CureGRIN Research Audit

June 5, 2021

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Prepared by:
Meagan Collins, CureGRIN Research Coordinator

With Assistance from:

Allan Bayat (Danish Epilepsy Centre)
Christian Brander (GRIN Parent Advocate, GRIN2B Europe)
Graham Collingridge (University of Toronto)
Ian Coombs (University College London)
Mark Farrant (University College London)
Amela Huskic (GRIN Parent Advocate, GRIN2B Europe)
Tali Garin Shkolnik (GRIN Parent Advocate, GDRF)
Keith McArthur (GRIN Parent Advocate, CureGRIN)
Jenny-Li Örsell (Rare Disease Parent Advocate)
Berardo Rinaldi (Policlinico of Milan)
Angie Serrano (University of Utah)
Sandra Silva (GRIN Parent Advocate, GRIN2B Europe)
Dr. Stephen Traynelis (Emory University)
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 (AMPARs), 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 cholesterols 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
GRIN1	glutamate ionotropic receptor NMDA type subunit 1	4379	GluN1	938	NR1	9q34.3
GRIN2A	glutamate ionotropic receptor NMDA type subunit 2A	14706	GluN2A	1464	NR2A	16p13.2
GRIN2B	glutamate ionotropic receptor NMDA type subunit 2B	30609	GluN2B	1484	NR2B	12p13.1
GRIN2C	glutamate ionotropic receptor NMDA type subunit 2C	4271	GluN2C	1233	NR2C	17q25.1
GRIN2D	glutamate ionotropic receptor NMDA type subunit 2D	5511	GluN2D	1336	NR2D	19q13.33
GRIN3A	glutamate ionotropic receptor NMDA type subunit 3A	7838	GluN3A	1115	NR3A	9q31.1
GRIN3B	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 Mg2+ voltage-dependent blocking, are highly permeable to Ca2+, 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 Ca2+ 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 extrasynatic 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

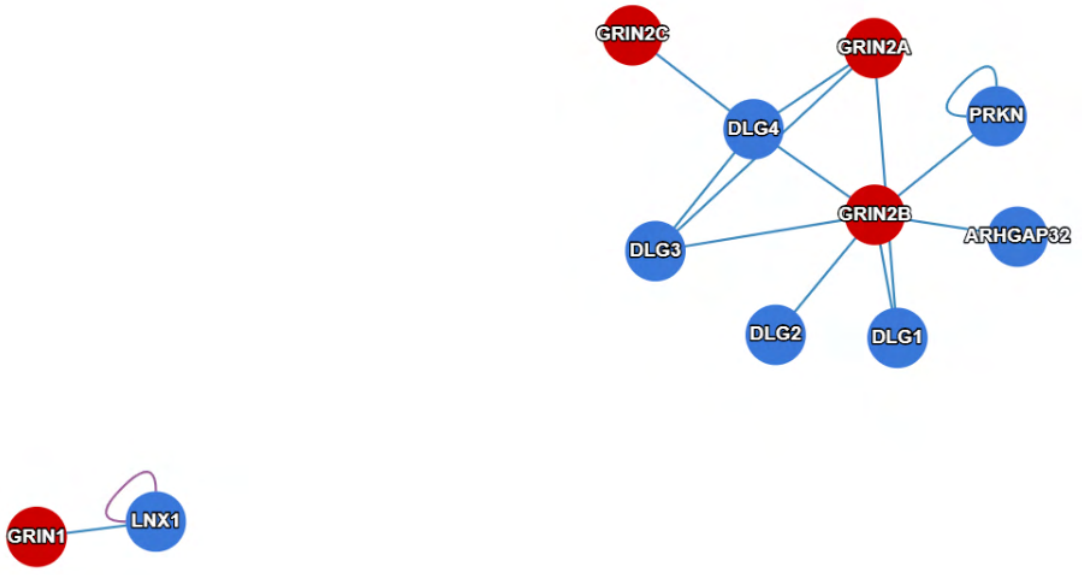


Figure 1: Interactome Map
Generated with Human Reference Protein Interactome Mapping Project
(http://www.interactome-atlas.org/about/)

- **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:ggaccggaaccagcgccgtccgcggagccgccgccgccgccgccgggcc 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): ggggactctggcccggagctgcggctgccttcctggaaacactcctgtcAGATGACT GCA
      - Sequence (TRAF2_1):

agcggcggcggcggcggcggcgttgggggcggtagctgggcgggcccttAGTTCCGGGCG

- 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): gccgcctgcccgctctagacgcgctgcacctgcgcggcaacccttggggCTGCGGGTGCG
  - Sequence (LRRC26_2): accgcgtccgtgcgctgccgccaggtgccttcgcgggagcgggcgcgctACAGCGCCTGG
- 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: ctcgtcccgccccggggcccctaccccgcggtcccgcggccccgcccgcCTCCGCCTCCG

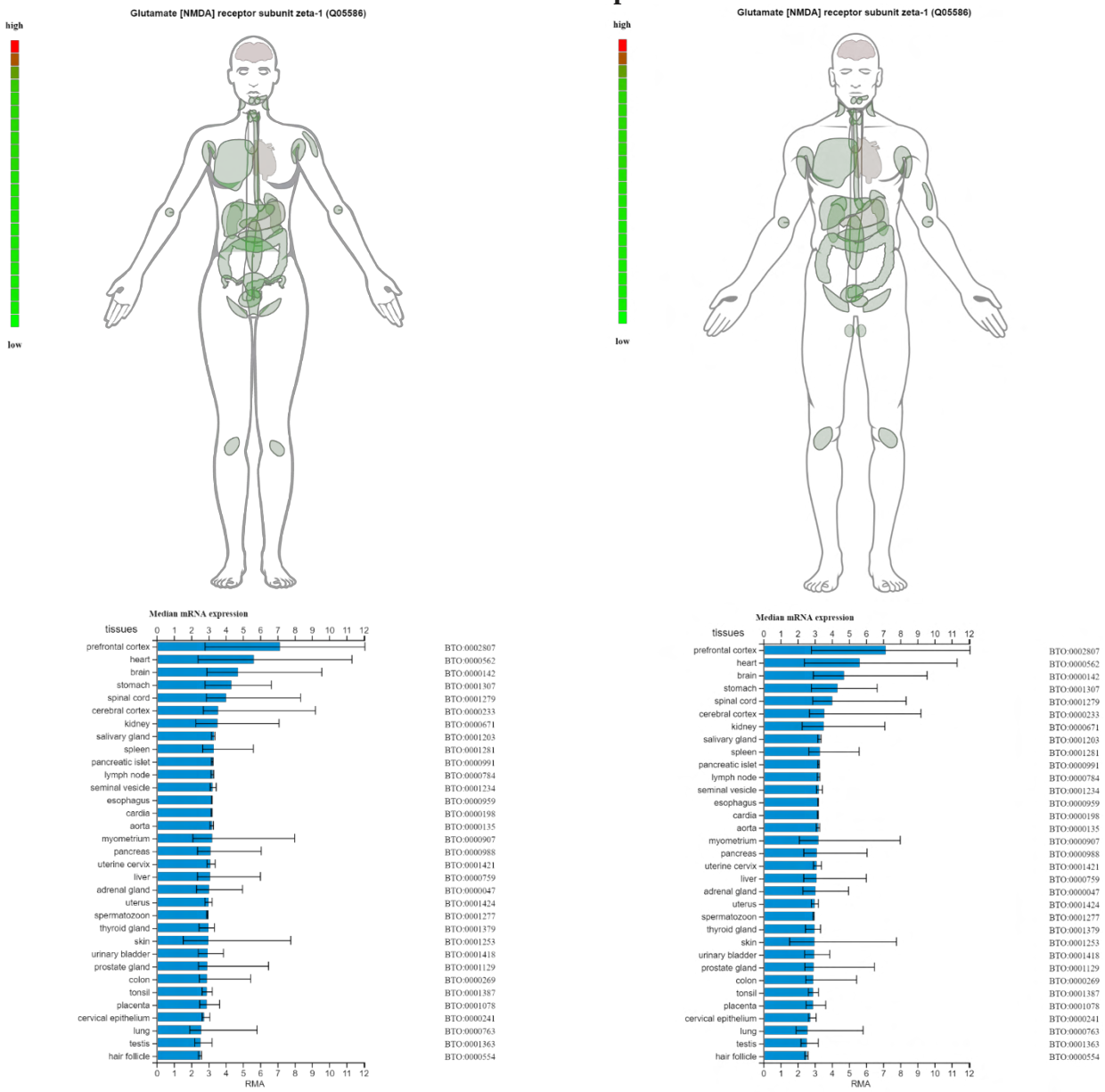
- GRIN2A
  - Promoter ID: GRIN2A_3, GRIN2A_2, GRIN2A_4, GRIN2A_1 (EPDNew (Dreos et al., 2014))
    - GeneHancer (GH) Identifier: GH16J010180
    - Genomic Location:chr16:10180601-10183401 (GRCh38/hg38);chr16:10274458-10277258 (GRCh37/hg19)
    - Sequence GRIN2A_3: agccaggggagcgcgctggggccgcagcatgcgggaacccgctaaacccGGTGGCTGCTG
    - Sequence GRIN2A_2: gttacctcctctttctctccctacctccctcgctcagcagctcccggtcGCACAACTCCC
    - Sequence GRIN2A_4: atgggaccgggtgagcgctgagaatcgcggccgcagccatcagccctggAGATGACCAGG
    - Sequence GRIN2A_1: gccacacgcgagcgcgctcccacactcacacacacactcgccctcaaacACACCAGCCCG
- GRIN2B
  - Promoter ID: EMP1_1 (Gene: *EMP1*)
    - GeneHancer (GH) Identifier: GH12J013193
    - Genomic Location: Genomic Location:chr12:13193348-13212836 (GRCh38/hg38); chr12:13346282-13365770 (GRCh37/hg19)
    - Sequence: tacaccagcagaggaaacttataacctcgggaggcaggtccttcccctcAGTGCGGTCAC

- Promoter ID: GRIN2B_3
  - GeneHancer (GH) Identifier: GH12J013967
  - Genomic Location:chr12:13967777-13967836 (GRCh38/hg38); chr12:14120711-14120770 (GRCh37/hg19)
  - Sequence: cacctcccctcatgcctgcaagtttcagctcagggatcctcagctccagGTCTTCCTGTC
- GRIN2C
  - Promoter ID: GRIN2C_1
    - GeneHancer (GH) Identifier: GH17J074859
    - Genomic Location: chr17:74859800-74860000 (GRCh38/hg38); chr17:72855923-72856123 (GRCh37/hg19)
    - Sequence: gcgtggtgctcagcttggccgccaggaggcgtggcgcgggtccccgcccGGAGCCGCCGC
  - Promoter ID: GRIN2C_3
    - GeneHancer (GH) Identifier: GH17J074861
    - Genomic Location: chr17:74861400-74861801 (GRCh38/hg38); chr17:72857523-72857924 (GRCh37/hg19)
    - Sequence: cggagctgagactgagcgcgccagccctccggggccgaggctctgggacAGACACCGCGA
- GRIN2D
  - Promoter ID: KDELR1_1 (Gene: KDELR1)
    - GeneHancer (GH) Identifier: GH19J048389
    - Genomic Location: chr19:48389414-48394001 (GRCh38/hg38); chr19:48892671-48897258 (GRCh37/hg19)
    - Sequence: ggggcggagcctctcctcccggactcctccccctctcgctctcctccctCTTCCCGGCTC
- 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: accgggcgggcagaggatgccaggcggagggacctgggagcgggatctgAGACTGCCGGA
    - Sequence GRIN3A_1: gaggcggggagaactttggcgctcggagcagagccacccttgctggccAGTCGCGTTGC
- GRIN3B
  - Promoter ID: GPX4_1 (Gene: *GPX4*)
    - GeneHancer (GH) Identifier: GH19J001097
    - Genomic Location: chr19:1097400-1108200 (GRCh38/hg38); chr19:1097399-1108199 (GRCh37/hg19)

        - Sequence: gaggagccgctggctcccagccccgccgcgatgagcctcggccgcctttGCCGCCTACTG
    - Promoter ID: KLF16_1 (Gene: *KLF16*)
        - GeneHancer (GH) Identifier: GH19J001851
        - Genomic Location: chr19:1850200-1866001 (GRCh38/hg38); chr19:1850199-1866000 (GRCh37/hg19)
        - Sequence: cggcggcggcgcgccgggcctcctcctcctcctccgcctcccgcACTCGAGCAGC
    - 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: gaagtgcgtgggggatgtgggaaggccggaaaccatttctgcagctgccAGTCCCCTTCC
        - Sequence CSNK1G2_1: gcagtggggcgcgtatggctgccgccccccgctggcagacgctggcggcGTAAGGCGCGC

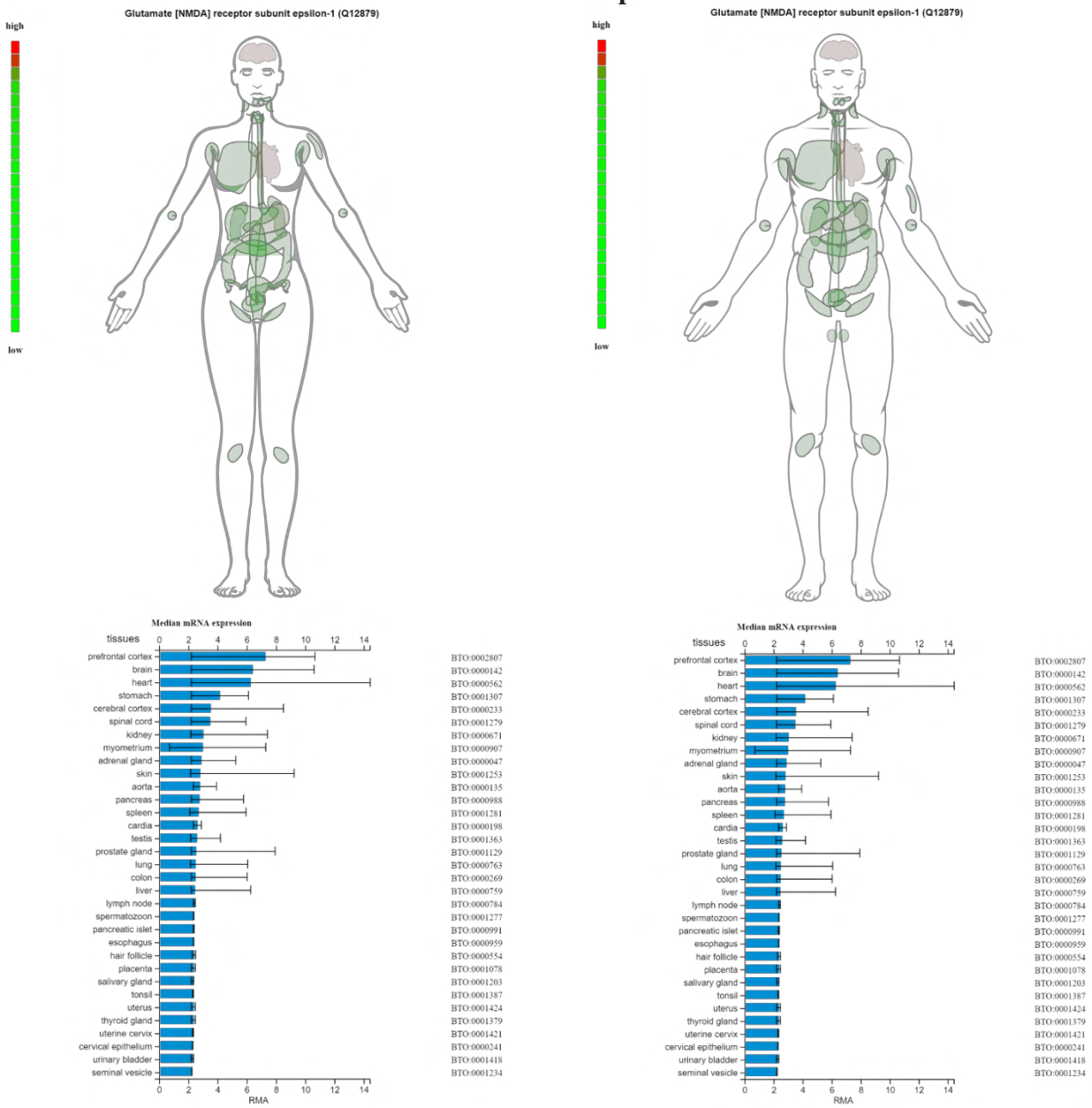
- **Spatiotemporal expression**
    - GluN1 subunit is ubiquitously expressed (Paoletti et al., 2013; Strehlow et al., 2019).
    - GluN2B and GluN2D subunits are mainly expressed prenatally (Paoletti et al., 2013; Strehlow et al., 2019).
    - GluN2A and GluN2C subunits have low expression prenatally. 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



