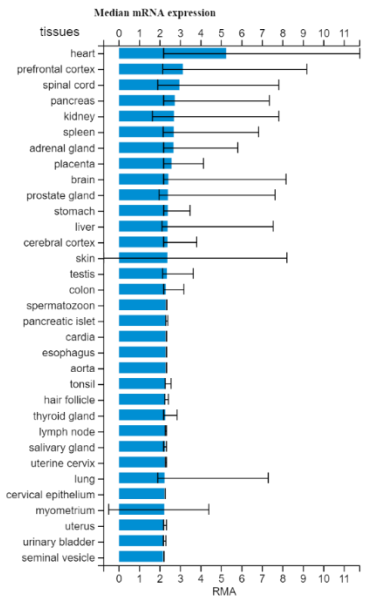
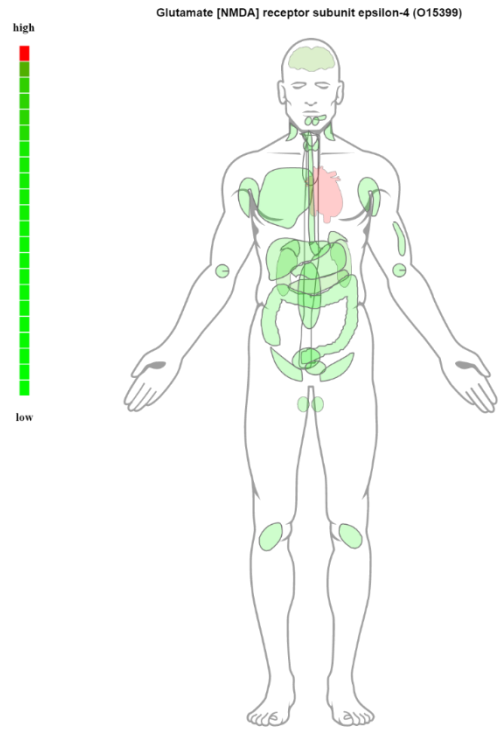
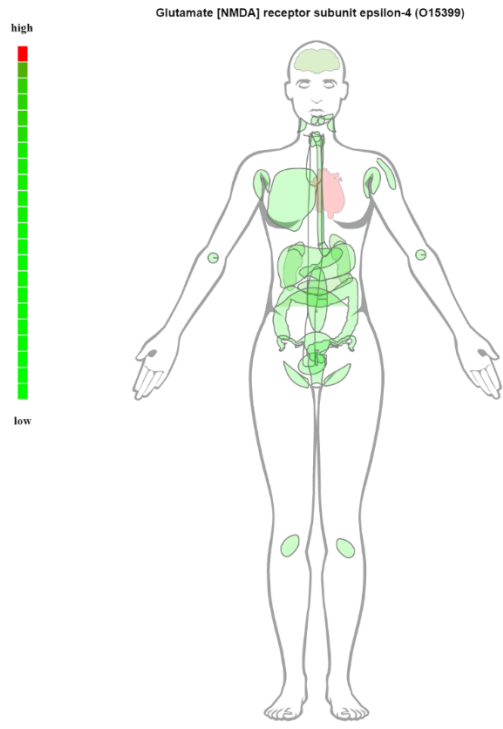
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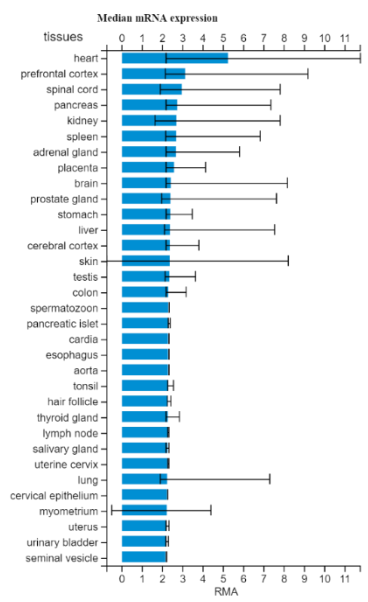
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GRIN2D mRNA Expression



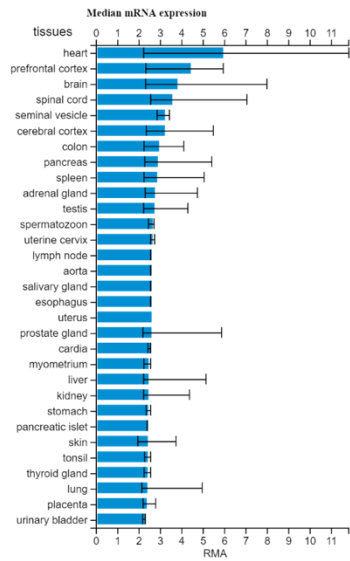
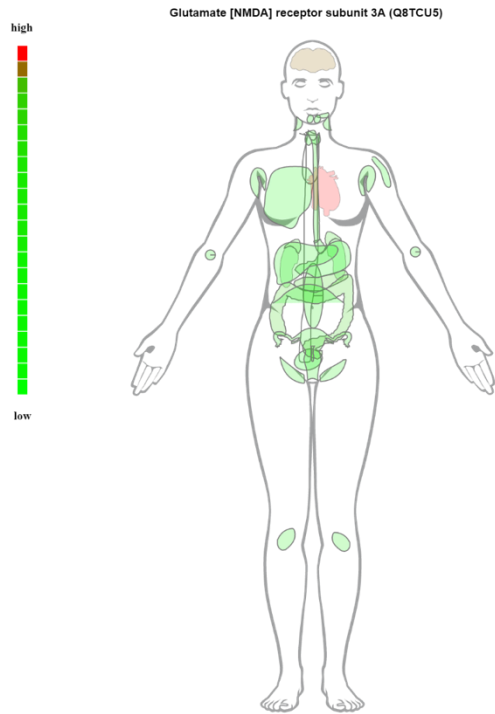
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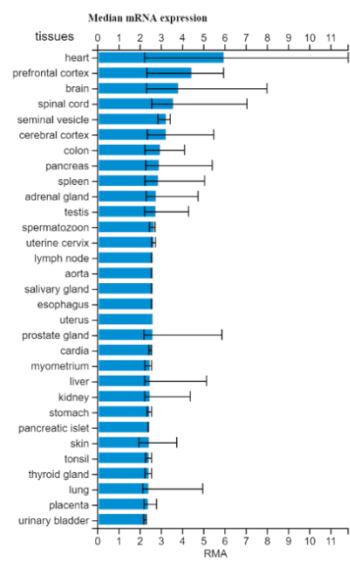
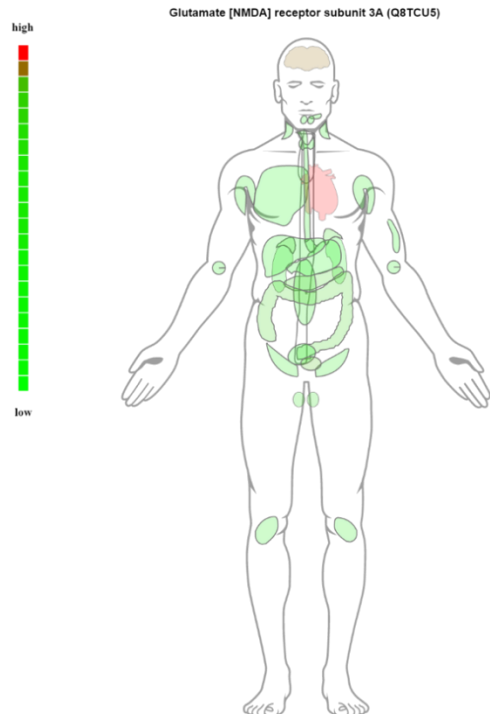
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GRIN3A mRNA Expression



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- **NMDAR expression in other cells/tissues**
 - NMDARs are expressed in neuronal cells and across a spectrum of non-neuronal cell which include glial cells, endothelium, bone, kidney, pancreas, etc. (Hogan-Cann & Anderson, 2016).
 - Functional NMDARs are expressed by astrocytes which are adept to responding to glutamatergic input and neuroinflammatory processes (Dzamba et al., 2013; Sofroniew, 2009; Ting et al., 2009).
 - Endothelial NMDARs are found to contribute to the functioning of the blood–brain barrier (BBB). When glutamate levels are unregulated in brain, this can be toxic to neurons, can damage the functioning of the endothelium, and can disturb the integrity of the BBB (András et al., 2007; Basuroy et al., 2013).
 - NMDARs expressed by osteoblasts have been shown to stimulate precursor differentiation and lead to higher bone mineralization and deposition of bone matrix (Hinoi et al., 2003; Li et al., 2011).
 - Renal NMDAR activity has been shown to stimulate vasodilation in the glomerulus, which influences blood flow, filtration, and reabsorption in the proximal tubule in the renal system (Deng and Thomson, 2009; Anderson et al., 2011; Sproul et al., 2011).
 - NMDARs expressed by insulin-producing islet β cells in the pancreas and contribute to the function of β cells (Inagaki et al., 1995; Molnár et al., 1995; Marquard et al., 2015).
 - Smooth muscle cells express NMDARs in the lung and may contribute to inflammatory bronchiole hyper-reactivity (Antošová and Strapková, 2013; Anaparti et al., 2015).