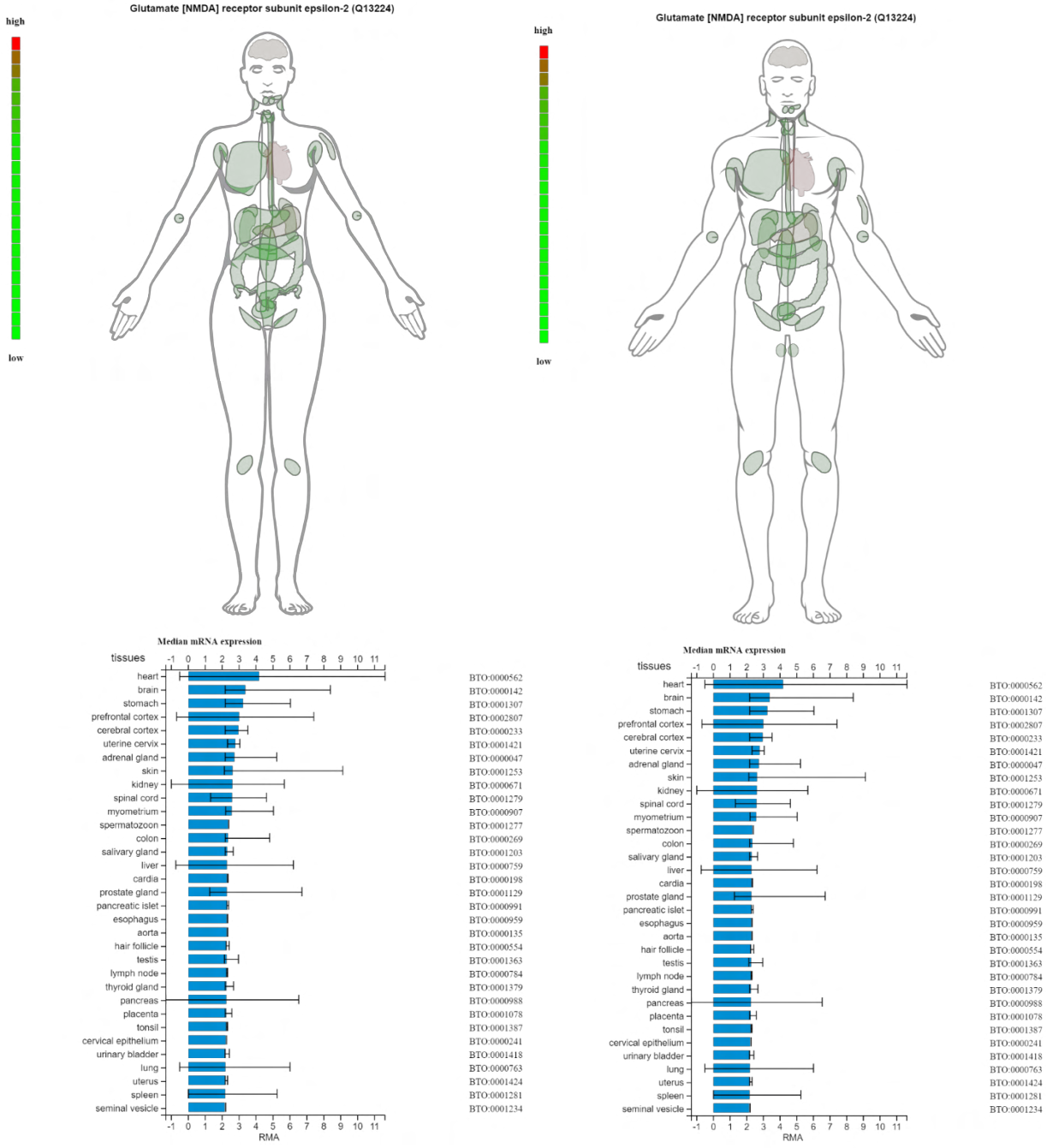
Retrieved from ProteomicsDB (Schmidt et al., ProteomicsDB. *Nucleic Acids Res.*, 2017)

GRIN2A mRNA Expression



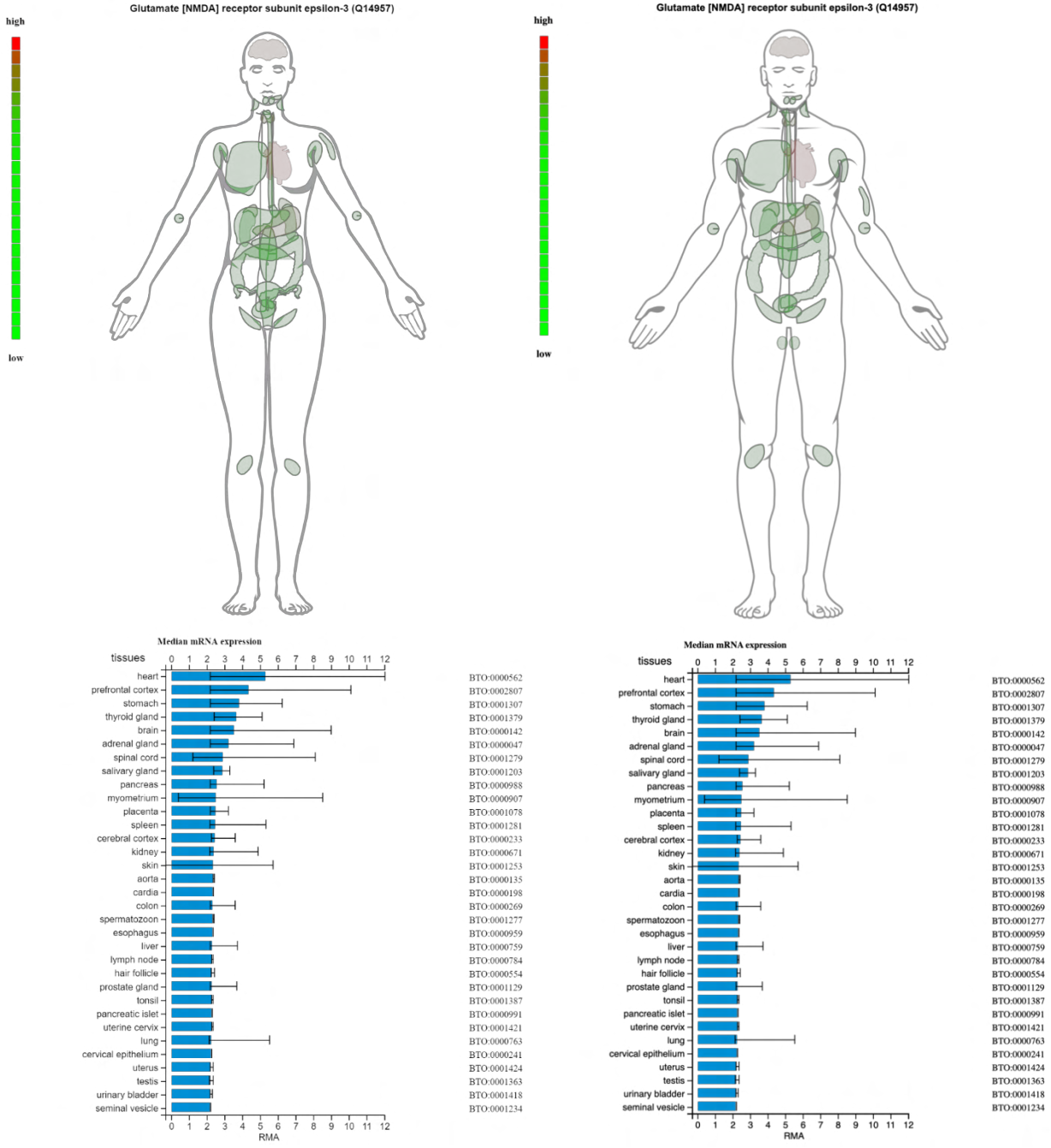
Retrieved from ProteomicsDB (Schmidt et al., ProteomicsDB. *Nucleic Acids Res.*, 2017)

GRIN2B mRNA Expression



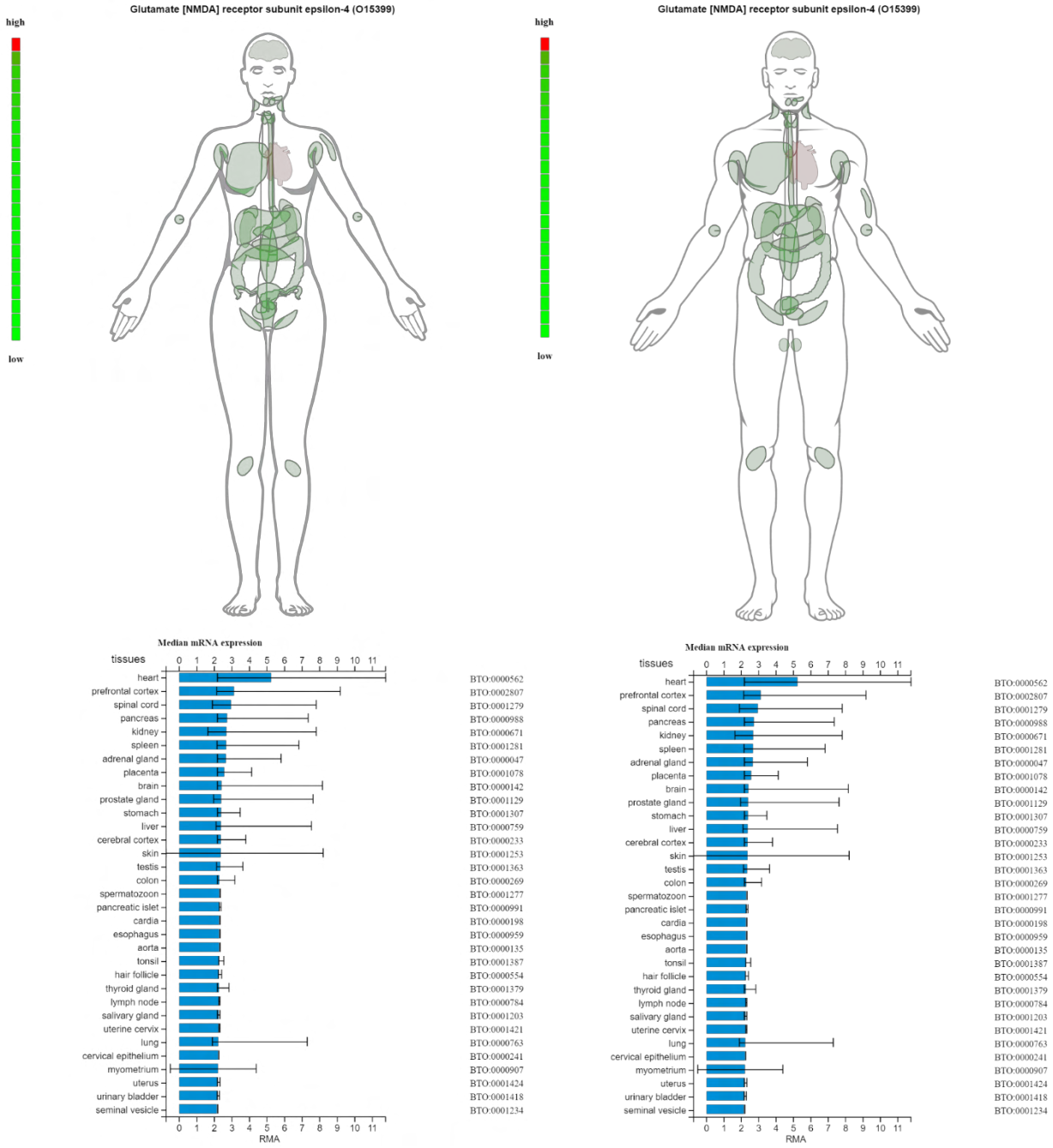
Retrieved from ProteomicsDB (Schmidt et al., ProteomicsDB. *Nucleic Acids Res.*, 2017)

GRIN2C mRNA Expression



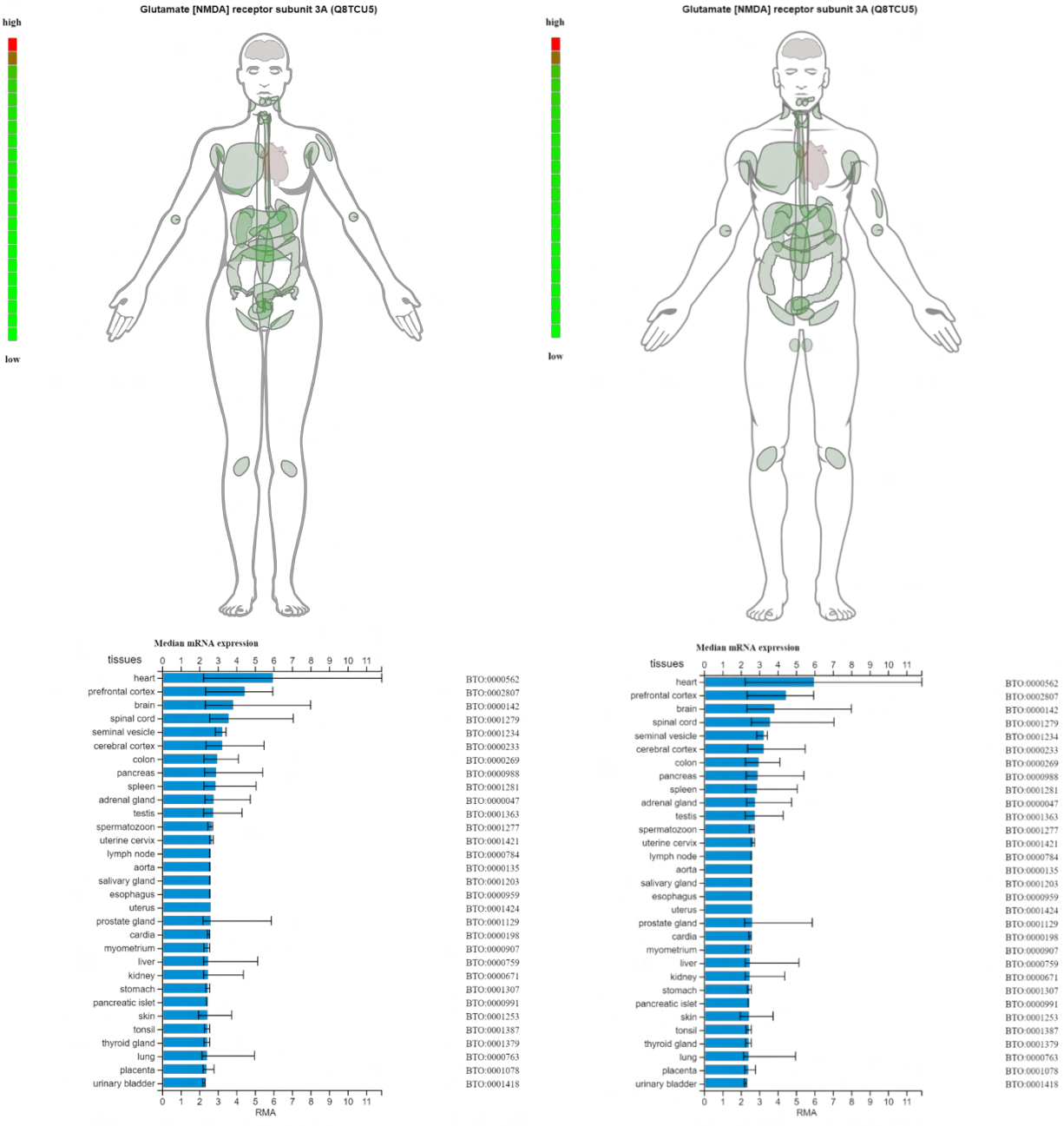
Retrieved from ProteomicsDB (Schmidt et al., ProteomicsDB. *Nucleic Acids Res.*, 2017)

GRIN2D mRNA Expression



Retrieved from ProteomicsDB (Schmidt et al., ProteomicsDB. *Nucleic Acids Res.*, 2017)

GRIN3A mRNA Expression



Retrieved from ProteomicsDB (Schmidt et al., ProteomicsDB. *Nucleic Acids Res.*, 2017)

- **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).
    - Aβ accumulation may activate NMDARs during the early stages of AD progression (Parameshwaran et al., 2008).
    - GluN2B-containing NMDARs are activated by Aβ 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*^{tm2Stl}
                - 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*$^{\Delta Ex5}$
                - 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 GluN1in 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
Pyrrolidinone	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-5β-pregnan-3α-yl sulfate (3α5βS 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
Trifluperidol	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).

        - For GRIN2D, the predicted incidence per 100,000 births is 4.61. Using the prediction model, the predicted number of affected babies with a variant in GRIN2D born in the U.S. in 2018 is 175. This finding appears to overestimate the prevalence of GRIN2D cases. We know of fewer than 20 individuals living with pathogenic GRIN2D variants (Lemke, 2020).