- **Other diseases connected to functioning of NMDARs**
 - Schizophrenia
 - Reduced expression of the GluN1 and GluN2C subunits has been reported in post-mortem prefrontal cortex tissue of schizophrenia patients (Weickert et al., 2013; Catts et al., 2016; Bygrave et al., 2019).
 - In addition, the GRIN2A and GRIN2B genes have been identified schizophrenia risk genes (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Allen, 2008; Bygrave et al., 2019).
 - Anti-NMDAR encephalitis
 - Complex syndrome characterized by neuropsychiatric symptoms and cerebrospinal fluid antibodies against the GluN1 subunit (Dalmau et al., 2019).
 - Major depressive disorder
 - Excessive activity of NMDARs induced by stressors could result in the pathogenesis of clinical depression (Marsden, 2011).
 - Alzheimer's Disease (AD)
 - NMDAR transmission is affected in AD (Mota et al., 2014).
 - $A\beta$ accumulation may activate NMDARs during the early stages of AD progression (Parameshwaran et al., 2008).
 - GluN2B-containing NMDARs are activated by $A\beta$ oligomeric species resulting in an increase in calcium (Ferreira et al., 2012).

- Memantine is an Federal Drug Admin (FDA) approved treatment for moderate to late-stage AD (de Oliveira et al., 2014).
 - Amyotrophic lateral sclerosis (ALS)
 - Calcium influx by NMDARs can trigger apoptosis resulting in ALS-related motor neuron death (Peng et al., 1998; Nguyen et al., 2011).
 - Huntington's Disease (HD)
 - Higher extrasynaptic NMDAR activity and dysregulated intracellular calcium signaling persist in in early HD (Cowan et al., 2008; Okamoto et al., 2009).
 - Parkinson's Disease (PD)
 - The abundance of GluN1 and GluN2B subunits of NMDARs in PD is decreased in striatal membranes (Johnson et al., 2009).
- **Animal models generated and phenotype description/characterization (not with patient specific mutations)**
 - Jackson Labs (<https://www.jax.org/>) mouse strains:
 - *Grin1^{tm2Stt}*
 - Floxed NR1 mice allow deletion of the GluN1 subunit of the N-methyl-D-aspartate receptor in Cre recombinase expressing cells/tissues (Tsien et al., 1996).
 - JAX stock #005246
 - *Grin1^{ΔEx5}*
 - Carry targeted deletion of *Grin1* exon 5.
 - Interrupts the maturation of excitatory synapses in the thalamus and cortex, increases seizure predisposition (Li et al., 2013).
 - JAX stock #033730
 - *Grin1^{2lox}*
 - *loxP* sites flanking exon 6 of the *Grin1* gene (Zhang et al., 2013).
 - JAX stock #018825
 - Tg-GluN2A^{2B(CT)}
 - Forebrain excitatory neuron overexpression of GluN2A^{2B(CTR)} (Jacobs et al., 2014).
 - JAX stock #029151
 - Tg-GluN2B^{2A(CT)}
 - Forebrain excitatory neuron over-expression of GluN2B^{2A(CTR)} (Jacobs et al., 2014).
 - JAX stock #029152
 - *Grin3b^{tm1Yaha}*
 - NR3B (*Grin3b*) homozygotes are viable and fertile, with no RNA expression from the targeted allele in the adult spinal cord (Niemann et al., 2007)
 - JAX stock #007808

- Zebrafish Models
 - ID: ZDB-CRISPR-180920-, Name: CRISPR1-grin1a (Gao et al., 2018)
 - ID: ZDB-CRISPR-201201-1, Name: CRISPR2-grin1a (Zoodsma et al., 2020)
 - 7-nucleotide deletion in *grin1a* (*grin1a*^{sbu90})
 - Chr 21: 11492823 - 11492829 (GRCz11)
 - 17-nucleotide insertion in *grin1b* (*grin1b*^{sbu94})

- **Pharmacological Antagonists/Agonists of the NMDAR**
 - For activation, synchronous binding of glycine to GluN1 and glutamate to GluN2 is required (Kleckner and Dingledine, 1988; Traynelis et al., 2010).
 - Serine and alanine D-isomers and L-isomers are agonists at for GluN1 in addition to glycine (Pullan et al., 1987; McBain et al., 1989; Traynelis et al., 2010).

Table 2: NMDAR Agonists and Antagonists*

Drug Name	Agonist/Antagonist	Reference
L-Serine	Agonist	Soto et al., 2019
D-Serine	Agonist	Wolosker, 2011
D-Cycloserine	Agonist	Urbano et al., 2015
Alanine (D-alanine, L-alanine)	Agonist	Tsai et al., 2006
D-Aspartate	Agonist	Errico et al., 2015
Quinolinic acid	Agonist	Stone, 1993
Sarcosine	Agonist	Zhang et al., 2009
DL-(Tetrazol-5-yl) glycine	Agonist	Schoepp et al., 1994
N-acetyl cysteine	Agonist	Tardiolo et al., 2018; Berk et al., 2013
Dextromethorphan (DM)	Antagonist	Siu & Drachtman, 2007
Amantadine	Antagonist	Kornhuber et al., 1994
Ketamine	Antagonist	Zorumski et al., 2016
Orphenadrine	Antagonist	Kornhuber et al., 1995
Dizocilpine (MK-801)	Antagonist	Kovacic & Somanathan, 2010
Ifenprodil	Antagonist	Williams, 2001
Memantine	Antagonist	Dravid et al., 2007
Kynurenic acid	Antagonist	Stone, 1993

*This is a partial list. We will update this list to include additional information.

Table 3: NMDAR Allosteric Modulators*

Drug Name	Positive Allosteric Modulator/ Negative Allosteric Modulator	Subunit Selectivity	Reference
Histamine	Positive Allosteric Modulator		Williams, 1994
Spermine	Positive Allosteric Modulator	GluN2B	Williams, 1995
Pregnenolone sulfate	Positive Allosteric Modulator	GluN2A, GluN2B	Wu et al., 1991
GNE-9278	Positive Allosteric Modulator		Wang et al., 2017
Rapastinel	Positive Allosteric Modulator	GluN1	Moskal et al., 2017
Pyrrrolidinone	Positive Allosteric Modulator	GluN2C	Khatri et al., 2014
24(S)-hydroxycholesterol	Positive Allosteric Modulator		Linsenbardt et al., 2014 ; Tang et al., 2020
Tobramycin	Positive Allosteric Modulator	GluN2B	Masuko et al., 1999; Tang et al., 2020
20-oxo-5 β -pregnan-3 α -yl sulfate (3 α 5 β S or PAS)	Negative Allosteric Modulator		Malayev et al., 2002
DQP-1105	Negative Allosteric Modulator	GluN2C, GluN2D	Acker et al., 2011
QNZ-46	Negative Allosteric Modulator	GluN2C, GluN2D	Hansen & Traynelis, 2011
UBP512	Negative Allosteric Modulator		Monaghan et al., 2012
UBP551	Negative Allosteric Modulator		Monaghan et al., 2012
UBP608	Negative Allosteric Modulator		Monaghan et al., 2012
TCN 201	Negative Allosteric Modulator	GluN2A	Monaghan et al., 2012
Radiprodil	Negative Allosteric Modulator	GluN2B	Mullier et al., 2017

*This is a partial list. We will update this list to include additional information.