- **Patient Registries**
    - Information being collected:
        - Medical records
        - Clinical genetic lab results
        - Conducting phone interviews to assess medical history, diagnosis, adaptive functioning/behavior, etc.
        - Conducting surveys to assess background, seizure history, neurological storms, child/adult behavior, social responsiveness, communication, etc.
    - Current Registries
        - **Simons Searchlight**: https://www.simonssearchlight.org/research/what-we-study/
        - **University of Leipzig- Europe, Asia, and Africa Registry**: GRIN@medizin.uni-leipzig.de, https://www.uniklinikum-leipzig.de/einrichtungen/humangenetik/forschung/grin
        - **GRIN Variant Patient Registry (GVPR) (University of Colorado)-North America Registry:** Jenifer.Sargent@childrenscolorado.org
- **Phenotype characterization of patients**

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 Oglionucleotides, 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/
Voyageur 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	*in vivo* 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**

AMPARs 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 Heineman 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 Ca^{2+} impermeable (CI-AMPARs) while those which lack GluA2 are Ca^{2+}-permeable (CP-AMPARs) (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
GRIA1	glutamate ionotropic receptor AMPA type subunit 1	5584	GluA1	906	GluR1, GLURA	5q33.2
GRIA2	glutamate ionotropic receptor AMPA type subunit 2	3398	GluA2	901	GluR2, GLURB	4q32.1
GRIA3	glutamate ionotropic receptor AMPA type subunit 3	5148	GluA3	894	GluR3, GLURC, MRX94	Xq25
GRIA4	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**:
  - **AMPAR Studies**:
    - α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs) 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).

  - **AMPAR protein partners**
    - GluA subunits assemble with each other as homomeric or hetreomeric tratramers. Native AMPARs have recently been shown by cyo-EM to exist as homomers, diheteromers or triheteromers (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: ggagccagcgctccagctagcatgaggacgggcttcttttcccgtgctcAGTTAATCTGG
    - GRIA2
        - Promoter ID: GRIA2_1
            - Genomic Location: chr4:157218727–157222727 (GRCh38/hg38); chr4:158139879–158143879 (GRCh37/hg19).
            - Sequence: cgcgcgtgagtgagagaggagagagggagaagagagcgcgagagagggtGAGTGTGTGTG
        - Promoter ID: GRIA2_2
            - Genomic Location: chr4:157218572–157222572 (GRCh38/hg38); chr4:158139724–158143724 (GRCh37/hg19).
            - Sequence: gtggtgcggggtgccgggcgccgtgcgggggaggggcgcgcgctcccgCCTCCTGCCGC
    - GRIA3
        - Promoter ID: GRIA3_1
            - Genomic Location: chrX:123181961–123185961 (GRCh38/hg38); chrX:122315814–122319814 (GRCh37/hg19).
            - Sequence: gagccttttcgctctttccttttttttccccccctctttagacctaccatCTTTTGCGGGG
        - Promoter ID: GRIA3_2
            - Genomic Location: chrX:123182344–123186344 (GRCh38/hg38); chrX:122316197–122320197 (GRCh37/hg19).
            - Sequence: gagcgagagagagcgagcgaataagagagagagtaagagggagagagaaGAAGAGGAAGA

          Promoter ID: GRIA3_3
            - Genomic Location: chrX:123181572–123185572 (GRCh38/hg38); chrX:122315425–122319425 (GRCh37/hg19).
            - Sequence: gcggcagagaccgggcatgcgcagcatcttcgggcgcattgtgatgggaACTGCTTCTCT
        - Promoter ID: GRIA3_4
            - Genomic Location: chrX:123182504–123186504 (GRCh38/hg38); chrX:122316357–122320357 (GRCh37/hg19).

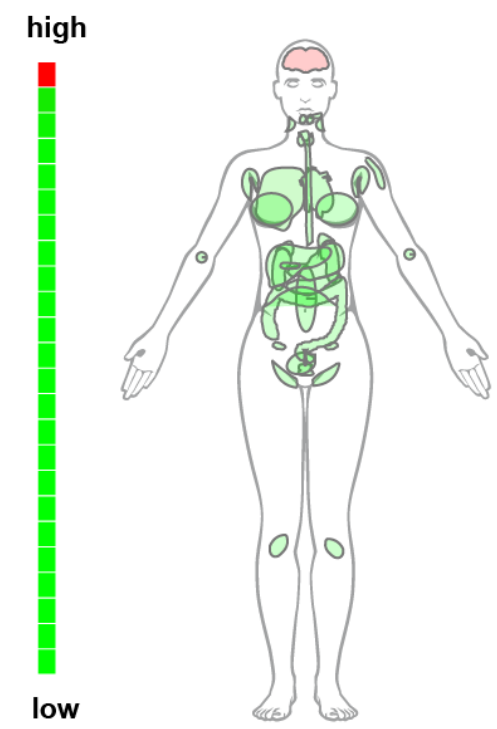
        - Sequence: attctttttctttttctattattattttgacgactcctgagttgcgcccATGCTCTTGTC

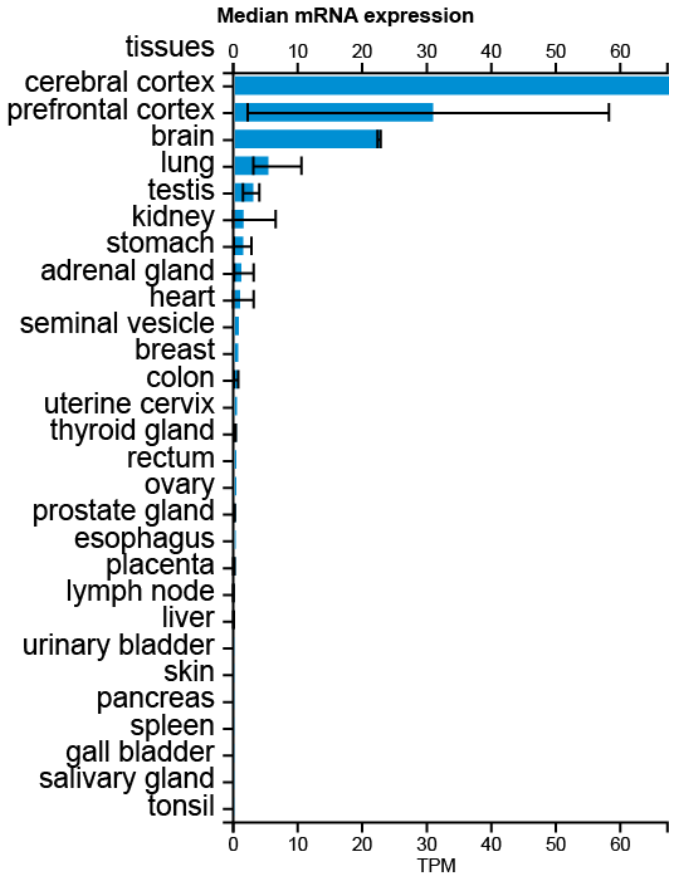
    - Promoter ID: GRIA3_5
        - Genomic Location: chrX:123182239–123186239 (GRCh38/hg38); chrX:122316092–122320092 (GRCh37/hg19).
        - Sequence: ttccagattggtgtgaagacagaagtgaggtgggggggaagggaggggggtGTGAGAGATCC

- GRIA4
    - Promoter ID: GRIA4_1
        - Genomic Location: chr11:105608072–105612072 (GRCh38/hg38); chr11:105478799–105482799 (GRCh37/hg19).
        - Sequence: gtgagaaatctttgctgcagcgaggaccggagtcccccgcgcgcagcccAGTGGCAGAAG
    - Promoter ID: GRIA4_2
        - Genomic Location: chr11:105608890–105612890 (GRCh38/hg38); chr11:105479617–105483617 (GRCh37/hg19).
        - Sequence: ccttttttttctttctttttctttctttttttttttttttttttttgGTTGATTTTAA
    - Promoter ID: GRIA4_3
        - Genomic Location: chr11:105608714–105612714 (GRCh38/hg38); chr11:105479441–105483441 (GRCh37/hg19).
        - tgtctcatccctgcgagcagccactagacgctccaccaccatcttttgcATGTGCAACAT

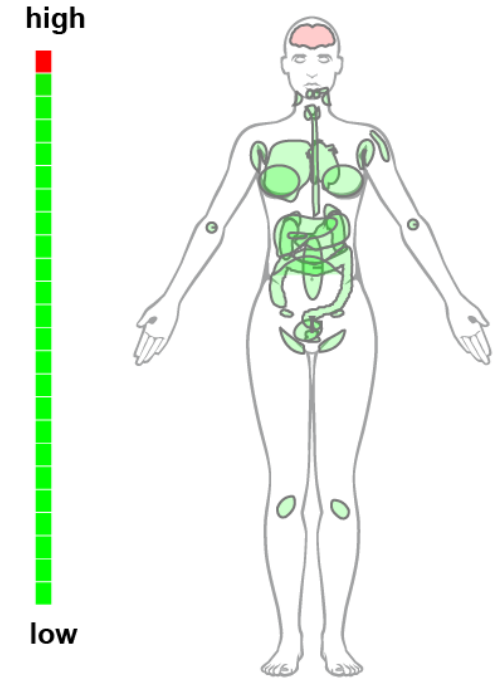
- **Expression patterns**
    - **GRIA expression in the brain**
        - AMPARs are found throughout the brain, however there is variation in the relative expression of AMPAR subunits by brain region and within different cell types within each region.
        - For detailed analysis of Allen brain 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 myencephalon.
        - 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).

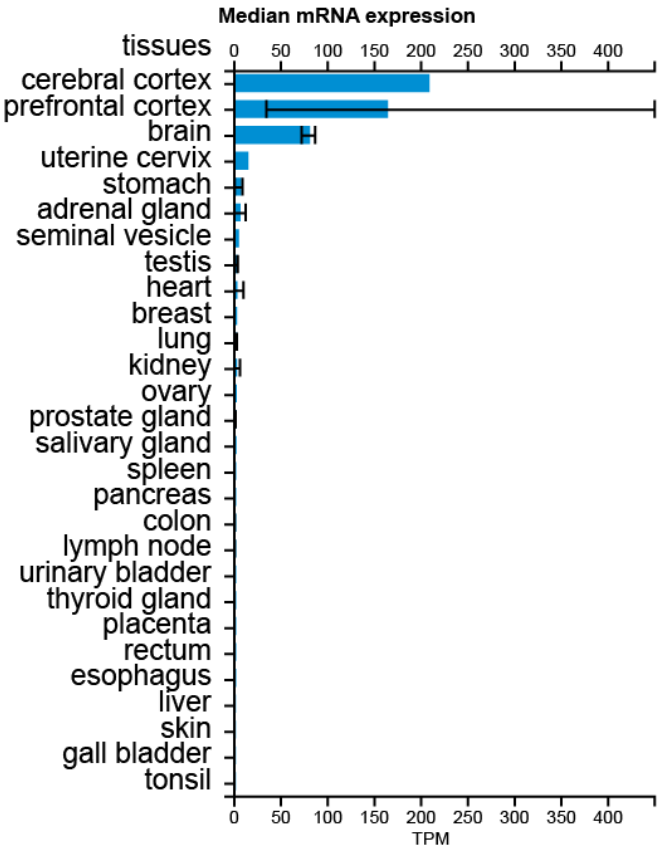
Glutamate receptor 1 (P42261)



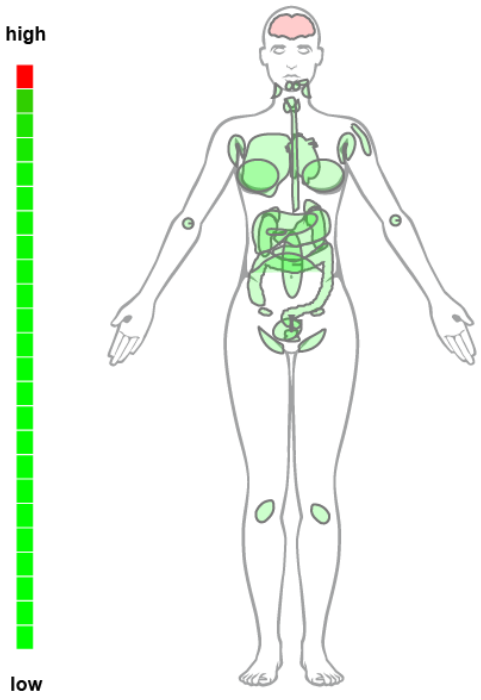


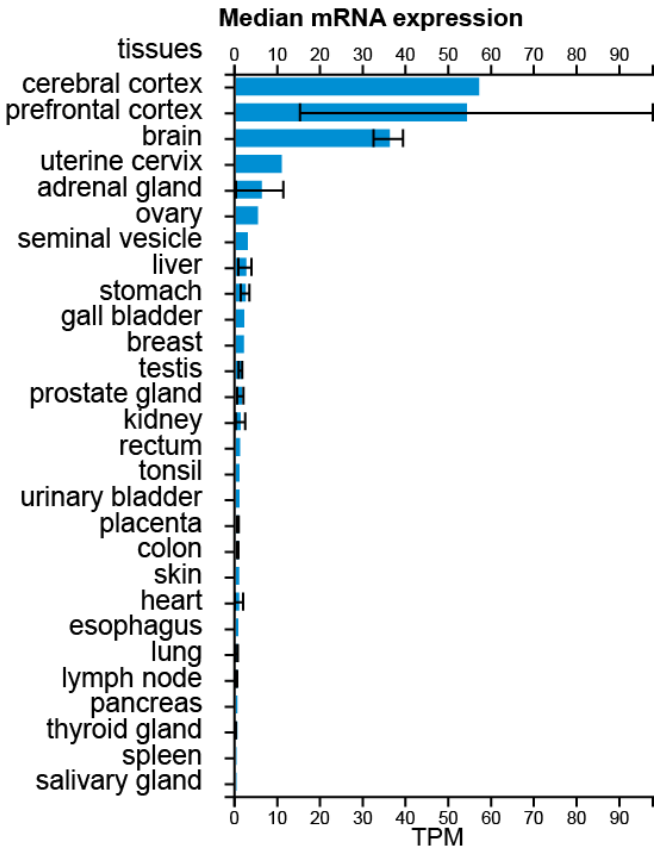
Glutamate receptor 2 (P42262)



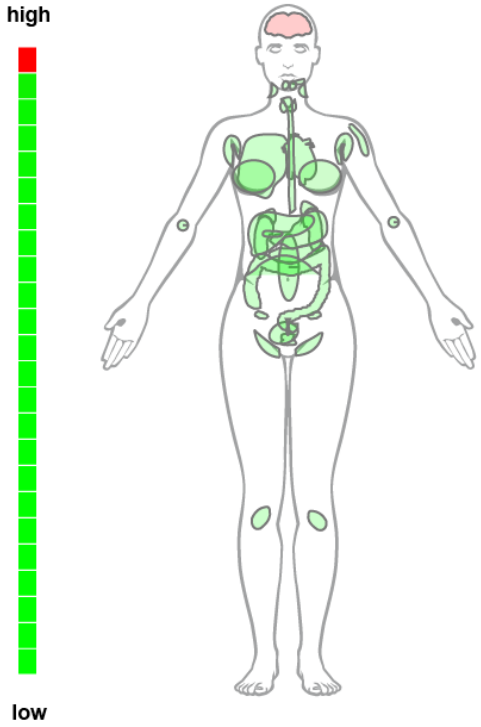


Glutamate receptor 3 (P42263)





Glutamate receptor 4 (P48058)



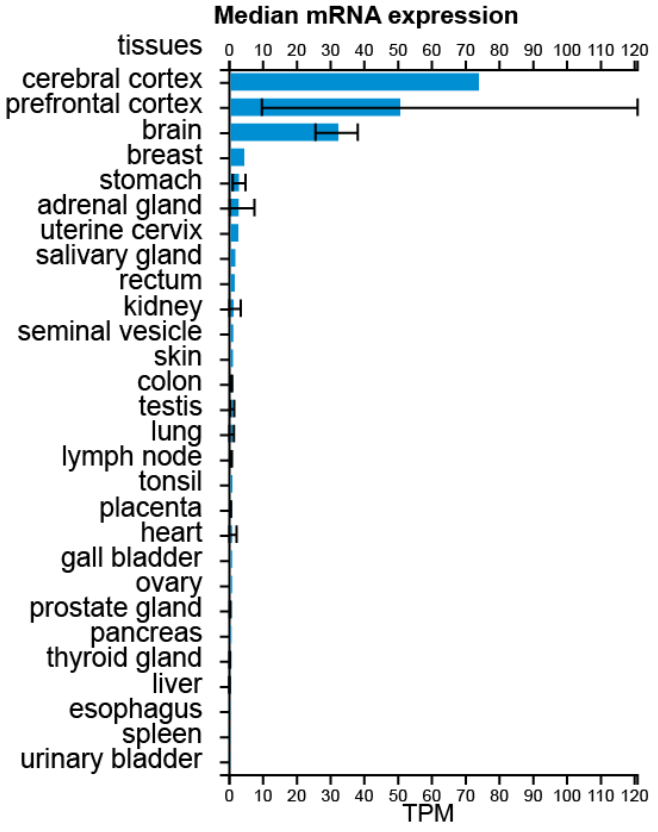


Table 14: AMPAR Agonists and Antagonists

Drug Name	Agonist/Antagonist	Reference
AMPA	Agonist (full)	Strange et al., 2006
L-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	Kizelsztein et al., 2000; Jin et al., 2003
5-Fluowillardine	Agonist	Greenwood et al., 2006
ACPA	Agonist	Strange et al., 2006
Cl-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 γ2)	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 γ2)	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
D-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 γ8-selective)	Gardinier et al., 2016; Kato et al., 2016; Knopp et al., 2019
JNJ-55511118	NAM (TARP γ8-selective)	Maher et al 2016; Dohrke et al., 2020; Yu et al., 2021
JNJ-61432059	NAM (TARP γ8-selective)	Savall et al., 2019
VU0612951	NAM (poss γ2-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 mildstone and have an unsteady gate. Some may experience developmental regression and many have behavioral difficulties including autistic features, reduced attention span, auto-aggresion, 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 gate.

- 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 metabotropically (Rodriguez-Moreno & Lerma, 1998).

Table 17: General information for GRIK genes

Symbol	Name	Base Pairs	Protein Name	Amino Acids	Alternate Protein Name	Chromosomal Location
GRIK1	glutamate ionotropic receptor kainate type subunit 1	3472	GluK1	918	GluR5	21q22.11
GRIK2	glutamate ionotropic receptor kainate type subunit 2	4802	GluK2	908	GluR6, MRT6	6q16.3
GRIK3	glutamate ionotropic receptor kainate type subunit 3	9491	GluK3	919	GluR7	1p34.3
GRIK4	glutamate ionotropic receptor kainate type subunit 4	4214	GluK4	956	KA1	11q23.3
GRIK5	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 Ca^{2+} (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
GRID1	glutamate ionotropic receptor delta type subunit 1	6154	GluD1	1009	d1, GluR delta-1	10q23.1-q23.2
GRID2	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.

- **References**

Abumaria N, Yin B, Zhang L, et al. Effects of elevation of brain magnesium on fear conditioning, fear extinction, and synaptic plasticity in the infralimbic prefrontal cortex and lateral amygdala. *J Neurosci*. 2011;31(42):14871-14881. doi:10.1523/JNEUROSCI.3782-11.2011

Acker TM, Yuan H, Hansen KB, et al. Mechanism for noncompetitive inhibition by novel GluN2C/D N-methyl-D-aspartate receptor subunit-selective modulators. *Mol Pharmacol*. 2011;80(5):782-795. doi:10.1124/mol.111.073239

Ady V, Perroy J, Tricoire L, Piochon C, Dadak S, Chen X, Dusart I, Fagni L, Lambolez B, Levenes C (2014) Type 1 metabotropic glutamate receptors (mGlu1) trigger the gating of GluD2 delta glutamate receptors. *EMBO Rep.* **15**(1):103-9.

Ahmed AH, Thompson MD, Fenwick MK, Romero B, Loh AP, Jane DE, Sondermann H and Oswald RE (2009a) Mechanisms of antagonism of the GluR2 AMPA receptor: structure and dynamics of the complex of two willardiine antagonists with the glutamate binding domain. *Biochemistry* **48**:3894-3903.

Ahmed AH, Ptak CP and Oswald RE (2010) Molecular mechanism of flop selectivity and subsite recognition for an AMPA receptor allosteric modulator: structures of GluA2 and GluA3 in complexes with PEPA. *Biochemistry* **49**:2843-2850.

Ahmed AH and Oswald RE (2010) Piracetam defines a new binding site for allosteric modulators of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. *J Med Chem* **53**:2197-2203.

Aizenman E, Jensen FE, Gallop PM, Rosenberg PA, Tang LH. Further evidence that pyrroloquinoline quinone interacts with the N-methyl-D-aspartate receptor redox site in rat cortical neurons in vitro. *Neurosci Lett*. 1994 Feb 28;168(1-2):189-92. doi: 10.1016/0304-3940(94)90447-2. PMID: 7518062.

Allen NC, Bagade S, McQueen MB, Ioannidis JPA, Kavvoura FK, Khoury MJ, et al. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. *Nat Genet* (2008) 40:827–34. doi: 10.1038/ng.171

Alonso P, Gratacós M, Segalàs C, Escaramís G, Real E, Bayés M, Labad J, López-Solà C, Estivill X, Menchón JM. Association between the NMDA glutamate receptor GRIN2B gene and obsessive-compulsive disorder. *J Psychiatry Neurosci*. 2012 Jul;37(4):273-81. doi: 10.1503/jpn.110109. PMID: 22433450; PMCID: PMC3380099.

Amador A, Bostick CD, Olson H, Peters J, Camp CR, Krizay D, Chen W, Han W, Tang W, Kanber A, Kim S, Teoh J, Sah M, Petri S, Paek H, Kim A, Lutz CM, Yang M, Myers SJ, Bhattacharya S, Yuan H, Goldstein DB, Poduri A, Boland MJ, Traynelis SF, Frankel WN. Modelling and treating GRIN2A developmental and epileptic encephalopathy in mice. *Brain*. 2020 Jul 1;143(7):2039-2057. doi: 10.1093/brain/awaa147. PMID: 32577763; PMCID: PMC7363493.

Anaparti V, Ilarraza R, Orihara K, Stelmack GL, Ojo OO, Mahood TH, et al. (2015). NMDA receptors mediate contractile responses in human airway smooth muscle cells. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 308 L1253–L1264. 10.1152/ajplung.00402.2014

Anderson M, Suh J M, Kim EY, Dryer SE. (2011). Functional NMDA receptors with atypical properties are expressed in podocytes. *Am. J. Physiol. Cell. Physiol.* 300 C22–C32. 10.1152/ajpcell.00268.2010

Andersson O, Stenqvist A, Attersand A and von Euler G (2001) Nucleotide sequence, genomic organization, and chromosomal localization of genes encoding the human NMDA receptor subunits NR3A and NR3B. *Genomics*.78:178-184.

András IE, Deli MA, Veszelka S, Hayashi K, Hennig B, Toborek M. (2007). The NMDA and AMPA KA receptors are involved in glutamate-induced alterations of occludin expression and phosphorylation in brain endothelial cells. *J. Cerebr. Blood Flow Mettab.* 27 1431–1443. 10.1038/sj.jcbfm.9600445

Antošová M, Strapková A. (2013). Study of the interaction of glutamatergic and nitrergic signalling in conditions of the experimental airways hyperreactivity. *Pharmacol. Rep.* 65 650–657. 10.1016/S1734-1140(13)71042-9

Aoki Y, Nakahara T, Asano D, Ushikubo H, Mori A, Sakamoto K, Ishii K. Preventive effects of rapamycin on inflammation and capillary degeneration in a rat model of NMDA-induced retinal injury. *Biol Pharm Bull*. 2015;38(2):321-4. doi: 10.1248/bpb.b14-00631. PMID: 25747992.

Arai AC, Kessler M, Rogers G and Lynch G (2000) Effects of the potent ampakine CX614 on hippocampal and recombinant AMPA receptors: interactions with cyclothiazide and GYKI 52466. *Mol Pharmacol* **58**:802-813.

Armstrong N and Gouaux E (2000) Mechanisms for activation and antagonism of an AMPA-sensitive glutamate receptor: crystal structures of the GluR2 ligand binding core. *Neuron* **28**:165-181.

Armstrong N, Sun Y, Chen G-Q and Gouaux E. (1998) Structure of a glutamate receptor ligand binding core in complex with kainate. *Nature*, 395, 913–917.

Auberson YP, Acklin P, Bischoff S, Moretti R, Ofner S, Schmutz M and Veenstra SJ (1999) N-phosphonoalkyl-5-aminomethylquinoxaline-2,3-diones: in vivo active AMPA and NMDA(glycine) antagonists. *Bioorg Med Chem Lett* **9**:249-254.

Azumaya CM, Days EL, Vinson PN, Stauffer S, Sulikowski G, Weaver CD and Nakagawa T (2017) Screening for AMPA receptor auxiliary subunit specific modulators. *PLoS ONE* **12**:e0174742.

Bai G, Hoffman PW. Transcriptional Regulation of NMDA Receptor Expression. In: Van Dongen AM, editor. *Biology of the NMDA Receptor*. Boca Raton (FL): CRC Press/Taylor & Francis; 2009. Chapter 5. Available from: https://www.ncbi.nlm.nih.gov/books/NBK5277/

Bai G, Kusiak JW. Nerve growth factor up-regulates the N-methyl-D-aspartate receptor subunit 1 promoter in PC12 cells. *J Biol Chem*. 1997 Feb 28;272(9):5936-42. doi: 10.1074/jbc.272.9.5936. PMID: 9038213.

Bain J. Simons Searchlight. "GRIN2B Family Meeting." Presented at 2019 CFERV Conference on GRIN Variants. 2019. Atlanta.

Balannik V, Menniti FS, Paternain AV, Lerma J and Stern-Bach Y (2005) Molecular mechanism of AMPA receptor noncompetitive antagonism. *Neuron* **48**:279-288.

Balu, D, Li Y, Takagi S. et al. An mGlu5-Positive Allosteric Modulator Rescues the Neuroplasticity Deficits in a Genetic Model of NMDA Receptor Hypofunction in Schizophrenia. *Neuropsychopharmacology* 41, 2052–2061 (2016).

Banke TG, Bowie D, Lee H, Huganir RL, Schousboe A and Traynelis SF (2000) Control of GluR1 AMPA receptor function by cAMP-dependent protein kinase. *J Neurosci* **20**:89-102.

Baranovic J, Braunbeck S, Zaki N, Minniberger S, Chebli M, and Plested AJR. 2021. The action of Con-ikot-ikot toxin on single AMPA-type glutamate receptors. *bioRxiv*.

Barbon A, and S. Barlati. 2011. Glutamate receptor RNA editing in health and disease. *Biochemistry* 76: 882-889.

Bar-Shira O, Maor R, Chechik G. Gene expression switching of receptor subunits in human brain development. *PLoS Comput Biol* 2015; 11: e1004559.

Basuroy S, Leffler CW, Parfenova H. (2013). CORM-A1 prevents blood-brain barrier dysfunction caused by ionotropic glutamate receptor-mediated endothelial oxidative stress and apoptosis. *Am. J. Physiol. Cell Physiol.* 304 C1105–C1115. 10.1152/ajpcell.00023.2013

Bats C, Soto D, Studniarczyk D, Farrant M and Cull-Candy SG (2012) Channel properties reveal differential expression of TARPed and TARPless AMPARs in *stargazer* neurons. *Nat Neurosci* **15**:853-861.

Baxter PS, Bell KF, Hasel P, Kaindl AM, Fricker M, Thomson D, Cregan SP, Gillingwater TH, Hardingham GE. Synaptic NMDA receptor activity is coupled to the transcriptional control of the glutathione system. *Nat Commun*. 2015 Apr 9;6:6761. doi: 10.1038/ncomms7761. Erratum in: Nat Commun. 2017 Sep 11;8:16158. PMID: 25854456; PMCID: PMC4403319.

Benke T, Drake A, Sargent J, Marsh E, Poduri A, Myers S. GRIN Variant Patient Registry (GVPR). Presented at 2019 CFERV Conference on GRIN Variants. 2019. Atlanta.

Berk M, Malhi GS, Gray LJ, Dean OM. The promise of N-acetylcysteine in neuropsychiatry. *Trends Pharmacol Sci*. 2013 Mar;34(3):167-77. doi: 10.1016/j.tips.2013.01.001. Epub 2013 Jan 29. PMID: 23369637.

Bernard LP, Zhang H. MARK/Par1 Kinase Is Activated Downstream of NMDA Receptors through a PKA-Dependent Mechanism. *PLoS One*. 2015 May 1;10(5):e0124816. doi: 10.1371/journal.pone.0124816. PMID: 25932647; PMCID: PMC4416788.

Bertolino M, Baraldi M, Parenti C, Braghiroli D, DiBella M, Vicini S, Costa E (1993) Modulation of AMPA/kainate receptors by analogues of diazoxide and cyclothiazide in thin slices of rat hippocampus. *Recept Channels* **1**(4):267-78.

Bjerrum EJ, Kristensen AS, Pickering DS, Greenwood JR, Nielsen B, Liljefors T, Schousboe A, Brauner-Osborne H and Madsen U (2003) Design, synthesis, and pharmacology of a highly subtype-selective GluR1/2 agonist, (RS)-2-amino-3-(4-chloro-3-hydroxy-5-isoxazolyl)propionic acid (Cl-HIBO). *J Med Chem* **46**:2246-2249.

Bliss TV, Collingridge GL 1993. A synaptic model of memory: Long-term potentiation in the hippocampus. *Nature* 361: 31–39

Bonnet C, Leheup B, Beri M, Philippe C, Gregoire MJ and Jonveaux P (2009) Aberrant GRIA3 transcripts with multi-exon duplications in a family with X-linked mental retardation. *Am J Med Genet A* **149A**:1280-1289.

Bowie D, and M. L. Mayer. 1995. Inward rectification of both AMPA and kainate subtype glutamate receptors generated by polyamine-mediated ion channel block. *Neuron* 15: 453-462.

Bozorgmehr A, Ghadirivasfi M, Shahsavand Ananloo E. Obsessive-compulsive disorder, which genes? Which functions? Which pathways? An integrated holistic view regarding OCD and its complex genetic etiology. *J Neurogenet*. 2017 Sep;31(3):153-160. doi: 10.1080/01677063.2017.1336236. Epub 2017 Jun 13. PMID: 28608743.

Bradley J, Carter SR, Rao VR, Wang J, Finkbeiner S. Splice variants of the NR1 subunit differentially induce NMDA receptor-dependent gene expression. *J Neurosci*. 2006;26(4):1065-1076. doi:10.1523/JNEUROSCI.3347-05.2006

Brancaccio M, Patton AP, Chesham JE, Maywood ES, Hastings MH. Astrocytes Control Circadian Timekeeping in the Suprachiasmatic Nucleus via Glutamatergic Signaling. *Neuron*. 2017 Mar 22;93(6):1420-1435.e5. doi: 10.1016/j.neuron.2017.02.030. Epub 2017 Mar 9. PMID: 28285822; PMCID: PMC5376383.

Bretin, S., C. Louis, L. Seguin, S. Wagner, J. Y. Thomas, S. Challal, N. Rogez, K. Albinet, F. Iop, N. Villain, S. Bertrand, A. Krazem, D. Bérachochéa, S. Billiald, C. Tordjman, A. Cordi, D. Bertrand, P. Lestage, and L. Danober. 2017. Pharmacological characterisation of S 47445, a novel positive allosteric modulator of AMPA receptors. *PLoS One* 12: e0184429.

Burada AP, Vinnakota R, Bharti P, Dutta P, Dubey N, Kumar J (2020) Emerging insights into the structure and function of ionotropic glutamate delta receptors. *Br J Pharmacol*. doi: 10.1111

Burnashev, N., H. Monyer, P. H. Seeburg, and B. Sakmann. 1992. Divalent ion permeability of AMPA receptor channels is dominated by the edited form of a single subunit. *Neuron* 8: 189-198.

Bygrave AM, Kilonzo K, Kullmann DM, Bannerman DM, Kätzel D. Can N-Methyl-D-Aspartate Receptor Hypofunction in Schizophrenia Be Localized to an Individual Cell Type? *Front Psychiatry*. 2019 Nov 21;10:835. doi: 10.3389/fpsyt.2019.00835. PMID: 31824347; PMCID: PMC6881463.

Cai L, Loo LS, Atlashkin V, Hanson BJ, Hong W. Deficiency of sorting nexin 27 (SNX27) leads to growth retardation and elevated levels of N-methyl-D-aspartate receptor 2C (NR2C). *Mol Cell Biol*. 2011 Apr;31(8):1734-47. doi: 10.1128/MCB.01044-10. Epub 2011 Feb 7. PMID: 21300787; PMCID: PMC3126336.

Callahan PM, Terry AV Jr, Nelson FR, Volkmann RA, Vinod AB, Zainuddin M, Menniti FS. Modulating inhibitory response control through potentiation of GluN2D subunit-containing NMDA receptors. *Neuropharmacology*. 2020 Aug 15;173:107994. doi: 10.1016/j.neuropharm.2020.107994. Epub 2020 Feb 11. PMID: 32057801; PMCID: PMC7293930.

Carvill GL, Regan BM, Yendle SC, O'Roak BJ, Lozovaya N, Bruneau N, Burnashev N, Khan A, Cook J, Geraghty E, Sadleir LG, Turner SJ, Tsai MH, Webster R, Ouvrier R, Damiano JA, Berkovic SF, Shendure J, Hildebrand MS, Szepetowski P, Scheffer IE, Mefford HC. GRIN2A mutations cause epilepsy-aphasia spectrum disorders. *Nat Genet*. 2013;45:1073–6.

Catts VS, Lai YL, Weickert CS, Weickert TW, Catts SV. A quantitative review of the postmortem evidence for decreased cortical N-methyl-d-aspartate receptor expression levels in schizophrenia: how can we link molecular abnormalities to mismatch negativity deficits?. *Biol Psychol* (2016) 116:57–67. doi: 10.1016/j.biopsycho.2015.10.013

Chang P, Augustin K, Boddum K, Williams S, Sun M, Terschak JA, Hardege JD, Chen PE, Walker MC, Williams RS. Seizure control by decanoic acid through direct AMPA receptor inhibition. *Brain*. 2016 Feb;139(Pt 2):431-43. doi: 10.1093/brain/awv325. Epub 2015 Nov 25. PMID: 26608744; PMCID: PMC4805082.

Chang P, Zuckermann AM, Williams S, Close AJ, Cano-Jaimez M, McEvoy JP, Spencer J, Walker MC and Williams RS (2015b) Seizure control by derivatives of medium chain fatty acids associated with the ketogenic diet show novel branching-point structure for enhanced potency. *J Pharmacol Exp Ther* **352**:43-52.