Table 4: Drugs with Off-Target Effects on NMDARs

Drug Name	Target Receptors	Description	NMDAR Modulation	Reference
Nylidrin	Adrenergic	Vasodilator	Negative Allosteric Modulator (GluN2B)	Whittemore et al., 1997a; Traynelis et al., 2010
Clobenprobit	Histamine	H3-receptor antagonist/ H4-receptor agonist	Negative Allosteric Modulator (GluN2B)	Hansen et al., 2010; Traynelis et al., 2010
Iodophenprobit	Histamine	H3-receptor antagonist	Negative Allosteric Modulator (GluN2B)	Hansen et al., 2010; Traynelis et al., 2010
Capsazepine	Trp	Synthetic capsaicin antagonist	Negative Allosteric Modulator (GluN2B)	Hansen et al., 2010; Traynelis et al., 2010
Haloperidol	Dopamine	Antipsychotic	Negative Allosteric Modulator (GluN2B)	Ilyin et al., 1996; Traynelis et al., 2010
Trifluoperidol	Dopamine	Antipsychotic	Negative Allosteric Modulator (GluN2B)	Whittemore et al., 1997b; Traynelis et al., 2010

- **GRIN Disorder**

- Overview

- GRIN Disorder is a collective term used to describe a group of rare conditions characterized by variants in the genes that encode the NMDA receptor, such as *GRIN1*, *GRIN2A*, *GRIN2B* and *GRIN2D* (Platzer & Lemke, 2019; Lemke et al., 2013; Platzer & Lemke, 2018; XiangWei et al., 2019).
 - GRIN Disorder has been referred to in the literature mostly by the specific GRIN gene in which a variant is found (see Table 6 for alternate names).

Table 5: GRIN Disorder Nomenclature

Gene Name	Disorder Name	Alternate Names	Links Referencing Nomenclature of Disorder
GRIN1	GRIN1-associated disorders	Neurodevelopmental disorder with or without hyperkinetic movements and seizures, autosomal dominant; NDHMSD; Neurodevelopmental disorder with or without hyperkinetic movements and seizures, autosomal recessive; NDHMSR; GRIN1-Related Neurodevelopmental Disorder; GRIN1-Related Developmental and Epileptic Encephalopathy	https://rarediseases.info.nih.gov/diseases/13686/grin1-associated-disorders
GRIN2A	GRIN2A-related disorders	GRIN2A-Related Speech Disorders and Epilepsy; Landau-Kleffner syndrome (LKS); Epileptic encephalopathy with continuous spike-and-wave during sleep (ECSWS)	https://www.chop.edu/conditions-diseases/grin2a-related-disorders#:~:text=GRIN2A%2Drelated%20disorders%3F-,What%20are%20GRIN2A%2Drelated%20disorders%3F,the%20disorder%20can%20vary%20widely.; https://www.ncbi.nlm.nih.gov/books/NBK385627/
GRIN2B	GRIN2B related syndrome	GRIN2B-related intellectual disability; Autosomal dominant intellectual disability-6; GRIN2B encephalopathy; Intellectual disability, autosomal dominant 6, with or without seizures; GRIN2B-related neurodevelopmental disorder	https://rarediseases.info.nih.gov/diseases/12851/grin2b-related-syndrome; https://www.ncbi.nlm.nih.gov/books/NBK501979/
GRIN2D	GRIN2D-Related Disorders	GRIN2D-related developmental and epileptic encephalopathy	https://www.chop.edu/conditions-diseases/grin2d-related-disorders

- Symptoms include: developmental delay, intellectual disability, autism, speech deficiency, inability to walk, low muscle tone, gastrointestinal issues, feeding difficulties, cortical visual impairments, dystonia, seizures, and neurological storms (Platzer & Lemke, 2019; Lemke et al., 2013; Platzer & Lemke, 2018; XiangWei et al., 2019).
- Most GRIN Disorder cases are caused by *de novo* missense variants (Platzer & Lemke, 2019; Lemke et al., 2013; Platzer & Lemke, 2018; XiangWei et al., 2019).
- It has been predicted that GRIN Disorders due to variants in either GRIN1, GRIN2A, GRIN2B or GRIN2D occur in one out of every 5,208 births (19.2 per 100,000) (Lemke, 2020).
 - For GRIN1, the predicted incidence per 100,000 births is 5.45. There were 3,791,712 babies born in the U.S. in 2018, and using the prediction model, this would mean that 207 babies born would be predicted to be affected with a variant in GRIN1 in the U.S. in 2018 (Lemke, 2020).
 - For GRIN2, the predicted incidence per 100,000 births is 3.23. Using the prediction model, the predicted number of affected babies with a variant in GRIN2A born in the U.S. in 2018 is 122. GRIN2A-related Disorder is likely significantly underestimated because these numbers do not capture individuals without intellectual disability, who are estimated to make up more than a third of the GRIN2A patient population (Lemke, 2020).
 - For GRIN2B, the predicted incidence per 100,000 births is 5.91. By using the prediction model, the number of affected babies predicted to have a variant in GRIN2B born in the U.S. in 2018 is 224. GRIN2B-related Disorder appears to have the highest incidence among all GRIN-related disorders (Lemke, 2020).

Table 6: Summary of Phenotypes (Created by CureGRIN using CureGRIN Patient Family survey data)

	GRIN1	GRIN2A	GRIN2B	GRIN2D*
Epilepsy	63%	69%	34%	90%
Intellectual Disability	93%	72%	97%	90%
Visual Disturbance	58%	44%	31%	70%
Speech Impairment	88%	69%	86%	70%
Hypotonia	72%	69%	78%	80%
Mood/Behavior Challenges	45%	44%	65%	30%
Neurostorms	52%	31%	23%	30%
Mobility Impairment	73%	28%	38%	90%

*Data for GRIN2D is extremely limited.

Table 7: Summary of Phenotypes (Created by CureGRIN using published and unpublished data (Li et al., 2020; Hansen et al., 2020; Strehlow et al., 2019; Platzer and Lemke, 2019; Benke et al., 2019; Bain, 2019; Helbig, 2019; Platzer and Lemke, 2018; Costello, 2018; Fry et al., 2018; Platzer et al., 2017; Myers and Scheffer, 2016))

	GRIN1	GRIN2A	GRIN2B	GRIN2D*
Epilepsy	65-75%	70-90%	20-51%	75-100%*
Intellectual Disability	83-100%	38-82%	94-100%	75-100%*
Visual Disturbance	75%	40%	40-80%	Unknown*
Speech Impairment	48-100%	90-100%	100%	100%*
Hypotonia	66-70%	17-29%	55-95%	100%*

*Data for GRIN2D is extremely limited.

Note: Ranges are provided where numerous sources provided different data. Percentages without a range are typically based on a single source (these are not to be considered more precise).

- **Identification of genotype-phenotype correlations**
 - In individuals with a malformation of cortical development (MCD), *de novo* heterozygous pathogenic variants have been identified. These variants are located in the S2 and M3 domains (Fry et al 2018; Platzer & Lemke, 2019). Since few individuals present without MCD and have causative GRIN1 variants in these domains, it is possible for there to be a genotype-phenotype correlation (Platzer & Lemke, 2019).
 - Most patients with heterozygous GRIN2A pathogenic variants present with epilepsy-aphasia syndrome (EAS) phenotype (Carvill et al. 2013; Lemke et al. 2013; Lesca et al. 2013; Turner et al., 2015a; Myers & Scheffer, 2016)
 - The class of variants and degree of severity of intellectual disability have been correlated (Platzer & Lemke, 2018). Heterozygous GRIN2B pathogenic variants resulting in a null allele (i.e., nonsense or frameshift variants, deletions of exons or the gene, translocation and inversion disrupting GRIN2B) tended to display mild or moderate ID, yet those presenting with heterozygous pathogenic missense variants displayed severe ID (Platzer et al., 2017; Platzer & Lemke, 2018).
 - GRIN2B missense variants that cause MCDs are found in the transmembrane domain M3, ligand-binding domain S2, and between S2 and the transmembrane domain M4, which is consistent with GRIN1 variants resulting an MCD (Fry et al. 2018; Platzer & Lemke, 2018).
- **Functional/Mechanistic Studies:**
 - LoF Studies:
 - Researchers assess reduced surface expression and/or reduced current activity which results from lower ion channel conductance, the affinity of agonist(s) (García-Recio et al., 2020)
 - Adult LoF Grin1 mouse model phenotype was rescued using gene editing with Cre recombinase (Mielnik et al, 2020).
 - Grin1 loss-of-function mutations result in reductions of dopaminergic structure volume earlier during development (Intson et al., 2019)
 - Electrophysiology of GRIN2A variants in misTMD+Linker were gain-of-function, while misATD+LBD resulted in loss-of-function (Strehlow et al., 2019)
 - GoF Studies (classified in research system/tissue where this is assessed):
 - GRIN variants are labeled as GoF when NMDAR surface expression is increased and/or NMDAR-mediated currents are increased (García-Recio et al., 2020)
 - Electrophysiology of GRIN2A variants in misTMD+Linker were gain-of-function, while misATD+LBD resulted in loss-of-function (Strehlow et al., 2019).
 - GRIN2A variant p.Met817Val results in GoF. Location of variant suggested to impact channel gating (Chen et al., 2017).