Chatterton JE, Awobuluyi M, Premkumar LS, Takahashi H, Talantova M, Shin Y, Cui J, Tu S, Sevarino KA, Nakanishi N, Tong G, Lipton SA, Zhang D. Excitatory glycine receptors containing the NR3 family of NMDA receptor subunits. *Nature*. 2002;415:793–798.

Chen BS, Braud S, Badger JD 2nd, Isaac JT, Roche KW. Regulation of NR1/NR2C N-methyl-D-aspartate (NMDA) receptors by phosphorylation. *J Biol Chem*. 2006 Jun 16;281(24):16583-90. doi: 10.1074/jbc.M513029200. Epub 2006 Apr 10. PMID: 16606616.

Chen CY, Matt L, Hell JW, Rogawski MA (2014) Perampanel inhibition of AMPA receptor currents in cultured hippocampal neurons. *PLoS One*. **9**(9):e108021.

Chen L, Chetkovich DM, Petralia RS, Sweeney NT, Kawasaki Y, Wenthold RJ, Bredt DS and Nicoll RA (2000) Stargazin regulates synaptic targeting of AMPA receptors by two distinct mechanisms. *Nature* **408**:936-943.

Chen P, Gu Z, Liu W, Yan Z. Glycogen synthase kinase 3 regulates N-methyl-D-aspartate receptor channel trafficking and function in cortical neurons. *Mol Pharmacol*. 2007 Jul;72(1):40-51. doi: 10.1124/mol.107.034942. Epub 2007 Mar 30. PMID: 17400762.

Chen W, Tankovic A, Burger PB, Kusumoto H, Traynelis SF, Yuan H. Functional Evaluation of a De Novo GRIN2A Mutation Identified in a Patient with Profound Global Developmental Delay and Refractory Epilepsy. *Mol Pharmacol*. 2017;91(4):317-330. doi:10.1124/mol.116.106781

Chou TH, Tajima N, Romero-Hernandez A, Furukawa H. Structural Basis of Functional Transitions in Mammalian NMDA Receptors [published online ahead of print, 2020 Jun 26]. *Cell*. 2020;S0092-8674(20)30685-1. doi:10.1016/j.cell.2020.05.052

Contractor A, Mulle C and Swanson GT (2011) Kainate receptors coming of age: milestones of two decades of research. *Trends Neurosci* **34**:154-163.

Coquelle T, Christensen JK, Banke TG, Madsen U, Schousboe A and Pickering DS (2000) Agonist discrimination between AMPA receptor subtypes. *Neuroreport* **11**:2643-2648.

Costello Z. GRIN2B Europe. "Survey Results." Presented at EU GRIN2B Symposium. 2018. Barcelona.

Cowan CM, Fan MM, Fan J, et al. Polyglutamine-modulated striatal calpain activity in YAC transgenic huntington disease mouse model: impact on NMDA receptor function and toxicity. *J Neurosci*. 2008;28(48):12725-12735. doi:10.1523/JNEUROSCI.4619-08.2008

Cull-Candy SG and Usowicz MM (1987) Multiple-conductance channels activated by excitatory amino acids in cerebellar neurons. *Nature* **325**:525-528.

Cull-Candy S, Kelly L and Farrant M (2006) Regulation of Ca^{2+}-permeable AMPA receptors: synaptic plasticity and beyond. *Curr Opin Neurobiol* **16**:288-297.

Dalmau J, Armangué T, Planagumà J, Radosevic M, Mannara F, Leypoldt F, Geis C, Lancaster E, Titulaer MJ, Rosenfeld MR, Graus F. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. *Lancet Neurol*. 2019 Nov;18(11):1045-1057. doi: 10.1016/S1474-4422(19)30244-3. Epub 2019 Jul 17. PMID: 31326280.

Davies B, Brown LA, Cais O, Watson J, Clayton AJ, Chang VT, Biggs D, Preece C, Hernandez-Pliego P, Krohn J, Bhomra A, Twigg SRF, Rimmer A, Kanapin A, Consortium WGS, Sen A, Zaiwalla Z, McVean G, Foster R, Donnelly P, Taylor JC, Blair E, Nutt D, Aricescu AR, Greger IH, Peirson SN, Flint J and Martin HC (2017) A point mutation in the ion conduction pore of AMPA receptor GRIA3 causes dramatically perturbed sleep patterns as well as intellectual disability. *Hum Mol Genet* **26**:3869-3882.

de Ligt, J., M. H. Willemsen, B. W. van Bon, T. Kleefstra, H. G. Yntema, T. Kroes, A. T. Vulto-van Silfhout, D. A. Koolen, P. de Vries, C. Gilissen, M. del Rosario, A. Hoischen, H. Scheffer, B. B. de Vries, H. G. Brunner, J. A. Veltman, and L. E. Vissers. 2012. Diagnostic exome sequencing in persons with severe intellectual disability. *N Engl J Med* 367: 1921-1929.

Deng A, Thomson SC. (2009). Renal NMDA receptors independently stimulate proximal reabsorption and glomerular filtration. *Am. J. Physiol. Renal Physiol.* 296 976–982. 10.1152/ajprenal.90391.2008

de Oliveira FF, Bertolucci PH, Chen ES, Smith Mde A. Pharmacological modulation of cognitive and behavioral symptoms in patients with dementia due to Alzheimer's disease. *J Neurol Sci*. 2014 Jan 15;336(1-2):103-8. doi: 10.1016/j.jns.2013.10.015. Epub 2013 Oct 14. PMID: 24189208.

Derkach V, Barria A and Soderling TR (1999) Ca2+/calmodulin-kinase II enhances channel conductance of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate type glutamate receptors. *Proc Natl Acad Sci U S A* **96**:3269-3274.

Dohrke JN, Watson JF, Birchall K and Greger IH (2020) Characterizing the binding and function of TARP gamma8-selective AMPA receptor modulators. *J Biol Chem* **295**:14565-14577.

Donevan SD, Beg A, Gunther JM and Twyman RE (1998) The methylglutamate, SYM 2081, is a potent and highly selective agonist at kainate receptors. *J Pharmacol Exp Ther* **285**:539-545.

Donevan SD and Rogawski MA (1993) GYKI 52466, a 2,3-benzodiazepine, is a highly selective, noncompetitive antagonist of AMPA/kainate receptor responses. *Neuron* **10**:51-59.

Donevan SD, Yamaguchi S, Rogawski MA. Non-N-methyl-D-aspartate receptor antagonism by 3-N-substituted 2,3-benzodiazepines: relationship to anticonvulsant activity. *J Pharmacol Exp Ther*. 1994 Oct;271(1):25-9. PMID: 7525924.

Dong YN, Hsu FC, Koziol-White CJ, Stepanova V, Jude J, Gritsiuta A, Rue R, Mott R, Coulter DA, Panettieri RA Jr, Krymskaya VP, Takano H, Goncharova EA, Goncharov DA, Cines DB, Lynch DR. Functional NMDA receptors are expressed by human pulmonary artery smooth muscle cells. *Sci Rep*. 2021 Apr 15;11(1):8205. doi: 10.1038/s41598-021-87667-0. PMID: 33859248; PMCID: PMC8050278.

Drapier T, Geubelle P, Bouckaert C, Nielsen L, Laulumaa S, Goffin E, Dilly S, Francotte P, Hanson J, Pochet L, Kastrup JS & Pirotte B (2018). Enhancing Action of Positive Allosteric Modulators through the Design of Dimeric Compounds. *J Med Chem* **61**, 5279-5291.

Dravid SM, Erreger K, Yuan H, Nicholson K, Le P, Lyuboslavsky P, Almonte A, Murray E, Mosely C, Barber J, French A, Balster R, Murray TF, Traynelis SF. Subunit-specific mechanisms and proton sensitivity of NMDA receptor channel block. *J Physiol*. 2007;581:107–128.

Dreos R, Ambrosini G, Périer RC, Bucher P. The Eukaryotic Promoter Database: expansion of EPDnew and new promoter analysis tools. *Nucleic Acids Res*. 2015 Jan;43(Database issue):D92-6. doi: 10.1093/nar/gku1111. Epub 2014 Nov 6. PMID: 25378343; PMCID: PMC4383928.

Dubois CJ, Lachamp PM, Sun L, Mishina M, Liu SJ. Presynaptic GluN2D receptors detect glutamate spillover and regulate cerebellar GABA release. *J Neurophysiol*. 2016 Jan 1;115(1):271-85. doi: 10.1152/jn.00687.2015. Epub 2015 Oct 28. PMID: 26510761; PMCID: PMC4760459.

Edbauer D, Neilson JR, Foster KA, et al. Regulation of synaptic structure and function by FMRP-associated microRNAs miR-125b and miR-132 [published correction appears in Neuron. 2010 Oct 6;68(1):161]. *Neuron*. 2010;65(3):373-384. doi:10.1016/j.neuron.2010.01.005

Errico F, Mothet JP, Usiello A. D-Aspartate: An endogenous NMDA receptor agonist enriched in the developing brain with potential involvement in schizophrenia. *J Pharm Biomed Anal*. 2015 Dec 10;116:7-17. doi: 10.1016/j.jpba.2015.03.024. Epub 2015 Mar 31. PMID: 25868730.

Farrow P, Khodosevich K, Sapir Y, Schulmann A, Aslam M, Stern-Bach Y, Monyer H and von Engelhardt J (2015) Auxiliary subunits of the CKAMP family differentially modulate AMPA receptor properties. *eLife* **4**:e09693.

Ferreira IL, Bajouco LM, Mota SI, Auberson YP, Oliveira CR, Rego AC. Amyloid beta peptide 1-42 disturbs intracellular calcium homeostasis through activation of GluN2B-containing N-methyl-d-aspartate receptors in cortical cultures. *Cell Calcium*. 2012 Feb;51(2):95-106. doi: 10.1016/j.ceca.2011.11.008. Epub 2011 Dec 15. PMID: 22177709.

Franchini L, Stanic J, Ponzoni L, Mellone M, Carrano N, Musardo S, Zianni E, Olivero G, Marcello E, Pittaluga A, Sala M, Bellone C, Racca C, Di Luca M, Gardoni F. Linking NMDA Receptor Synaptic Retention to Synaptic Plasticity and Cognition. *iScience*. 2019 Sep 27;19:927-939. doi: 10.1016/j.isci.2019.08.036. Epub 2019 Aug 27. PMID: 31518901; PMCID: PMC6742927.

Fry AE, Fawcett KA, Zelnik N, Yuan H, Thompson BAN, Shemer-Meiri L, Cushion TD, Mugalaasi H, Sims D, Stoodley N, Chung SK, Rees MI, Patel CV, Brueton LA, Layet V, Giuliano F, Kerr MP, Banne E, Meiner V, Lerman-Sagie T, Helbig KL, Kofman LH, Knight KM, Chen W, Kannan V, Hu C, Kusumoto H, Zhang J, Swanger SA, Shaulsky GH, Mirzaa GM, Muir AM, Mefford HC, Dobyns WB, Mackenzie AB, Mullins JGL, Lemke JR, Bahi-Buisson N, Traynelis SF, Iago HF, Pilz DT. De novo mutations in GRIN1 cause extensive bilateral polymicrogyria. *Brain*. 2018;141:698–712.

Gao J, Maison SF, Wu X, Hirose K, Jones SM, Bayazitov I, Tian Y, Mittleman G, Matthews DB, Zakharenko SS, Liberman MC and Zuo J (2007) Orphan glutamate receptor delta1 subunit required for high-frequency hearing. *Mol Cell Biol* 27:4500-4512.

Gao J, Stevenson TJ, Douglass AD, Barrios JP, Bonkowsky JL. (2018) The Midline Axon Crossing Decision Is Regulated through an Activity-Dependent Mechanism by the NMDA Receptor. *eNeuro*. 5(2)

García-Recio A, Santos-Gómez A, Soto D, Julia-Palacios N, García-Cazorla À, Altafaj X, Olivella M. GRIN database: A unified and manually curated repertoire of GRIN variants. *Hum Mutat.* 2020 Nov 30. doi: 10.1002/humu.24141. Epub ahead of print. PMID: 33252190.

Gardinier KM, Gernert DL, Porter WJ, Reel JK, Ornstein PL, Spinazze P, Stevens FC, Hahn P, Hollinshead SP, Mayhugh D, Schkeryantz J, Khilevich A, De Frutos O, Gleason SD, Kato AS, Luffer-Atlas D, Desai PV, Swanson S, Burris KD, Ding C, Heinz BA, Need AB, Barth VN, Stephenson GA, Diseroad BA, Woods TA, Yu H, Bredt D and Witkin JM (2016) Discovery of the First alpha-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid (AMPA) Receptor Antagonist Dependent upon Transmembrane AMPA Receptor Regulatory Protein (TARP) gamma-8. *J Med Chem* **59**:4753-4768.

Geisheker MR, Heymann G, Wang T, Coe BP, Turner TN, Stessman HAF, Hoekzema K, Kvarnung M, Shaw M, Friend K, Liebelt J, Barnett C, Thompson EM, Haan E, Guo H, Anderlid BM, Nordgren A, Lindstrand A, Vandeweyer G, Alberti A, Avola E, Vinci M, Giusto S, Pramparo T, Pierce K, Nalabolu S, Michaelson JJ, Sedlacek Z, Santen GWE, Peeters H, Hakonarson H, Courchesne E, Romano C, Kooy RF, Bernier RA, Nordenskjold M, Gecz J, Xia K, Zweifel LS and Eichler EE (2017) Hotspots of missense mutation identify neurodevelopmental disorder genes and functional domains. *Nat Neurosci* **20**:1043-1051.

Gill MB, Frausto S, Ikoma M, Sasaki M, Oikawa M, Sakai R and Swanson GT (2010) A series of structurally novel heterotricyclic alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor-selective antagonists. *Br J Pharmacol* **160**:1417-1429.

Gong, X. Q., A. Frandsen, W. Y. Lu, Y. Wan, R. L. Zabek, D. S. Pickering, and D. Bai. 2005. D-aspartate and NMDA, but not L-aspartate, block AMPA receptors in rat hippocampal neurons. *Br J Pharmacol* 145: 449-459.

Grand T, Abi Gerges S, David M, Diana MA, Paoletti P. Unmasking GluN1/GluN3A excitatory glycine NMDA receptors. *Nat Commun*. 2018 Nov 13;9(1):4769. doi: 10.1038/s41467-018-07236-4. PMID: 30425244; PMCID: PMC6233196.

Greenwood JR, Mewett KN, Allan RD, Martin BO and Pickering DS (2006) 3-hydroxypyridazine 1-oxides as carboxylate bioisosteres: a new series of subtype-selective AMPA receptor agonists. *Neuropharmacology* **51**:52-59.

Hackos DH, Lupardus PJ, Grand T, Chen Y, Wang TM, Reynen P, Gustafson A, Wallweber HJ, Volgraf M, Sellers BD, Schwarz JB, Paoletti P, Sheng M, Zhou Q, Hanson JE. Positive Allosteric Modulators of GluN2A-Containing NMDARs with Distinct Modes of Action and Impacts on Circuit Function. *Neuron*. 2016 Mar 2;89(5):983-99. doi: 10.1016/j.neuron.2016.01.016. Epub 2016 Feb 11. PMID: 26875626.

Hald H, Naur P, Pickering DS, Sprogoe D, Madsen U, Timmermann DB, Ahring PK, Liljefors T, Schousboe A, Egebjerg J, Gajhede M and Kastrup JS (2007) Partial agonism and antagonism of the ionotropic glutamate receptor iGLuR5: structures of the ligand-binding core in complex with domoic acid and 2-amino-3-[5-tert-butyl-3-(phosphonomethoxy)-4-isoxazolyl]propionic acid. *J Biol Chem* **282**:25726-25736.

Hald H, Ahring PK, Timmermann DB, Liljefors T, Gajhede M and Kastrup JS (2009) Distinct structural features of cyclothiazide are responsible for effects on peak current amplitude and desensitization kinetics at iGluR2. *J Mol Biol* **391**:906-917.

Hanada T, Hashizume Y, Tokuhara N, Takenaka O, Kohmura N, Ogasawara A, Hatakeyama S, Ohgoh M, Ueno M and Nishizawa Y (2011) Perampanel: a novel, orally active, noncompetitive AMPA-receptor antagonist that reduces seizure activity in rodent models of epilepsy. *Epilepsia* **52**:1331-1340.

Hansen KB, Naur P, Kurtkaya NL, Kristensen AS, Gajhede M, Kastrup JS, Traynelis SF (2009) Modulation of the dimer interface at ionotropic glutamate-like receptor delta2 by D-serine and extracellular calcium. *J Neurosci* **29**(4):907-17.

Hansen KB, Mullasseril P, Dawit S, Kurtkaya NL, Yuan H, Vance KM, Orr AG, Kvist T, Ogden KK, Le P, Vellano KM, Lewis I, Kurtkaya S, Du Y, Qui M, Murphy TJ, Snyder JP, Brauner-Osborne H and Traynelis SF (2010) Implementation of a fluorescence-based screening assay identifies histamine H3 receptor antagonists clobenpropit and iodophenpropit as subunit-selective N-methyl-D-aspartate receptor antagonists. *J Pharmacol Exp Ther* 333:650-662.