- Animal models generated and phenotype description/ characterization

Table 8: Summary of Known GRIN Disorder Knock-in Mouse Models (Created by CureGRIN using published and unpublished data)*

Gene	Variant	Domain	LOF/GOF	Institution	Country
GRIN1	Q536R	S1	LOF	University of Toronto	Canada
GRIN1	G620R	M2	LOF	University of Toronto	Canada
GRIN1	Y647S	M3	GOF	University of Toronto	Canada
GRIN1	L655Q	M3	GOF?	Zhejiang People's Hospital of Hangzhou	China
GRIN1	M813T	M4	LOF	University of Toronto	Canada
GRIN1	G827R	M4	LOF	University of Toronto	Canada
GRIN2A	S644G	M3	GOF	Columbia University	United States
GRIN2B	E413G	S1	LOF	Emory University	United States
GRIN2B	C456Y	S1	?	Institute for Basic Science	Korea
GRIN2B	M818T	M4	GOF	National University of Singapore	Singapore
GRIN2B	L825V	M5	?	Institute of Physiology	Czech Republic
GRIN2B*	S1415L	CTD	LOF	National Institute of Health	United States
GRIN2D	V667I	M3	GOF	Columbia University	United States
GRIN2D	V667I	M3	GOF	Tel Aviv University	Israel

* There are numerous additional generic LOF/GOF mouse models.

▪ **Testing of small molecules ameliorating molecular/biological phenotype**

- Memantine

- GRIN2A gain-of-function (Pierson et al., 2014)
 - GRIN2A missense variant (c.2434C>A; p.L812M) (Pierson et al., 2014)
 - As a result of increased activation at low agonist concentrations, GluN2A-L812M-containing NMDARs are overactive (Pierson et al., 2014).
 - A memantine dosage of ~0.5 mg/kg per day was administered, and the treatment resulted in decreased seizure frequency (Pierson et al., 2014).
- GRIN2A gain-of-function (Amador et al., 2020)
 - GRIN2A missense variant c.1930A4G (S644G) (Amador et al., 2020)
 - Treated with off-label memantine and dextromethorphan
 - Memantine started at 2 years old and following treatment, the daily seizure burden was reduced by half (Amador et al., 2020)
 - 5 mg/kg/day increasing to 10 mg/kg/day (Amador et al., 2020)

- Patient is now 6.5 years old and has 3-5 brief tonic seizures and 1-2 myoclonic seizures daily. Patient is on a combination of memantine, dextromethorphan, and zonisamide. (Amador et al., 2020)
 - GRIN2B
 - Memantine treatment offered to patients after functional confirmation of a gain-of-function variant retaining memantine sensitivity *in vitro* (Platzer et al., 2017)
 - Oral memantine treatment: doses of 0.5–0.6 mg/kg body weight/day (Platzer et al., 2017)
- L-Serine
 - GRIN2B loss-of-function N=1 study (Soto et al., 2019)
 - GRIN2B(P553T) variant
 - For 4 weeks, patient was given a dose of 250 mg/kg per day. Then, the dose was increased to 500 mg/kg per day. The dose was administered by dietary supplements (3) and was mixed with food or drink.
 - Improvements in motor impairments, cognition, and communication was noted after 11 and 17 months of L-Serine dietary supplementation.
 - L-Serine Clinical Trial in GRIN LOF: Tolerability and Efficacy of L-Serine in Patients With GRIN-related Encephalopathy (<https://clinicaltrials.gov/ct2/show/NCT04646447>)
 - Led by Barcelona GRIN Team (Spain)
 - 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
- Radiprodil (Xenopus oocytes)
 - GRIN2B gain-of-function mutations
 - Negative allosteric modulator of GluN2B-containing NMDA receptors (Mullier et al., 2017)
 - Phase I completed. Phase II trial in children with Infantile spasm- trail was not completed, low number of enrolled patients.
<https://clinicaltrials.gov/ct2/show/NCT02829827?cond=radiprodil&draw=2&rank=2>

- **Pharmaceutical and Biotechnology Companies of Interest**

Table 9: Companies with compounds targeting NMDARs

Company Name	General Information	Website
Sage Therapeutics*	Library of compounds that modulate NMDA receptor activity (i.e. SAGE-904, SAGE-421)	https://www.sagerx.com/
Novartis	Acquired Cadent* in 2020 and its NMDAR compounds (CAD-9303: NMDAR PAM developed for schizophrenia; and MIJ-821: NMDAR NAM)	https://www.novartis.com/ https://www.novartis.com/news/media-releases/novartis-builds-commitment-addressing-need-neuropsychiatric-disorders-cadent-therapeutics-acquisition
Genentech*	small molecule drugs targeting ion channels	https://www.gene.com/
Relmada Therapeutics	REL-1017: NMDAR channel blocker	https://www.relmada.com/

*=CureGRIN has connected with this company

Table 10: Companies focused on rare diseases

Company Name	General Information	Website
Collaborations Pharmaceuticals*	Using artificial intelligence and drug discovery to develop clinical candidates	https://www.collaborationspharma.com/

*=CureGRIN has connected with this company

Table 11: Companies with relevant gene therapies (Including CRISPR/Cas9, mRNA, Antisense Oligonucleotides, etc.)

Company Name	General Information	Website
Homology Medicines*	Gene editing/ AAVHSC-mediated gene therapy	https://www.homologymedicines.com/gene-editing
Beam Therapeutics*	CRISPR/Cas9-base editing	https://beamtx.com/
Moderna*	mRNA Therapeutics and Vaccines for Rare Diseases	https://www.modernatx.com/pipeline/therapeutic-areas/mrna-therapeutics-and-vaccines-rare-diseases
Intellia Therapeutics*	CRISPR/Cas9-based medicines	https://www.intelliatx.com/
Neurogene*	AAV gene therapy	https://www.neurogene.com/
Voyager Therapeutics*	AAV gene therapy	https://www.voyagertherapeutics.com/
Wave Life Sciences	Nucleic acid therapeutics	https://wavelifesciences.com/
Stoke Therapeutics	Using antisense oligonucleotide medicines to increase gene expression for treating genetic epilepsies and other monogenic diseases	https://www.stoketherapeutics.com/
Handl Therapeutics	<i>in vivo</i> gene therapy	https://www.handltherapeutics.com/

*=CureGRIN has connected with this company

Table 12: Other Companies of Interest

Company Name	General Information	Website
Biogen*	Biomarkers, small molecules, biologics, antisense oligonucleotides, and gene therapy	https://www.biogen.com/en_us/home.html
Sarepta Therapeutics*	RNA technologies, gene therapy, and gene editing	https://www.sarepta.com/
LogicBio Therapeutics	genome-editing technology, GeneRide™	https://www.logicbio.com
Janssen Pharmaceuticals	Biomarkers	https://www.janssen.com/neuroscience

*=CureGRIN has connected with this company

▪ **AMPA Receptors**

AMPA receptors mediate the fast component of the glutamatergic EPSC throughout the brain. Their low affinity binding of glutamate allows them to transmit extremely short acting signals (1-5 ms depending on composition). They act in synergy with NMDARs to produce the synaptic plasticity which likely underlies learning and memory.

○ **Key historical AMPAR discoveries**

- 1980s
 - Single-channel recordings of glutamate receptors including receptors activated by kainate (Cull-Candy and Usowicz, 1987; Jahr and Stevens, 1987; Nowak et al., 1984).
 - Drugs CNQX and DNQX developed to distinguish AMPA/KAR signalling from NMDARs (Honore et al., 1988).
- 1990s
 - Between 1989 and 1992, Hollmann and Heinemann performed research on the cloning of cDNAs encoding glutamate receptor subunits (Hollmann and Heinemann, 1994). GluA1-4 identified (GRIA1-4).
 - GluA2 identified as functionally critical due to RNA editing which affects the channel's ion selectivity filter. GluA2-containing receptors are Ca²⁺ impermeable (CI-AMPA receptors) while those which lack GluA2 are Ca²⁺-permeable (CP-AMPA receptors) (Burnashev et al., 1992).
 - Alternative splicing region discovered (the flip/flop cassette) present in all four genes. Flop forms display faster decay kinetics. (Sommer et al., 1990).
 - AMPAR non-competitive inhibitor GYKI 52466 discovered (Donevan & Rogawski, 1993).

- The AMPAR positive allosteric modulator cyclothiazide identified (Bertolino et al., 1993).
- Block of CP-AMPARs by intracellular polyamines discovered (Bowie & Mayer 1995; Kamboj et al., 1995).
- AMPAR properties can be modulated by phosphorylation (Derkach et al., 1999; Banke et al., 2000).
- 2000s
 - AMPAR ligand binding domain structures resolved in the presence of agonists and antagonists (Armstrong and Gouaux, 2000)
 - Stargazin, the first transmembrane AMPAR regulatory subunit (TARP) shown to be critical for expression of synaptic AMPARs. (Chen et al., 2000)
 - TARPs are a family of six proteins (Tomita et al., 2003; Soto et al., 2009).
 - The cornichons, another family of AMPAR auxiliary proteins identified (Schwenk et al., 2009).
 - Full-length AMPAR structure produced (Sobolevsky et al., 2009).
- 2010s
 - The AMPAR proteome reveals over 40 associated proteins involved in receptor biosynthesis, trafficking and modulation (Schwenk et al., 2012).
 - Perampanel licensed for treating certain types of epilepsy (2012-2016).
 - Structures of native AMPA receptors elucidated by cryo-EM (Zhao et al., 2019).

- **GRIA genes**

Table 13: General information for GRIA Genes

Symbol	Name	Base Pairs	Protein Name	Amino Acids	Alternate Protein Name	Chromosomal Location
<i>GRIA1</i>	glutamate ionotropic receptor AMPA type subunit 1	5584	GluA1	906	GluR1, GLURA	5q33.2
<i>GRIA2</i>	glutamate ionotropic receptor AMPA type subunit 2	3398	GluA2	901	GluR2, GLURB	4q32.1
<i>GRIA3</i>	glutamate ionotropic receptor AMPA type subunit 3	5148	GluA3	894	GluR3, GLURC, MRX94	Xq25
<i>GRIA4</i>	glutamate ionotropic receptor AMPA type subunit 4	5506	GluA4	902	GluR4, GLURD	11q22.3

- **Identification of variants**

gnomAD: Over 800 missense variants have been identified in *GRIA* genes some of which are known to be pathogenic. There are around 30 other changes producing predicted loss of function (pLoF). Numbers correct as of 27th May, 2021.

- GRIA1: 302 missense, 6 pLoF
- GRIA2: 197 missense, 5 pLoF
- GRIA3: 130 missense, 2 pLoF
- GRIA4: 278 missense, 13 pLoF
- GRIA mutation database? As yet there is no dedicated database to collate GRIA mutations, their natural history, their functional effect and their symptoms. Assembling such a collection should be a priority.

- **Descriptive Studies:**

- **AMPA Studies:**

- α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA receptors) are formed from subunit proteins (GluA1, GluA2, GluA3 and GluA4) encoded by four genes (*GRIA1-4*) (Traynelis et al., 2010).
 - AMPARs are formed as homo- or heterotetrameric assemblies of these subunits, with a central ion pore (Traynelis et al., 2010).
 - The majority of native AMPARs contain two GluA2 subunits meaning they are Ca^{2+} -impermeable (Sommer et al., 1990, Wenthold 1996; Zhao et al., 2019; Barbon and Barlati, 2011).
 - Ca^{2+} -permeable, GluA2-lacking, AMPARs have important roles in plasticity and disease (Cull-Candy et al., 2006).
 - The AMPAR-mediated synaptic current is brief (~1 to 5 milliseconds) (Traynelis et al., 2010).
 - AMPAR activation produces excitatory depolarizing signals. This mediates the majority of excitatory transmission in the brain and can cause liberation of NMDARs from Mg^{2+} block, allowing their activation ().
 - Alterations in AMPAR number are crucial for synaptic plasticity including the processes of long-term potentiation and long-term depression (Huganir & Nicoll, 2013).

- **AMPA protein partners**

- GluA subunits assemble with each other as homomeric or heteromeric tetramers. Native AMPARs have recently been shown by cryo-EM to exist as homomers, dimeromers or trimeromers (Zhao et al., 2019, Yu et al., 2021).
 - *In vivo* subunit composition and expression levels may vary (UniProt, 2019).
 - Interacts with auxiliary subunits the type 1 TARPs (CACNG2, CACNG3, CACNG4, CACNG8) (Tomita et al., 2003).
 - Interacts with auxiliary subunits the type 2 TARPs (CACNG5, CACNG7) (Kato et al., 2007; Kato et al., 2008; Soto et al., 2009)
 - Interacts with auxiliary subunits the cornichons (CNIH2, CNIH3) (Schwenk et al., 2009).
 - Interacts with auxiliary subunit GSG1L (Shanks et al., 2012).
 - Interacts with CKAMP proteins, also known as Shisa proteins (CKAMP39/Shisa8, CKAMP44/Shisa9, CKAMP52/Shisa6, CKAMP59/Shisa7) (Farrow et al., 2015).
 - Interacts with numerous other proteins involved in biosynthesis, trafficking and subcellular localization (Schwenk et al., 2012).
 - Human Reference Protein Interactome Mapping Project (<http://www.interactome-atlas.org/about/>)
 - Luck, K., Kim, DK., Lambourne, L. et al. A reference map of the human binary protein interactome. *Nature* 580, 402–408 (2020). <https://doi.org/10.1038/s41586-020-2188-x>

- **Promoters/Enhancers** (Retrieved from Eukaryotic Promoter Database (EPDNew) (Dreos et al., 2015))
 - GRIA1
 - Promoter ID: GRIA1_1
 - Genomic Location: chr5:153488669–153492669 (GRCh38/hg38); chr5:152868229–152872229 (GRCh37/hg19).
 - Sequence:


```
ggagccagcgctccagctagcatgaggacgggctctttcccgtgctcAGTTAATCTG
G
```
 - GRIA2
 - Promoter ID: GRIA2_1
 - Genomic Location: chr4:157218727–157222727 (GRCh38/hg38); chr4:158139879–158143879 (GRCh37/hg19).
 - Sequence:


```
cgcgcgtgagtgagagaggagagagggagaagagagcgcgagagagggtGAGTGTG
TGTG
```
 - Promoter ID: GRIA2_2
 - Genomic Location: chr4:157218572–157222572 (GRCh38/hg38); chr4:158139724–158143724 (GRCh37/hg19).
 - Sequence:


```
gtggtgcggggtgccgggcccgtgccccggggagggggcgcgcgctcccGCTCCTGC
CGC
```
 - GRIA3
 - Promoter ID: GRIA3_1
 - Genomic Location: chrX:123181961–123185961 (GRCh38/hg38); chrX:122315814–122319814 (GRCh37/hg19).
 - Sequence:


```
gagcctttcgctctttctttttccccctcttagacctaccatCTTTTGCGGGG
```
 - Promoter ID: GRIA3_2
 - Genomic Location: chrX:123182344–123186344 (GRCh38/hg38); chrX:122316197–122320197 (GRCh37/hg19).
 - Sequence:


```
gagcgagagagagcgagcgaataagagagagagtaagaggagagagaaGAAGAGG
AAGA
```
 - Promoter ID: GRIA3_3
 - Genomic Location: chrX:123181572–123185572 (GRCh38/hg38); chrX:122315425–122319425 (GRCh37/hg19).
 - Sequence:


```
gcggcagagaccgggcatgcccagcatctcgggcccattgtgatgggaACTGCTTCT
CT
```
 - Promoter ID: GRIA3_4
 - Genomic Location: chrX:123182504–123186504 (GRCh38/hg38); chrX:122316357–122320357 (GRCh37/hg19).