Hansen KB, Traynelis SF. Structural and mechanistic determinants of a novel site for noncompetitive inhibition of GluN2D-containing NMDA receptors. *Journal of Neuroscience*. 2011;31:3650–3661. doi: 10.1523/JNEUROSCI.5565-10.2011.

Hansen KB, Yi F, Perszyk RE, Furukawa H, Wollmuth LP, Gibb AJ, Traynelis SF. Structure, function, and allosteric modulation of NMDA receptors. *J Gen Physiol*. 2018 Aug 6;150(8):1081-1105. doi: 10.1085/jgp.201812032. Epub 2018 Jul 23. PMID: 30037851; PMCID: PMC6080888.

Hanson JE, Ma K, Elstrott J, Weber M, Saillet S, Khan AS, Simms J, Liu B, Kim TA, Yu GQ, Chen Y, Wang TM, Jiang Z, Liederer BM, Deshmukh G, Solanoy H, Chan C, Sellers BD, Volgraf M, Schwarz JB, Hackos DH, Weimer RM, Sheng M, Gill TM, Scearce-Levie K, Palop JJ. GluN2A NMDA Receptor Enhancement Improves Brain Oscillations, Synchrony, and Cognitive Functions in Dravet Syndrome and Alzheimer's Disease Models. *Cell Rep*. 2020 Jan 14;30(2):381-396.e4. doi: 10.1016/j.celrep.2019.12.030. PMID: 31940483; PMCID: PMC7017907.

Hardingham GE, Bading H. Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. *Nat Rev Neurosci*. 2010:11:682-696.

Hardingham GE, Do KQ. Linking early-life NMDAR hypofunction and oxidative stress in schizophrenia pathogenesis. *Nat Rev Neurosci*. 2016 Feb;17(2):125-34. doi: 10.1038/nrn.2015.19. Epub 2016 Jan 14. PMID: 26763624.

Hashimoto R, Hough C, Nakazawa T, Yamamoto T, Chuang DM. Lithium protection against glutamate excitotoxicity in rat cerebral cortical neurons: involvement of NMDA receptor inhibition possibly by decreasing NR2B tyrosine phosphorylation. *J Neurochem*. 2002 Feb;80(4):589-97. doi: 10.1046/j.0022-3042.2001.00728.x. PMID: 11841566.

Hausman-Kedem M, Menascu S, Greenstein Y, Fattal-Valevski A. Immunotherapy for GRIN2A and GRIN2D-related epileptic encephalopathy. *Epilepsy Res*. 2020 Jul;163:106325. doi: 10.1016/j.eplepsyres.2020.106325. Epub 2020 Apr 2. PMID: 32289570.

Helbig I. Children's Hospital of Philadelphia. "The Where, When and What of the GRIN landscape." Presented at 2019 CFERV Conference on GRIN Variants. 2019. Atlanta.

HGNC Database, HUGO Gene Nomenclature Committee (HGNC), European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Welcome Genome Campus, Hinxton, Cambridge CB10 1SD, United Kingdom www.genenames.org.

Hibi S, Ueno K, Nagato S, Kawano K, Ito K, Norimine Y, Takenaka O, Hanada T and Yonaga M (2012) Discovery of 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile (perampanel): a novel, noncompetitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropanoic acid (AMPA) receptor antagonist. *J Med Chem* **55**:10584-10600.

Hinoi E, Fujimori S, Yoneda Y. (2003). Modulation of cellular differentiation by N-methyl-D-aspartate receptors in osteoblasts. *FASEB J.* 17 1532–1534. 10.1096/fj.02-0820fje

Hofmann SG. D-cycloserine for treating anxiety disorders: making good exposures better and bad exposures worse. *Depress Anxiety*. 2014 Mar;31(3):175-7. doi: 10.1002/da.22257. PMID: 24677604; PMCID: PMC4006201.

Hogan-Cann AD, Anderson CM. (2016). Physiological roles of non-neuronal NMDA receptors. *Trends Pharmacol. Sci.* 37 750–767. 10.1016/j.tips.2016.05.012

Hogan-Cann AD, Lu P, Anderson CM. Endothelial NMDA receptors mediate activity-dependent brain hemodynamic responses in mice. *Proc Natl Acad Sci U S A*. 2019 May 21;116(21):10229-10231. doi: 10.1073/pnas.1902647116. Epub 2019 May 6. PMID: 31061120; PMCID: PMC6535036.

Hogner A, Greenwood JR, Liljefors T, Lunn ML, Egebjerg J, Larsen IK, Gouaux E and Kastrup JS (2003) Competitive antagonism of AMPA receptors by ligands of different classes: crystal structure of ATPO bound to the GluR2 ligand-binding core, in comparison with DNQX. *J Med Chem* **46**:214-221.

Hollmann M, Boulter J, Maron C, Beasley L, Sullivan J, Pecht G, Heinemann S. Zinc potentiates agonist-induced currents at certain splice variants of the NMDA receptor. *Neuron*. 1993 May;10(5):943-54. doi: 10.1016/0896-6273(93)90209-a. PMID: 7684237.

Hollmann M, Heinemann S. Cloned glutamate receptors. *Annu Rev Neurosci*. 1994;17:31-108. doi: 10.1146/annurev.ne.17.030194.000335. PMID: 8210177.

Homayoun H, Moghaddam B. NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. *J Neurosci*. 2007 Oct 24;27(43):11496-500. doi: 10.1523/JNEUROSCI.2213-07.2007. PMID: 17959792; PMCID: PMC2954603.

Honore T, Davies SN, Drejer J, Fletcher EJ, Jacobsen P, Lodge D and Nielsen FE (1988) Quinoxalinediones: potent competitive non-NMDA glutamate receptor antagonists. *Science* **241**:701-703.

Hrcka Krausova B, Kysilov B, Cerny J, Vyklicky V, Smejkalova T, Ladislav M, Balik A, Korinek M, Chodounska H, Kudova E, Vyklicky L. Site of Action of Brain Neurosteroid Pregnenolone Sulfate at the N-Methyl-D-Aspartate Receptor. *J Neurosci*. 2020 Jul 29;40(31):5922-5936. doi: 10.1523/JNEUROSCI.3010-19.2020. Epub 2020 Jul 1. PMID: 32611707; PMCID: PMC7392504.

Huganir RL, Nicoll RA. AMPARs and synaptic plasticity: the last 25 years. *Neuron*. 2013 Oct 30;80(3):704-17. doi: 10.1016/j.neuron.2013.10.025. PMID: 24183021; PMCID: PMC4195488.

Inagaki N, Kuromi H, Gonoi T, Okamoto Y, Ishida H, Seino Y, Kaneko T, Iwanaga T, Seino S. Expression and role of ionotropic glutamate receptors in pancreatic islet cells. *FASEB Journal*. 1995;9:686–691

Intson K, van Eede MC, Islam R, Milenkovic M, Yan Y, Salahpour A, Henkelman RM, Ramsey AJ. Progressive neuroanatomical changes caused by Grin1 loss-of-function mutation. *Neurobiol Dis.* 2019 Dec;132:104527. doi: 10.1016/j.nbd.2019.104527. Epub 2019 Jul 9. PMID: 31299220.

Ishii T, Stolz JR and Swanson GT (2020) Auxiliary Proteins are the Predominant Determinants of Differential Efficacy of Clinical Candidates Acting as AMPA Receptor Positive Allosteric Modulators. *Mol Pharmacol* **97**:336-350.

Jacobs S, Cui Z, Feng R, Wang H, Wang D, Tsien JZ. Molecular and genetic determinants of the NMDA receptor for superior learning and memory functions. *PLoS One*. 2014 Oct 31;9(10):e111865. doi: 10.1371/journal.pone.0111865. PMID: 25360708; PMCID: PMC4216132.

Jahr CE and Stevens CF (1987) Glutamate activates multiple single channel conductances in hippocampal neurons. *Nature* **325**:522-525.

Jensen AA, Christesen T, Bolcho U, Greenwood JR, Postorino G, Vogensen SB, Johansen TN, Egebjerg J, Brauner-Osborne H and Clausen RP (2007) Functional characterization of Tet-AMPA [tetrazolyl-2-amino-3-(3-hydroxy-5-methyl- 4-isoxazolyl)propionic acid] analogues at ionotropic glutamate receptors GluR1-GluR4. The molecular basis for the functional selectivity profile of 2-Bn-Tet-AMPA. *J Med Chem* **50**:4177-4185.

Jin R, Banke TG, Mayer ML, Traynelis SF and Gouaux E (2003) Structural basis for partial agonist action at ionotropic glutamate receptors. *Nat Neurosci* **6**:803-810.

Johansen TH, Chaudhary A and Verdoorn TA (1995) Interactions among GYKI-52466, cyclothiazide, and aniracetam at recombinant AMPA and kainate receptors. *Mol Pharmacol* **48**:946-955.

Johnson KA, Conn PJ, Niswender CM. Glutamate receptors as therapeutic targets for Parkinson's disease. *CNS Neurol Disord Drug Targets*. 2009;8(6):475-491. doi:10.2174/187152709789824606

Juknaite L, Sugamata Y, Tokiwa K, Ishikawa Y, Takamizawa S, Eng A, Sakai R, Pickering DS, Frydenvang K, Swanson GT, Kastrup JS and Oikawa M (2013) Studies on an (S)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA) receptor antagonist IKM-159: asymmetric synthesis, neuroactivity, and structural characterization. *J Med Chem* **56**:2283-2293.

Kaae BH, Harpsoe K, Kastrup JS, Sanz AC, Pickering DS, Metzler B, Clausen RP, Gajhede M, Sauerberg P, Liljefors T and Madsen U (2007) Structural proof of a dimeric positive modulator bridging two identical AMPA receptor-binding sites. *Chem Biol* **14**:1294-1303.

Kamboj SK, Swanson GT and Cull-Candy SG (1995) Intracellular spermine confers rectification on rat calcium-permeable AMPA and kainate receptors. *J Physiol* **486**:297-303.

Karakas E, Furukawa H. Crystal structure of a heterotetrameric NMDA receptor ion channel. *Science*. 2014 May 30;344(6187):992-7. doi: 10.1126/science.1251915. PMID: 24876489; PMCID: PMC4113085.

Karczewski, K.J., Francioli, L.C., Tiao, G. *et al.* The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature* 581, 434–443 (2020). https://doi.org/10.1038/s41586-020-2308-7

Kasper C, Pickering DS, Mirza O, Olsen L, Kristensen AS, Greenwood JR, Liljefors T, Schousboe A, Watjen F, Gajhede M, Sigurskjold BW and Kastrup JS (2006) The structure of a mixed GluR2 ligand-binding core dimer in complex with (S)-glutamate and the antagonist (S)-NS1209. *J Mol Biol* **357**:1184-1201.

Kato AS, Zhou W, Milstein AD, Knierman MD, Siuda ER, Dotzlaf JE, Yu H, Hale JE, Nisenbaum ES, Nicoll RA and Bredt DS (2007) New transmembrane AMPA receptor regulatory protein isoform, gamma-7, differentially regulates AMPA receptors. *J Neurosci* **27**:4969-4977.

Kato AS, Siuda ER, Nisenbaum ES and Bredt DS (2008) AMPA receptor subunit-specific regulation by a distinct family of type II TARPs. *Neuron* **59**:986-996.

Kato AS, Burris KD, Gardinier KM, Gernert DL, Porter WJ, Reel J, Ding C, Tu Y, Schober DA, Lee MR, Heinz BA, Fitch TE, Gleason SD, Catlow JT, Yu H, Fitzjohn SM, Pasqui F, Wang H, Qian Y, Sher E, Zwart R, Wafford KA, Rasmussen K, Ornstein PL, Isaac JT, Nisenbaum ES, Bredt DS and Witkin JM (2016) Forebrain-selective AMPA-receptor antagonism guided by TARP gamma-8 as an antiepileptic mechanism. *Nat Med* **22**:1496-1501.

Khatri A, Burger PB, Swanger SA, Hansen KB, Zimmerman S, Karakas E, Liotta DC, Furukawa H, Snyder JP, Traynelis SF. Structural determinants and mechanism of action of a GluN2C-selective NMDA receptor positive allosteric modulator. *Mol Pharmacol*. 2014 Nov;86(5):548-60. doi: 10.1124/mol.114.094516. Epub 2014 Sep 9. PMID: 25205677; PMCID: PMC4201136.

Kinney JW, Davis CN, Tabarean I, Conti B, Bartfai T, Behrens MM. A specific role for NR2A-containing NMDA receptors in the maintenance of parvalbumin and GAD67 immunoreactivity in cultured interneurons. *J Neurosci*. 2006 Feb 1;26(5):1604-15. doi: 10.1523/JNEUROSCI.4722-05.2006. PMID: 16452684; PMCID: PMC6675509.

Kizelsztein P, Eisenstein M, Strutz N, Hollmann M and Teichberg VI (2000) Mutant cycle analysis of the active and desensitized states of an AMPA receptor induced by willardiines. *Biochemistry* **39**:12819-12827.

Kleckner NW, Dingledine R. Requirement for glycine in activation of NMDA-receptors expressed in Xenopus oocytes. *Science*. 1988;241:835–837. doi: 10.1126/science.2841759.

Kloda A, Clements JD, Lewis RJ, Adams DJ. Adenosine triphosphate acts as both a competitive antagonist and a positive allosteric modulator at recombinant N-methyl-D-aspartate receptors. *Mol Pharmacol*. 2004 Jun;65(6):1386-96. doi: 10.1124/mol.65.6.1386. PMID: 15155832.

Knopp KL, Simmons RMA, Guo W, Adams BL, Gardinier KM, Gernert DL, Ornstein PL, Porter W, Reel J, Ding C, Wang H, Qian Y, Burris KD, Need A, Barth V, Swanson S, Catlow J, Witkin JM, Zwart R, Sher E, Choong KC, Wall TM, Schober D, Felder CC, Kato AS, Bredt DS and Nisenbaum ES (2019) Modulation of TARP gamma8-Containing AMPA Receptors as a Novel Therapeutic Approach for Chronic Pain. *J Pharmacol Exp Ther* **369**:345-363.

Kornhuber J, Weller M, Schoppmeyer K, Riederer P. Amantadine and memantine are NMDA receptor antagonists with neuroprotective properties. *J Neural Transm Suppl*. 1994;43:91-104. PMID: 7884411.

Kornhuber J, Quack G, Danysz W, Jellinger K, Danielczyk W, Gsell W, Riederer P. Therapeutic brain concentration of the NMDA receptor antagonist amantadine. *Neuropharmacology*. 1995 Jul;34(7):713-21. doi: 10.1016/0028-3908(95)00056-c. PMID: 8532138.

Kornhuber J, Parsons CG, Hartmann S, Retz W, Kamolz S, Thome J, Riederer P. Orphenadrine is an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist: binding and patch clamp studies. *J Neural Transm Gen Sect*. 1995;102(3):237-46. doi: 10.1007/BF01281158. PMID: 8788072.

Kovacic P, Somanathan R. Clinical physiology and mechanism of dizocilpine (MK-801): electron transfer, radicals, redox metabolites and bioactivity. *Oxid Med Cell Longev*. 2010;3(1):13-22. doi:10.4161/oxim.3.1.10028

Kravchick DO, Karpova A, Hrdinka M, Lopez-Rojas J, Iacobas S, Carbonell AU, Iacobas DA, Kreutz MR, Jordan BA. Synaptonuclear messenger PRR7 inhibits c-Jun ubiquitination and regulates NMDA-mediated excitotoxicity. *EMBO J*. 2016 Sep 1;35(17):1923-34. doi: 10.15252/embj.201593070. Epub 2016 Jul 25. PMID: 27458189; PMCID: PMC5007554.

Kroken RA, Løberg EM, Drønen T, Grüner R, Hugdahl K, Kompus K, Skrede S, Johnsen E. A critical review of pro-cognitive drug targets in psychosis: convergence on myelination and inflammation. *Front Psychiatry*. 2014 Feb 4;5:11. doi: 10.3389/fpsyt.2014.00011. PMID: 24550848; PMCID: PMC3912739.

Kunugi, A., Y. Tajima, H. Kuno, S. Sogabe, and H. Kimura. 2018. HBT1, a Novel AMPA Receptor Potentiator with Lower Agonistic Effect, Avoided Bell-Shaped Response in In Vitro BDNF Production. *J Pharmacol Exp Ther* 364: 377-389.

Kunugi, A., M. Tanaka, A. Suzuki, Y. Tajima, N. Suzuki, M. Suzuki, S. Nakamura, H. Kuno, A. Yokota, S. Sogabe, Y. Kosugi, Y. Awasaki, T. Kaku, and H. Kimura. 2019. TAK-137, an AMPA-R potentiator with little agonistic effect, has a wide therapeutic window. *Neuropsychopharmacology* 44: 961-970.

Kvist T, Greenwood JR, Hansen KB, Traynelis SF, Bräuner-Osborne H. Structure-based discovery of antagonists for GluN3-containing N-methyl-D-aspartate receptors. *Neuropharmacology*. 2013 Dec;75:324-36. doi: 10.1016/j.neuropharm.2013.08.003. Epub 2013 Aug 22. PMID: 23973313; PMCID: PMC3865070.