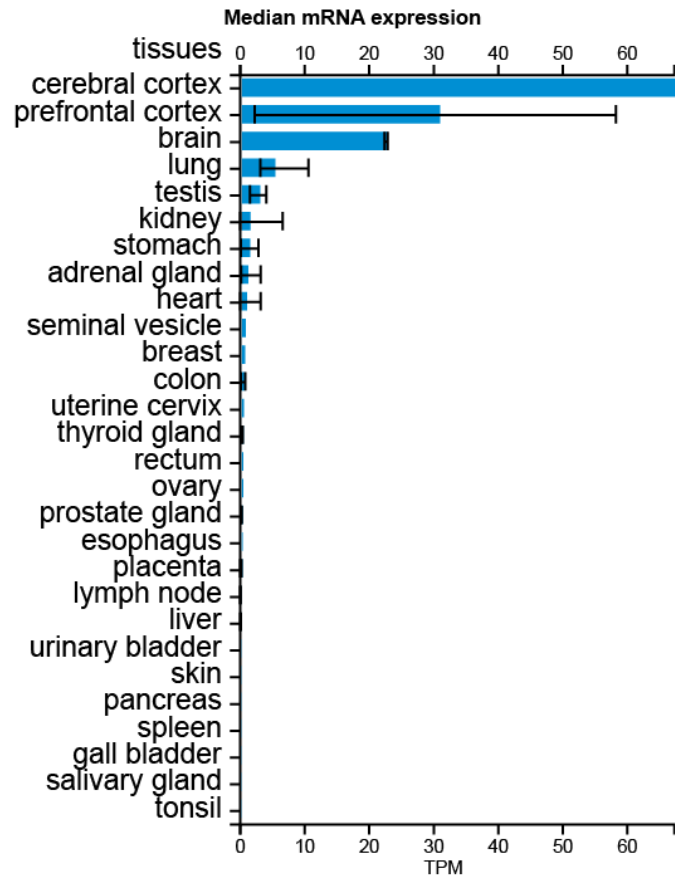
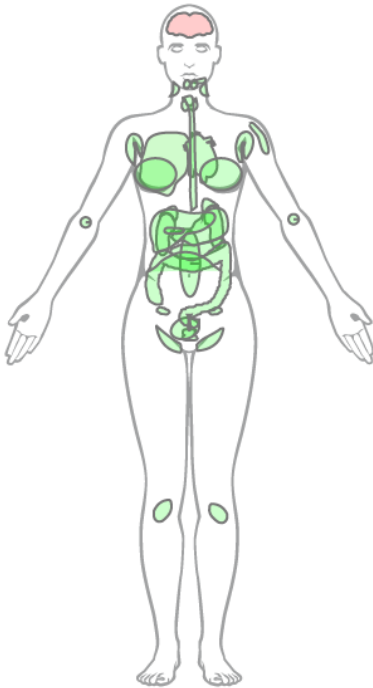
- Sequence:
 - attcttttcttttctattatttttgacgactcctgagttgcgcccATGCTCTTGTC
 - Promoter ID: GRIA3_5
 - Genomic Location: chrX:123182239–123186239 (GRCh38/hg38); chrX:122316092–122320092 (GRCh37/hg19).
 - Sequence:
 - ttccagattggtgtgaagacagaagtgaggtggggggaagggaggggtGTGAGAGATCC
- GRIA4
 - Promoter ID: GRIA4_1
 - Genomic Location: chr11:105608072–105612072 (GRCh38/hg38); chr11:105478799–105482799 (GRCh37/hg19).
 - Sequence:
 - gtgagaaatctttgctgcagcgaggaccggagtcccccgcgcgcagcccAGTGGCAGAGAG
 - Promoter ID: GRIA4_2
 - Genomic Location: chr11:105608890–105612890 (GRCh38/hg38); chr11:105479617–105483617 (GRCh37/hg19).
 - Sequence: ccttttttctttcttttctttcttttttttttttttttttGTTGATTTTAA
 - Promoter ID: GRIA4_3
 - Genomic Location: chr11:105608714–105612714 (GRCh38/hg38); chr11:105479441–105483441 (GRCh37/hg19).
 - tgttcatcctgcgagcagccactagacgctccaccaccttttgcATGTGCAACAT
- **Expression patterns**
 - **GRIA expression in the brain**
 - AMPARs are found throughout the brain, however there is variation in the relative expression of AMPAR subunits by brain region and within different cell types within each region.
 - For detailed analysis of Allen brain expression data see Shen et al., 2020.
 - In terms of total GRIA mRNA detected, GRIA2 is the most strongly expressed gene brain-wide and is nearly ubiquitous.
 - GRIA4 is expressed at high levels in a number of brain regions including the cerebellum, thalamus, hypothalamus and myelencephalon.
 - GRIA1 and 3 are the lesser expressed subunits throughout the brain but are enriched in the hippocampus.
 - **GRIA expression in other tissues (beyond the nervous system)**
 - The GRIA genes are, in general, expressed at extremely low levels outside of the central nervous system. However, this does not preclude an important role in certain non-neuronal cell types.
 - The following body-wide distribution data is from RNAseq examination of GRIA gene expression (Schmidt et al., ProteomicsDB, 2018).

Glutamate receptor 1 (P42261)

high

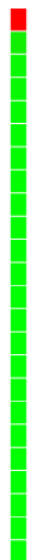


low

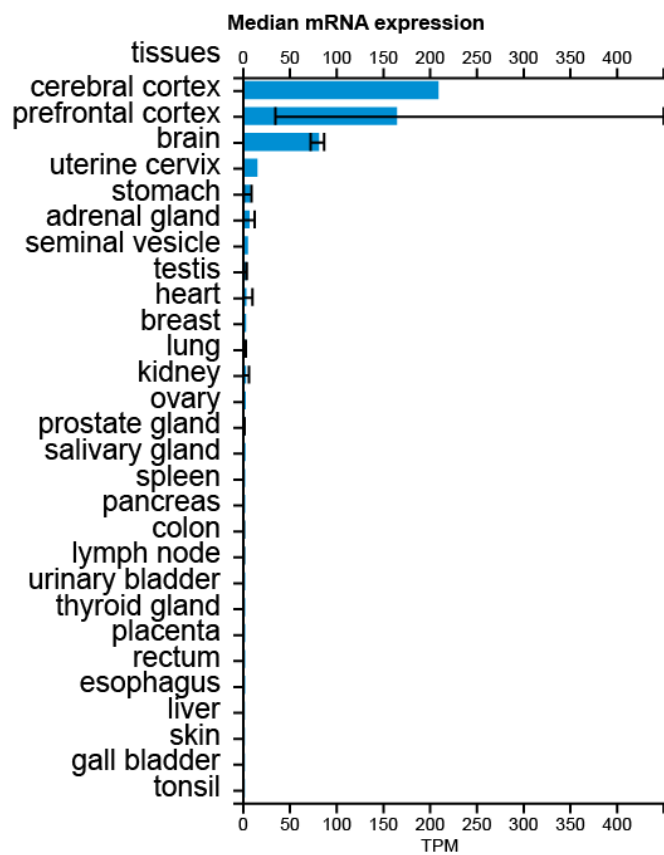
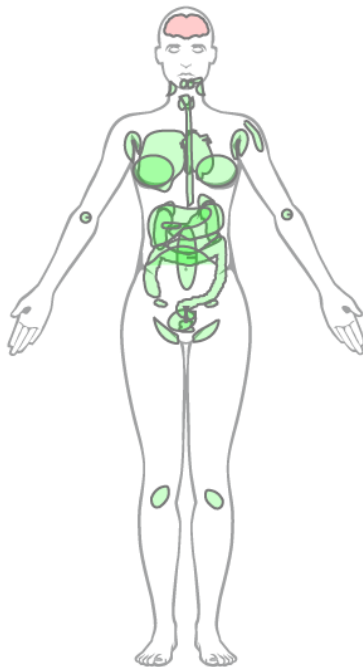


Glutamate receptor 2 (P42262)

high



low

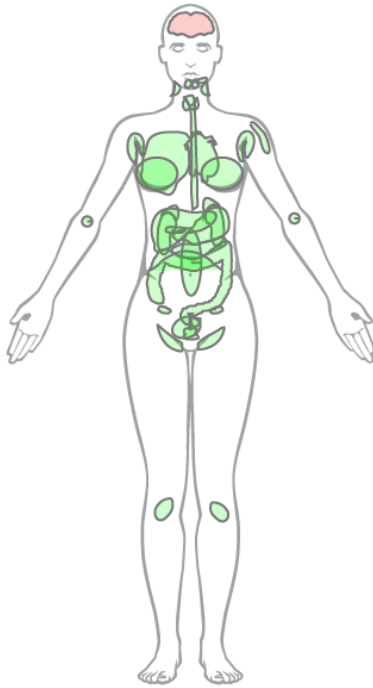


Glutamate receptor 3 (P42263)

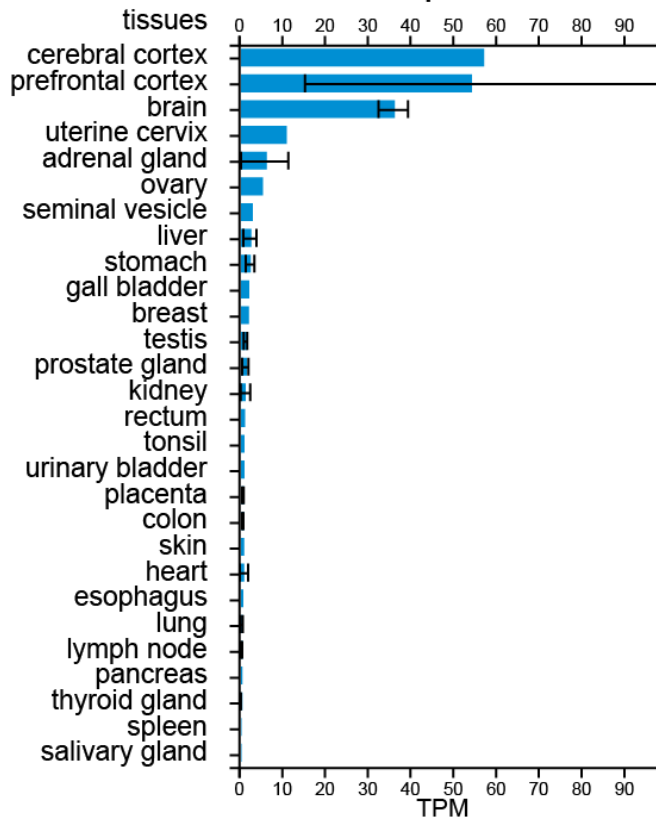
high



low



Median mRNA expression

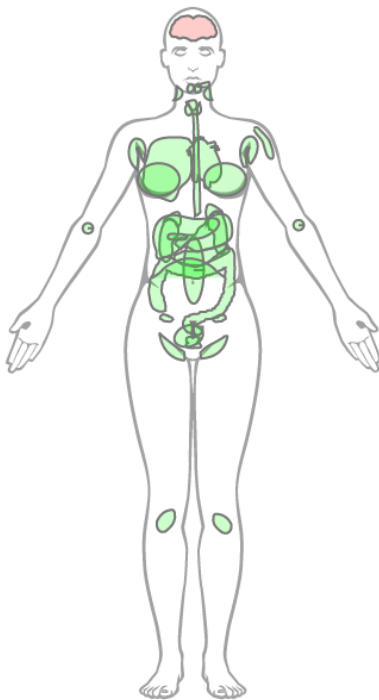


Glutamate receptor 4 (P48058)

high



low



Median mRNA expression

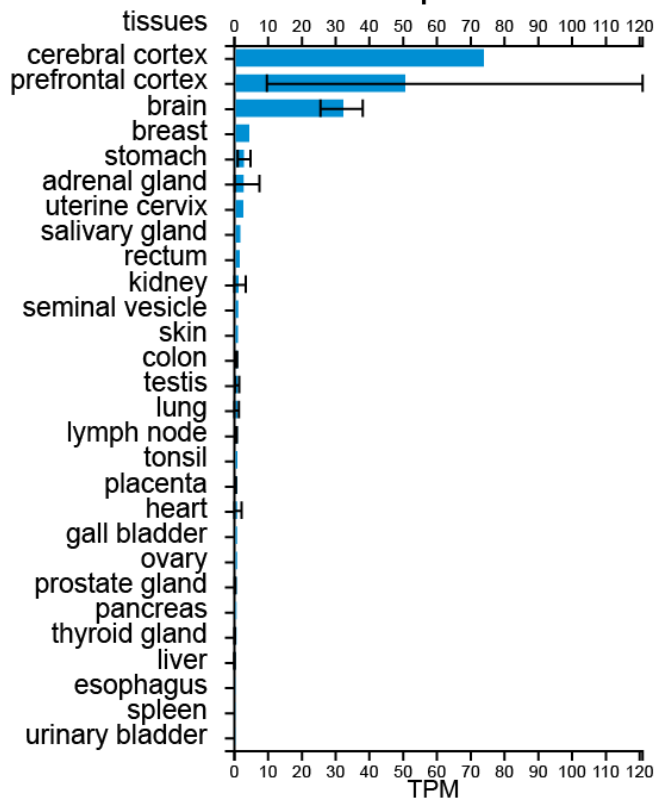


Table 14: AMPAR Agonists and Antagonists

Drug Name	Agonist/Antagonist	Reference
AMPA	Agonist (full)	Strange et al., 2006
<i>L</i> -Glutamate	Agonist (full)	Coquelle et al., 2000; Strange et al., 2006; Jensen et al., 2007;
Quisqualate	Agonist	Strange et al., 2006
Kainate	Agonist	Strange et al., 2006
Domoate	Agonist	Donevan et al., 1988
Willardine	Agonist	Kizelsztejn et al., 2000; Jin et al., 2003
5-Fluowillardine	Agonist	Greenwood et al., 2006
ACPA	Agonist	Strange et al., 2006
CI-HIBO	Agonist (GluA1, -2 selective)	Bjerrum et al., 2003; Ahmed et al., 2009
2-Bn-Tet-AMPA	Agonist (modest GluA4 preference)	Jensen et al., 2007
CNQX	Competitive Antagonist (partial agonist in presence of TARP γ 2)	Honore et al., 1988; Sheardown et al., 1990; Menuz et al., 2007; Bats et al., 2012
DNQX	Competitive Antagonist (partial agonist in presence of TARP γ 2)	Honore et al., 1988; Sheardown et al., 1990; Menuz et al., 2007; Bats et al., 2012
NBQX	Competitive Antagonist	Sheardown et al., 1990; Wilding & Huettner, 1995
ZK200775 (MPQX, fanapanel)	Competitive Antagonist	Turski et al., 1998
YM90K	Competitive Antagonist	Ohmori et al., 1994
YM872	Competitive Antagonist	Takahashi et al., 2002

AMP397	Competitive Antagonist	Auberson et al., 1999
BGG492	Competitive Antagonist	Orain et al., 2007
ATPO	Competitive Antagonist	Hogner et al., 2003; Hald et al., 2007
NS1209	Competitive Antagonist	Kasper et al., 2006
IKM-159	Competitive Antagonist	Gill et al., 2010; Juknaite et al., 2013
<i>D</i> -Aspartate	Competitive Antagonist	Gong et al., 2005

Table 15: AMPAR Allosteric Modulators

Drug Name	Positive / Negative Allosteric Modulators (PAM/NAM)	Reference
Cyclothiazide	PAM	Partin et al., 1994; Johansen et al., 1995; Partin et al., 1996; Sekiguchi et al 2002; Mitchell & Fleck, 2007; Hald et al., 2009; Timm et al., 2011
NS1493	PAM	Hald et al., 2009
Aniracetam	PAM	Johansen et al. 1995; Partin et al 1996; Sekiguchi et al 2002
Piracetam	PAM	Ahmed et al., 2010; Ahmed & Oswald 2010
CX614	PAM	Arai et al., 2000

PF-04958242 (BIIB104)	PAM	Shaffer et al., 2015; Ishii et al., 2020
S 47445	PAM	Bretin et al., 2017
TAK-137	PAM	Kunugi et al., 2019; Suzuki et al., 2019
HBT1	PAM	Kunugi et al., 2018
LY-451395 (mibampator)	PAM	Ishii et al., 2020
LY-404187	PAM	Miu et al., 2001; Quirk and Nisenbaum, 2002; Sobolevsky et al., 2009
PEPA	PAM	Sekiguchi et al., 1997; Ahmed et al., 2010
CMPDA	PAM	Timm et al., 2011
TDPAM02		Drapier et al., 2018; Laulumaa et al., 2019;
BPSA	PAM	Kaae et al., 2007
MDI-222	PAM	Ward et al., 2020
Con-ikot-ikot	PAM (cone snail toxin)	Walker et al., 2009; Chen et al., 2014; Baranovic et al., bioRxiv 2021
GYKI-52466	NAM	Solyom and Tarnawa, 2002