Lal D, Steinbrücker S, Schubert J, Sander T, Becker F, Weber Y, Lerche H, Thiele H, Krause R, Lehesjoki AE, Nürnberg P, Palotie A, Neubauer BA, Muhle H, Stephani U, Helbig I, Becker AJ, Schoch S, Hansen J, Dorn T, Hohl C, Lüscher N; Epicure consortium; EuroEPINOMICS-CoGIE consortium, von Spiczak S, Lemke JR. Investigation of GRIN2A in common epilepsy phenotypes. *Epilepsy Res*. 2015 Sep;115:95-9. doi: 10.1016/j.eplepsyres.2015.05.010. Epub 2015 Jun 2. PMID: 26220384.

Laulumaa S, Hansen KV, Masternak M, Drapier T, Francotte P, Pirotte B, Frydenvang K & Kastrup JS (2019). Crystal Structures of Potent Dimeric Positive Allosteric Modulators at the Ligand-Binding Domain of the GluA2 Receptor. *ACS Med Chem Lett* **10**, 243-247.

Lauterbach EC, Cummings JL, Kuppuswamy PS. Toward a more precise, clinically—informed pathophysiology of pathological laughing and crying. *Neurosci Biobehav Rev*. 2013 Sep;37(8):1893-916. doi: 10.1016/j.neubiorev.2013.03.002. Epub 2013 Mar 18. PMID: 23518269.

Lazzaro JT, Paternain AV, Lerma J, Chenard BL, Ewing FE, Huang J, Welch WM, Ganong AH and Menniti FS (2002) Functional characterization of CP-465,022, a selective, noncompetitive AMPA receptor antagonist. *Neuropharmacology* **42**:143-153.

Lee CH, Lü W, Michel JC, Goehring A, Du J, Song X, Gouaux E. NMDA receptor structures reveal subunit arrangement and pore architecture. *Nature*. 2014 Jul 10;511(7508):191-7. doi: 10.1038/nature13548. Epub 2014 Jun 22. PMID: 25008524; PMCID: PMC4263351.

Lee HH, Deeb TZ, Walker JA, Davies PA, Moss SJ. NMDA receptor activity downregulates KCC2 resulting in depolarizing GABAA receptor-mediated currents. *Nat Neurosci*. 2011 Jun;14(6):736-43. doi: 10.1038/nn.2806. Epub 2011 May 1. PMID: 21532577; PMCID: PMC3102766.

Lemke JR, Lal D, Reinthaler EM, Steiner I, Nothnagel M, Alber M, Geider K, Laube B, Schwake M, Finsterwalder K, Franke A, Schilhabel M, Jähn JA, Muhle H, Boor R, Van Paesschen W, Caraballo R, Fejerman N, Weckhuysen S, De Jonghe P, Larsen J, Møller RS, Hjalgrim H, Addis L, Tang S, Hughes E, Pal DK, Veri K, Vaher U, Talvik T, Dimova P, Guerrero López R, Serratosa JM, Linnankivi T, Lehesjoki AE, Ruf S, Wolff M, Buerki S, Wohlrab G, Kroell J, Datta AN, Fiedler B, Kurlemann G, Kluger G, Hahn A, Haberlandt DE, Kutzer C, Sperner J, Becker F, Weber YG, Feucht M, Steinböck H, Neophythou B, Ronen GM, Gruber-Sedlmayr U, Geldner J, Harvey RJ, Hoffmann P, Herms S, Altmüller J, Toliat MR, Thiele H, Nürnberg P, Wilhelm C, Stephani U, Helbig I, Lerche H, Zimprich F, Neubauer BA, Biskup S, von Spiczak S. Mutations in GRIN2A cause idiopathic focal epilepsy with rolandic spikes. *Nat Genet*. 2013 Sep;45(9):1067-72. doi: 10.1038/ng.2728. Epub 2013 Aug 11. PMID: 23933819.

Lemke JR, Geider K, Helbig KL, et al. Delineating the GRIN1 phenotypic spectrum: A distinct genetic NMDA receptor encephalopathy. *Neurology*. 2016;86(23):2171-2178. doi:10.1212/WNL.0000000000002740

Lemke JR. "Clinical and genetic spectrum of GRIN2A and GRIN2B variants." University of Leipzig. Presented at 2019 CFERV Conference on GRIN Variants. 2019. Atlanta.

Lemke JR. Predicting incidences of neurodevelopmental disorders. *Brain*. 2020 Apr 1;143(4):1046-1048. doi: 10.1093/brain/awaa079. PMID: 32318731.

Lesca G, Rudolf G, Bruneau N, Lozovaya N, Labalme A, Boutry-Kryza N, Salmi M, Tsintsadze T, Addis L, Motte J, Wright S, Tsintsadze V, Michel A, Doummar D, Lascelles K, Strug L, Waters P, de Bellescize J, Vrielynck P, de Saint Martin A, Ville D, Ryvlin P, Arzimanoglou A, Hirsch E, Vincent A, Pal D, Burnashev N, Sanlaville D, Szepetowski P. GRIN2A mutations in acquired epileptic aphasia and related childhood focal epilepsies and encephalopathies with speech and language dysfunction. *Nat Genet*. 2013;45:1061–6.

Li J, Zhao L, Cui B, Deng L, Ning G, Liu J. (2011). Multiple signaling pathways involved in stimulation of osteoblast differentiation by N-methyl-D-aspartate receptors activation in vitro. *Acta Pharmacol. Sin.* 32 895–903. 10.1038/aps.2011.38

Li X, Xu C, Yang P. 2013. c-Jun NH2-terminal kinase 1/2 and endoplasmic reticulum stress as interdependent and reciprocal causation in diabetic embryopathy. *Diabetes* 62(2):599-608.

Linsenbardt AJ, Taylor A, Emnett CM, Doherty JJ, Krishnan K, Covey DF, Paul SM, Zorumski CF, Mennerick S, 2014. Different oxysterols have opposing actions at N-methyl-D-aspartate receptors. *Neuropharmacology* 85, 232–242.

Liu J, Chang L, Song Y, Li H, Wu Y. The Role of NMDA Receptors in Alzheimer's Disease. *Front Neurosci*. 2019;13:43. Published 2019 Feb 8. doi:10.3389/fnins.2019.00043

Lockridge A, Gustafson E, Wong A, Miller RF, Alejandro EU. Acute D-Serine Co-Agonism of β-Cell NMDA Receptors Potentiates Glucose-Stimulated Insulin Secretion and Excitatory β-Cell Membrane Activity. *Cells*. 2021 Jan 7;10(1):93. doi: 10.3390/cells10010093. PMID: 33430405; PMCID: PMC7826616.

López-Rivera JA, Pérez-Palma E, Symonds J, Lindy AS, McKnight DA, Leu C, Zuberi S, Brunklaus A, Møller RS, Lal D. A catalogue of new incidence estimates of monogenic neurodevelopmental disorders caused by de novo variants. *Brain*. 2020 Apr 1;143(4):1099-1105. doi: 10.1093/brain/awaa051. PMID: 32168371; PMCID: PMC7174049.

Luck K, Kim DK, Lambourne L, Spirohn K, Begg BE, Bian W, Brignall R, Cafarelli T, Campos-Laborie FJ, Charloteaux B, Choi D, Coté AG, Daley M, Deimling S, Desbuleux A, Dricot A, Gebbia M, Hardy MF, Kishore N, Knapp JJ, Kovács IA, Lemmens I, Mee MW, Mellor JC, Pollis C, Pons C, Richardson AD, Schlabach S, Teeking B, Yadav A, Babor M, Balcha D, Basha O, Bowman-Colin C, Chin SF, Choi SG, Colabella C, Coppin G, D'Amata C, De Ridder D, De Rouck S, Duran-Frigola M, Ennajdaoui H, Goebels F, Goehring L, Gopal A, Haddad G, Hatchi E, Helmy M, Jacob Y, Kassa Y, Landini S, Li R, van Lieshout N, MacWilliams A, Markey D, Paulson JN, Rangarajan S, Rasla J, Rayhan A, Rolland T, San-Miguel A, Shen Y, Sheykhkarimli D, Sheynkman GM, Simonovsky E, Taşan M, Tejeda

A, Tropepe V, Twizere JC, Wang Y, Weatheritt RJ, Weile J, Xia Y, Yang X, Yeger-Lotem E, Zhong Q, Aloy P, Bader GD, De Las Rivas J, Gaudet S, Hao T, Rak J, Tavernier J, Hill DE, Vidal M, Roth FP, Calderwood MA. A reference map of the human binary protein interactome. *Nature*. 2020 Apr;580(7803):402-408. doi: 10.1038/s41586-020-2188-x. Epub 2020 Apr 8. PMID: 32296183; PMCID: PMC7169983.

Ma T, Cheng Q, Chen C. *et al.* Excessive Activation of NMDA Receptors in the Pathogenesis of Multiple Peripheral Organs via Mitochondrial Dysfunction, Oxidative Stress, and Inflammation. *SN Compr. Clin. Med.* **2,** 551–569 (2020). https://doi.org/10.1007/s42399-020-00298-w

Maher MP, Wu N, Ravula S, Ameriks MK, Savall BM, Liu C, Lord B, Wyatt RM, Matta JA, Dugovic C, Yun S, Ver Donck L, Steckler T, Wickenden AD, Carruthers NI and Lovenberg TW (2016) Discovery and Characterization of AMPA Receptor Modulators Selective for TARP-gamma8. *J Pharmacol Exp Ther* **357**:394-414.

Malayev A, Gibbs TT, Farb DH. Inhibition of the NMDA response by pregnenolone sulphate reveals subtype selective modulation of NMDA receptors by sulphated steroids. *Br J Pharmacol* 2002, 135, 901–909.

Mao Z, He S, Mesnard C, et al. NMDA receptors containing GluN2C and GluN2D subunits have opposing roles in modulating neuronal oscillations; potential mechanism for bidirectional feedback. *Brain Res*. 2020;1727:146571. doi:10.1016/j.brainres.2019.146571

Marquard J, Otter S, Welters A, Stirban A, Fischer A, Eglinger J, et al. (2015). Characterization of pancreatic NMDA receptors as possible drug targets for diabetes treatment. *Nat. Med.* 21 363–372. 10.1038/nm.3822

Marsden WN. Stressor-induced NMDAR dysfunction as a unifying hypothesis for the aetiology, pathogenesis and comorbidity of clinical depression. *Med Hypotheses*. 2011 Oct;77(4):508-28. doi: 10.1016/j.mehy.2011.06.021. Epub 2011 Jul 8. PMID: 21741771.

Martin S, Chamberlin A, Shinde DN, Hempel M, Strom TM, Schreiber A, Johannsen J, Ousager LB, Larsen MJ, Hansen LK, Fatemi A, Cohen JS, Lemke J, Sorensen KP, Helbig KL, Lessel D and Abou Jamra R (2017) De Novo Variants in GRIA4 Lead to Intellectual Disability with or without Seizures and Gait Abnormalities. *Am J Hum Genet* **101**:1013-1020.

Martínez-Pinteño A, García-Cerro S, Mas S, Torres T, Boloc D, Rodríguez N, Lafuente A, Gassó P, Arnaiz JA, Parellada E. The positive allosteric modulator of the mGlu2 receptor JNJ-46356479 partially improves neuropathological deficits and schizophrenia-like behaviors in a postnatal ketamine mice model. *J Psychiatr Res*. 2020 Jul;126:8-18. doi: 10.1016/j.jpsychires.2020.04.005. Epub 2020 Apr 26. PMID: 32407891.

Masuko T, Kuno T, Kashiwagi K, Kusama T, Williams K, Igarashi K. 1999. Stimulatory and inhibitory properties of aminoglycoside antibiotics at N-methyl-D- aspartate receptors. *J. Pharmacol. Exp. Ther*. 290, 1026–1033.

McBain CJ, Kleckner NW, Wyrick S, Dingledine R. Structural requirements for activation of the glycine coagonist site of N-methyl-d-aspartate receptors expressed in Xenopus oocytes. *Mol Pharmacol*. 1989;36:556–565.

Mehra A, Guérit S, Macrez R, Gosselet F, Sevin E, Lebas H, Maubert E, De Vries HE, Bardou I, Vivien D, Docagne F. Nonionotropic Action of Endothelial NMDA Receptors on Blood-Brain Barrier Permeability via Rho/ROCK-Mediated Phosphorylation of Myosin. *J Neurosci*. 2020 Feb 19;40(8):1778-1787. doi: 10.1523/JNEUROSCI.0969-19.2019. Epub 2020 Jan 17. PMID: 31953371; PMCID: PMC7046331.

Menniti FS, Chenard BL, Collins MB, Ducat MF, Elliott ML, Ewing FE, Huang JI, Kelly KA, Lazzaro JT, Pagnozzi MJ, Weeks JL, Welch WM and White WF (2000) Characterization of the binding site for a novel class of noncompetitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonists. *Mol Pharmacol* **58**:1310-1317.

Menuz K, Stroud RM, Nicoll RA and Hays FA (2007) TARP auxiliary subunits switch AMPA receptor antagonists into partial agonists. *Science* **318**:815-817.

Mielnik CA, Binko MA, Chen Y, Funk AJ, Johansson EM, Intson K, Sivananthan N, Islam R, Milenkovic M, Horsfall W, Ross RA, Groc L, Salahpour A, McCullumsmith RE, Tripathy S, Lambe EK, Ramsey AJ. Consequences of NMDA receptor deficiency can be rescued in the adult brain. *Mol Psychiatry*. 2020 Aug 17. doi: 10.1038/s41380-020-00859-4. Epub ahead of print. PMID: 32807843.

Mitchell NA, Fleck MW. Targeting AMPA receptor gating processes with allosteric modulators and mutations. *Biophys J*. 2007 Apr 1;92(7):2392-402. doi: 10.1529/biophysj.106.095091. Epub 2007 Jan 5. PMID: 17208968; PMCID: PMC1864835.

Miu, P., K. R. Jarvie, V. Radhakrishnan, M. R. Gates, A. Ogden, P. L. Ornstein, H. Zarrinmayeh, K. Ho, D. Peters, J. Grabell, A. Gupta, D. M. Zimmerman, and D. Bleakman. 2001. Novel AMPA receptor potentiators LY392098 and LY404187: effects on recombinant human AMPA receptors in vitro. *Neuropharmacology* 40: 976-983.

Molnar E, Va Radi A, McIlhinney RAJ, Ashcroft SJH. (1995). Identification of functional ionotropic glutamate receptor proteins in pancreatic β-cells and in islets of langerhans. *FEBS Lett.* 371 253–257. 10.1016/0014-5793(95)00890-L

Monaco SA, Ferguson BR, Gao WJ. Lithium Inhibits GSK3β and Augments GluN2A Receptor Expression in the Prefrontal Cortex. *Front Cell Neurosci*. 2018;12:16. Published 2018 Feb 1. doi:10.3389/fncel.2018.00016

Monaghan DT, Irvine MW, Costa BM, Fang G, Jane DE. Pharmacological modulation of NMDA receptor activity and the advent of negative and positive allosteric modulators. *Neurochem Int*. 2012;61(4):581-592. doi:10.1016/j.neuint.2012.01.004

Monyer H, Sprengel R, Schoepfer R, Herb A, Higuchi M, Lomeli H, Burnashev N, Sakmann B, and Seeburg PH. 1992. Heteromeric NMDA receptors: molecular and functional distinction of subtypes. *Science*. 256:1217–1221. 10.1126/science.256.5060.1217

Moskal JR, Burgdorf JS, Stanton PK, Kroes RA, Disterhoft JF, Burch RM, Khan MA. The Development of Rapastinel (Formerly GLYX-13); A Rapid Acting and Long Lasting Antidepressant. *Curr Neuropharmacol*. 2017;15(1):47-56. doi: 10.2174/1570159x14666160321122703. PMID: 26997507; PMCID: PMC5327451.

Mota SI, Ferreira IL, Rego AC. Dysfunctional synapse in Alzheimer's disease - A focus on NMDA receptors. *Neuropharmacology*. 2014 Jan;76 Pt A:16-26. doi: 10.1016/j.neuropharm.2013.08.013. Epub 2013 Aug 22. PMID: 23973316.

Mullier B, Wolff C, Sands ZA, Ghisdal P, Muglia P, Kaminski RM, André VM. GRIN2B gain of function mutations are sensitive to radiprodil, a negative allosteric modulator of GluN2B-containing NMDA receptors. *Neuropharmacology*. 2017 Sep 1;123:322-331. doi: 10.1016/j.neuropharm.2017.05.017. Epub 2017 May 19. PMID: 28533163.

Myers KA, Scheffer IE. GRIN2A-Related Speech Disorders and Epilepsy. 2016 Sep 29. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK385627/

Naur P, Hansen KB, Kristensen AS, Dravid SM, Pickering DS, Olsen L, Vestergaard B, Egebjerg J, Gajhede M, Traynelis SF, Kastrup JS (2007) Ionotropic glutamate-like receptor delta2 binds D-serine and glycine. *Proc Natl Acad Sci U S A*. **104**(35):14116-21.