GYKI 53655 (LY-300168)	NAM	Donevan and Rogawski 1993; Donevan et al., 1994; Partin and Mayer, 1996; Balannik et; Balannik et al., 2005; Yelshanskaya et al., 2016
CP-465,022	NAM	Menniti et al., 2000; Lazzaro et al., 2002; Balannik et al., 2005; Yelshanskaya et al., 2016
Perampanel	NAM	Hanada et al., 2011; Hibi et al., 2012; Chen et al., 2014; Yelshanskaya et al., 2016; Kato et al., 2016; Tsai et al., 2018
Decanoic acid	NAM	Chang et al., 2016
4-BCCA	NAM	Chang et al., 2105; Yelshankya et al., 2020
LY-3130481 (CERC-611)	NAM (TARP γ 8-selective)	Gardinier et al., 2016; Kato et al., 2016; Knopp et al., 2019
JNJ-55511118	NAM (TARP γ 8-selective)	Maher et al 2016; Dohrke et al., 2020; Yu et al., 2021
JNJ-61432059	NAM (TARP γ 8-selective)	Savall et al., 2019
VU0612951	NAM (poss γ 2-selective)	Azumaya et al., 2017

*This is a partial list. We will update this list to include additional information.

- GRIA Disorder
 - Overview
 - GRIA Disorder is a collective term used to describe a group of rare conditions characterized by variants in the genes that encode the AMPA receptor.
 - Disease causing mutations have been found in every GRIA gene.
 - GRIA1: de Ligt et al., 2012; Geisheker et al., 2017
 - GRIA2: Salpietro et al., 2019
 - GRIA3: Wu et al., 2007; Bonnet et al., 2009; Philippe et al., 2013; Davies et al., 2017; Trivisano et al., 2020; Piard et al., 2020
 - GRIA4: Martin et al., 2017
 - Variants in all genes have been associated with intellectual disability and ASD.
 - While GRIA1 is not yet assigned to a with human disorder, GRIA2- and GRIA4-deficiencies are inherited in an autosomal dominant pattern while GRIA3-deficiency is X-linked.
 - The phenotypical spectrum is characterized by global developmental delay which is apparent from infancy or early childhood, resulting in variable intellectual disability ranging from profound with absent speech and none to limited social skills to mild with an ability to attend special schools.
 - Although the majority of subjects eventually learn to walk, most are late to reach this milestone and have an unsteady gait. Some may experience developmental regression and many have behavioral difficulties including autistic features, reduced attention span, auto-aggression, anxiety and hypersensitivity to stimuli.
 - While some subjects have congenital hypotonia (loss of body tone) other affected infants show irritability, stiffness, and hypertonia early in life, which progresses to spasticity and impaired gait later. Some patients may develop seizures of variable severity early in life.
 - As for other genes encoding neuronal channels, also *GRIA* genes are more and more associated to rare neurodevelopmental disorders. While the role of *GRIA1* is still pending confirmation, likely due to the scarcity of subjects described, the other three GRIA genes have been already enlisted as causative of genetic conditions.
 - GRIA2- and GRIA4-deficiencies are autosomal dominant usually caused by *de novo* variants whereas GRIA3-deficiency is X-linked disorder and thus affects mainly males, though some female patients have been currently reported.
 - The phenotypical spectrum is characterized by global developmental delay and intellectual disability of variable degree.
 - Speech may be absent and social skills range from severe to mild, being some children able to attend special schools.
 - Although the majority of subjects eventually learn to walk, most are late to reach this milestone and have an unsteady gait.

- Some may experience developmental regression, and many have behavioral difficulties including autistic features, reduced attention span, auto-aggression, anxiety and hypersensitivity to stimuli.
- While some subjects have congenital hypotonia (loss of body tone) other affected infants show irritability, stiffness, and hypertonia early in life, which progresses to spasticity and impaired gait later.
- Some patients may develop seizures of variable severity early in life.

○ Group of patients

Table 16: GRIA/GRIK/GRID Facebook Group Members

52 members	
GRIA1	3
GRIA2	12
GRIA3	23
GRIA4	1
GRIK2	1
Not confirmed (GRIA2 or GRIA3, possibly 1 GRIK)	12

○ **Animal models generated with patient variants**

- A GRIA3 A653T mouse – next door to the Lurcher site, LoF – was found to show aberrant sleep patterns (Davies et al., 2017).

○ **Functional/mechanistic studies:**

○ LoF Studies

- Multiple GRIA2 LoF mutations shown to underlie intellectual disability (Salpietro et al., 2019).
- GRIA3 variant with slowed recovery from desensitization found in patient with intellectual disability (Wu et al. 2007)
- GRIA3 variant showed total LoF in patients with dramatically altered sleep/wake cycle and intellectual disability (Davies et al., 2017).
- GRIA3 variant with reduced expression causes ID and movement disorder (Piard et al., 2020)

○ GoF Studies

- GRIA1 gain of function mutations found to cause ASD (de Ligt et al., 2012; Geisheker et al., 2017)
- GRIA3 variants in patients with intellectual disability showed slowed deactivation and reduced desensitization (Wu et al. 2007)

○ **Testing of small molecules ameliorating molecular/biological phenotype**

- The only widely licensed drug specifically targeting AMPARs is the non-competitive antagonist (NAM) perampanel (brand name Fycompa).

○ **GRIK Genes**

- The GRIK genes GRIK1-5 code for kainate receptors (KARs).
- GRIK1-3 produce low glutamate affinity receptors that can form homomers or heteromers.
- GRIK4 and 5 produce high glutamate affinity receptors that are obligate heteromers and must assemble with GRIK1-3.
- The roles of kainate receptors in the nervous system are diverse (Contractor et al., 2011).
- Kainate receptors can contribute to fast excitatory signalling post-synaptically in a similar vein to AMPARs, but also have pre-synaptic roles (Contractor et al., 2011).
- Kainate receptor can even act metabotopically (Rodriguez-Moreno & Lerma, 1998).

Table 17: General information for GRIK genes

Symbol	Name	Base Pairs	Protein Name	Amino Acids	Alternate Protein Name	Chromosomal Location
<i>GRIK1</i>	glutamate ionotropic receptor kainate type subunit 1	3472	GluK1	918	GluR5	21q22.11
<i>GRIK2</i>	glutamate ionotropic receptor kainate type subunit 2	4802	GluK2	908	GluR6, MRT6	6q16.3
<i>GRIK3</i>	glutamate ionotropic receptor kainate type subunit 3	9491	GluK3	919	GluR7	1p34.3
<i>GRIK4</i>	glutamate ionotropic receptor kainate type subunit 4	4214	GluK4	956	KA1	11q23.3
<i>GRIK5</i>	glutamate ionotropic receptor kainate type subunit 5	3310	GluK5	981	KA2	19q13.2

- **GRID Genes**

- The GRID genes GRID1 and GRID2 code for the delta subunit.
- They are members of the glutamate receptor superfamily and are membrane bound tetramers with the same modular structure as NMDARs, AMPARs and KARs (Traynelis et al., 2010; Burada et al., 2020).
- These proteins are important for development and neurogenesis (Uemura et al., 2010).
- They form connections across synapses helping to establish and maintain connections between the pre- and post-synapse (Uemura et al., 2010).
- They do not bind glutamate and instead bind glycine and D-serine. This binding is modulated by Ca²⁺ (Naur et al., 2007; Hansen et al., 2009).
- They have a conserved ion channel, but whether it can be gated is still uncertain – there is some evidence that they may be gated by activation of metabotropic receptors including mGlu1 (Ady et al., 2014).
- A mouse mutant with a change in the putative channel gate region called *Lurcher* has a constitutively open GRID2 channel

Table 18: General Information for GRID genes

Symbol	Name	Base Pairs	Protein Name	Amino Acids	Alternate Protein Name	Chromosomal Location
<i>GRID1</i>	glutamate ionotropic receptor delta type subunit 1	6154	GluD1	1009	d1, GluR delta-1	10q23.1-q23.2
<i>GRID2</i>	glutamate ionotropic receptor delta type subunit 2	5783	GluD2	1007	d1, GluR delta-2	4q22.1-q22.2

- **Conclusions**

- Based on the results of this audit and the GRIN Patient Family Survey, CureGRIN will identify our research goals and priorities for funding.

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