Nguyen D, Alavi MV, Kim KY, et al. A new vicious cycle involving glutamate excitotoxicity, oxidative stress and mitochondrial dynamics. *Cell Death Dis*. 2011;2(12):e240. Published 2011 Dec 8. doi:10.1038/cddis.2011.117

Niemann S, Kanki H, Fukui Y, Takao K, Fukaya M, Hynynen MN, Churchill MJ, Shefner JM, Bronson RT, Brown RH Jr, Watanabe M, Miyakawa T, Itohara S, Hayashi Y. 2007. Genetic ablation of NMDA receptor subunit NR3B in mouse reveals motoneuronal and nonmotoneuronal phenotypes. *Eur J Neurosci* 26(6):1407-20.

Nowak L, Bregestovski P, Ascher P, Herbet A & Prochiantz A. (1984). Magnesium gates glutamate-activated channels in mouse central neurones. *Nature* 307,462-465.

Ohmori J, Sakamoto S, Kubota H, Shimizu-Sasamata M, Okada M, Kawasaki S, Hidaka K, Togami J, Furuya T and Murase K (1994) 6-(1H-imidazol-1-yl)-7-nitro-2,3(1H,4H)-quinoxalinedione hydrochloride (YM90K) and related compounds: structure-activity relationships for the AMPA-type non-NMDA receptor. *J Med Chem* **37**:467-475.

Okamoto S, Pouladi MA, Talantova M, Yao D, Xia P, Ehrnhoefer DE, Zaidi R, Clemente A, Kaul M, Graham RK, Zhang D, Vincent Chen HS, Tong G, Hayden MR, Lipton SA. Balance between synaptic versus extrasynaptic NMDA receptor activity influences inclusions and neurotoxicity of mutant huntingtin. *Nat Med*. 2009 Dec;15(12):1407-13. doi: 10.1038/nm.2056. Epub 2009 Nov 15. PMID: 19915593; PMCID: PMC2789858.

Orain D, Tasdelen E, Haessig S, Koller M, Picard A, Dubois C, Lingenhoehl K, Desrayaud S, Floersheim P, Carcache D, Urwyler S, Kallen J, Mattes H. Design and Synthesis of Selurampanel, a Novel Orally Active and Competitive AMPA Receptor Antagonist. *ChemMedChem*. 2017 Feb 3;12(3):197-201. doi: 10.1002/cmdc.201600467. Epub 2016 Nov 15. PMID: 27863026.

Otsu Y, Darcq E, Pietrajtis K, Mátyás F, Schwartz E, Bessaih T, Abi Gerges S, Rousseau CV, Grand T, Dieudonné S, Paoletti P, Acsády L, Agulhon C, Kieffer BL, Diana MA. Control of aversion by glycine-gated GluN1/GluN3A NMDA receptors in the adult medial habenula. *Science*. 2019 Oct 11;366(6462):250-254. doi: 10.1126/science.aax1522. PMID: 31601771; PMCID: PMC7556698.

Pabba M, Sibille E. Sigma-1 and N-Methyl-d-Aspartate Receptors: A Partnership with Beneficial Outcomes. *Mol Neuropsychiatry*. 2015 May;1(1):47-51. doi: 10.1159/000376549. Epub 2015 Mar 11. PMID: 27602356; PMCID: PMC4996022.

Pan Y, Chen J, Guo H, Ou J, Peng Y, Liu Q, Shen Y, Shi L, Liu Y, Xiong Z, Zhu T, Luo S, Hu Z, Zhao J, Xia K. Association of genetic variants of GRIN2B with autism. *Sci Rep*. 2015 Feb 6;5:8296. doi: 10.1038/srep08296. PMID: 25656819; PMCID: PMC4319152.

Papadia S, Soriano FX, Léveillé F, Martel MA, Dakin KA, Hansen HH, Kaindl A, Sifringer M, Fowler J, Stefovska V, McKenzie G, Craigon M, Corriveau R, Ghazal P, Horsburgh K, Yankner BA, Wyllie DJ, Ikonomidou C, Hardingham GE. Synaptic NMDA receptor activity boosts intrinsic antioxidant defenses. *Nat Neurosci*. 2008 Apr;11(4):476-87. doi: 10.1038/nn2071. Epub 2008 Mar 23. PMID: 18344994; PMCID: PMC2556874.

Paoletti P, Bellone C, Zhou Q. NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nat Rev Neurosci*. 2013 Jun;14(6):383-400. doi: 10.1038/nrn3504. PMID: 23686171.

Parameshwaran K, Dhanasekaran M, Suppiramaniam V. Amyloid beta peptides and glutamatergic synaptic dysregulation. *Exp Neurol*. 2008 Mar;210(1):7-13. doi: 10.1016/j.expneurol.2007.10.008. Epub 2007 Oct 24. PMID: 18053990.

Partin KM, Patneau DK and Mayer ML (1994) Cyclothiazide differentially modulates desensitization of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor splice variants. *Mol Pharmacol* **46**:129-138.

Partin KM, Fleck MW and Mayer ML (1996) AMPA receptor flip/flop mutants affecting deactivation, desensitization, and modulation by cyclothiazide, aniracetam, and thiocyanate. *J Neurosci* **16**:6634-6647.

Partin KM and Mayer ML (1996) Negative allosteric modulation of wild-type and mutant AMPA receptors by GYKI 53655. *Mol Pharmacol* **49**:142-148.

Peng TI, Jou MJ, Sheu SS, Greenamyre JT. Visualization of NMDA receptor-induced mitochondrial calcium accumulation in striatal neurons. *Exp Neurol*. 1998 Jan;149(1):1-12. doi: 10.1006/exnr.1997.6599. PMID: 9454610.

Phensy A, Driskill C, Lindquist K, Guo L, Jeevakumar V, Fowler B, Du H, Kroener S. Antioxidant Treatment in Male Mice Prevents Mitochondrial and Synaptic Changes in an NMDA Receptor Dysfunction Model of Schizophrenia. *eNeuro*. 2017 Aug 17;4(4):ENEURO.0081-17.2017. doi: 10.1523/ENEURO.0081-17.2017. PMID: 28819639; PMCID: PMC5559903.

Phensy A, Lindquist KL, Lindquist KA, Bairuty D, Gauba E, Guo L, Tian J, Du H, Kroener S. Deletion of the Mitochondrial Matrix Protein CyclophilinD Prevents Parvalbumin Interneuron Dysfunctionand Cognitive Deficits in a Mouse Model of NMDA Hypofunction. *J Neurosci*. 2020 Aug 5;40(32):6121-6132. doi: 10.1523/JNEUROSCI.0880-20.2020. Epub 2020 Jun 30. PMID: 32605939; PMCID: PMC7406283.

Philippe A, Malan V, Jacquemont ML, Boddaert N, Bonnefont JP, Odent S, Munnich A, Colleaux L, Cormier-Daire V. (2013) Xq25 duplications encompassing GRIA3 and STAG2 genes in two families convey recognizable X-linked intellectual disability with distinctive facial appearance. *Am J Med Genet A.* **161A**(6):1370-5.

Piard J, Bereau M, XiangWei W, Wirth T, Amsallem D, Buisson L, Richard P, Liu N, Xu Y, Myers SJ, Traynelis SF, Chelly J, Anheim M, Raynaud M, Maldergem LV and Yuan H (2020) The GRIA3 c.2477G > A Variant Causes an Exaggerated Startle Reflex, Chorea, and Multifocal Myoclonus. *Mov Disord* **35**:1224-1232.

Pierson TM, Yuan H, Marsh ED, Fuentes-Fajardo K, Adams DR, Markello T, Golas G, Simeonov DR, Holloman C, Tankovic A, Karamchandani MM, Schreiber JM, Mullikin JC; PhD for the NISC Comparative Sequencing Program, Tifft CJ, Toro C, Boerkoel CF, Traynelis SF, Gahl WA. GRIN2A mutation and early-onset epileptic encephalopathy: personalized therapy with memantine. *Ann Clin Transl Neurol*. 2014 Mar 1;**1**(3):190-198. doi: 10.1002/acn3.39. PMID: 24839611; PMCID: PMC4019449.

Planells-Cases R, Sun W, Ferrer-Montiel AV, Montal M. Molecular cloning, functional expression, and pharmacological characterization of an N-methyl-D-aspartate receptor subunit from human brain. *Proc Natl Acad Sc*i U S A. 1993 Jun 1;**90**(11):5057-61. doi: 10.1073/pnas.90.11.5057. PMID: 7685113; PMCID: PMC46653.

Platzer K, Yuan H, Schütz H, Winschel A, Chen W, Hu C, Kusumoto H, Heyne HO, Helbig KL, Tang S, Willing MC, Tinkle BT, Adams DJ, Depienne C, Keren B, Mignot C, Frengen E, Strømme P, Biskup S, Döcker D, Strom TM, Mefford HC, Myers CT, Muir AM, LaCroix A, Sadleir L, Scheffer IE, Brilstra E, van Haelst MM, van der Smagt JJ, Bok LA, Møller RS, Jensen UB, Millichap JJ, Berg AT, Goldberg EM, De Bie I, Fox S, Major P, Jones JR, Zackai EH, Abou Jamra R, Rolfs A, Leventer RJ, Lawson JA, Roscioli T, Jansen FE, Ranza E, Korff CM, Lehesjoki AE, Courage C, Linnankivi T, Smith DR, Stanley C, Mintz M, McKnight D, Decker A, Tan WH, Tarnopolsky MA, Brady LI, Wolff M, Dondit L, Pedro HF, Parisotto SE, Jones KL, Patel AD, Franz DN, Vanzo R, Marco E, Ranells JD, Di Donato N, Dobyns WB, Laube B, Traynelis SF, Lemke JR. GRIN2B encephalopathy: novel findings on phenotype, variant clustering, functional consequences and treatment aspects. *J Med Genet.* 2017;**54**:460–70.

Platzer K, Lemke JR. GRIN2B-Related Neurodevelopmental Disorder. 2018 May 31. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2020. PMID: 29851452.

Platzer K, Lemke JR. GRIN1-Related Neurodevelopmental Disorder. 2019 Jun 20. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK542807/

Priya A, Johar K, Wong-Riley MT. Nuclear respiratory factor 2 regulates the expression of the same NMDA receptor subunit genes as NRF-1: both factors act by a concurrent and parallel mechanism to couple energy metabolism and synaptic transmission. *Biochim Biophys Acta*. 2013;1833(1):48-58. doi:10.1016/j.bbamcr.2012.10.014

Pullan LM, Obey JW, Priece MT, Compton RP, Hood WF, Michel J, and Monahan JB. (1987) Excitatory amino acid receptor potency and subclass specificity of sulfur-containing amino acids. *J. Neurochem*. 49, 1301 — 1307.

Quirk JC, Nisenbaum ES. LY404187: a novel positive allosteric modulator of AMPA receptors. *CNS Drug Rev*. 2002 Fall;8(3):255-82. doi: 10.1111/j.1527-3458.2002.tb00228.x. PMID: 12353058; PMCID: PMC6741690.

Raghunatha P, Vosoughi A, Kauppinen TM, Jackson MF. Microglial NMDA receptors drive pro-inflammatory responses via PARP-1/TRMP2 signaling. *Glia*. 2020 Jul;68(7):1421-1434. doi: 10.1002/glia.23790. Epub 2020 Feb 8. PMID: 32036619.

Reutlinger C, Helbig I, Gawelczyk B, Subero JI, Tönnies H, Muhle H, Finsterwalder K, Vermeer S, Pfundt R, Sperner J, Stefanova I, Gillessen-Kaesbach G, von Spiczak S, van Baalen A, Boor R, Siebert R, Stephani U, Caliebe A. Deletions in 16p13 including GRIN2A in patients with intellectual disability, various dysmorphic features, and seizure disorders of the rolandic region. *Epilepsia*. 2010 Sep;51(9):1870-3. doi: 10.1111/j.1528-1167.2010.02555.x. PMID: 20384727.

Reyes RC, Brennan AM, Shen Y, Baldwin Y, Swanson RA. Activation of neuronal NMDA receptors induces superoxide-mediated oxidative stress in neighboring neurons and astrocytes. *J Neurosci*. 2012 Sep 12;32(37):12973-8. doi: 10.1523/JNEUROSCI.1597-12.2012. PMID: 22973021; PMCID: PMC3478885.

Rodriguez-Moreno A and Lerma J (1998) Kainate receptor modulation of GABA release involves a metabotropic function. *Neuron* **20**:1211-1218.

Rodríguez-Muñoz M, Sánchez-Blázquez P, Merlos M, Garzón-Niño J. Endocannabinoid control of glutamate NMDA receptors: the therapeutic potential and consequences of dysfunction. *Oncotarget*. 2016 Aug 23;7(34):55840-55862. doi: 10.18632/oncotarget.10095. PMID: 27323834; PMCID: PMC5342457.

Roginski RS, Goubaeva F, Mikami M, Fried-Cassorla E, Nair MR, Yang J. GRINL1A colocalizes with N-methyl D-aspartate receptor NR1 subunit and reduces N-methyl D-aspartate toxicity. *Neuroreport*. 2008 Nov 19;19(17):1721-6. doi: 10.1097/WNR.0b013e328317f05f. PMID: 18849881.

Rosi S, Ramirez-Amaya V, Hauss-Wegrzyniak B, Wenk GL. Chronic brain inflammation leads to a decline in hippocampal NMDA-R1 receptors. *J Neuroinflammation*. 2004 Jul 7;1(1):12. doi: 10.1186/1742-2094-1-12. PMID: 15285803; PMCID: PMC500869.

Salpietro V, Dixon CL, Guo H, Bello OD, Vandrovcova J, Efthymiou S, Maroofian R, Heimer G, Burglen L, Valence S, Torti E, Hacke M, Rankin J, Tariq H, Colin E, Procaccio V, Striano P, Mankad K, Lieb A, Chen S, Pisani L, Bettencourt C, Mannikko R, Manole A, Brusco A, Grosso E, Ferrero GB, Armstrong-Moron J, Gueden S, Bar-Yosef O, Tzadok M, Monaghan KG, Santiago-Sim T, Person RE, Cho MT, Willaert R, Yoo Y, Chae JH, Quan Y, Wu H, Wang T, Bernier RA, Xia K, Blesson A, Jain M, Motazacker MM, Jaeger B, Schneider AL, Boysen K, Muir AM, Myers CT, Gavrilova RH, Gunderson L, Schultz-Rogers L, Klee EW, Dyment D, Osmond M, Parellada M, Llorente C, Gonzalez-Penas J, Carracedo A, Van Haeringen A, Ruivenkamp C, Nava C, Heron D, Nardello R, Iacomino M, Minetti C, Skabar A, Fabretto A, Group SS, Raspall-Chaure M, Chez M, Tsai A, Fassi E, Shinawi M, Constantino JN, De Zorzi R, Fortuna S, Kok F, Keren B, Bonneau D, Choi M, Benzeev B, Zara F, Mefford HC, Scheffer IE, Clayton-Smith J, Macaya A, Rothman JE, Eichler EE, Kullmann DM and Houlden H (2019) AMPA receptor GluA2 subunit defects are a cause of neurodevelopmental disorders. *Nat Commun* **10**:3094.

Sapkota K, Mao Z, Synowicki P, Lieber D, Liu M, Ikezu T, Gautam V, Monaghan DT. GluN2D N-Methyl-d-Aspartate Receptor Subunit Contribution to the Stimulation of Brain Activity and Gamma Oscillations by Ketamine: Implications for Schizophrenia. *J Pharmacol Exp Ther*. 2016 Mar;356(3):702-11. doi: 10.1124/jpet.115.230391. Epub 2015 Dec 16. PMID: 26675679; PMCID: PMC4767398.

Savall BM, Wu D, Swanson DM, Seierstad M, Wu N, Vives Martinez J, Garcia Olmos B, Lord B, Coe K, Koudriakova T, Lovenberg TW, Carruthers NI, Maher MP and Ameriks MK (2019) Discovery of Imidazo[1,2-a]pyrazines and Pyrazolo[1,5-c]pyrimidines as TARP gamma-8 Selective AMPAR Negative Modulators. *ACS Med Chem Lett* **10**:267-272.

Savignac HM, Corona G, Mills H, Chen L, Spencer JP, Tzortzis G, Burnet PW. Prebiotic feeding elevates central brain derived neurotrophic factor, N-methyl-D-aspartate receptor subunits and D-serine. *Neurochem Int*. 2013 Dec;63(8):756-64. doi: 10.1016/j.neuint.2013.10.006. Epub 2013 Oct 16. PMID: 24140431; PMCID: PMC3858812.

Schinder AF, Olson EC, Spitzer NC, Montal M. Mitochondrial dysfunction is a primary event in glutamate neurotoxicity. *J Neurosci*. 1996 Oct 1;16(19):6125-33. doi: 10.1523/JNEUROSCI.16-19-06125.1996. PMID: 8815895; PMCID: PMC6579180.

Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014 Jul 24;511(7510):421-7. doi: 10.1038/nature13595. Epub 2014 Jul 22. PMID: 25056061; PMCID: PMC4112379.

Schmidt T, Samaras P, Frejno M, Gessulat S, Barnert M, Kienegger H, Krcmar H, Schlegl J, Ehrlich HC, Aiche S, Kuster B, Wilhelm M. ProteomicsDB. *Nucleic Acids Res*. 2018 Jan 4;46(D1):D1271-D1281. doi: 10.1093/nar/gkx1029. PMID: 29106664; PMCID: PMC5753189.

Schoepp DD, Lunn WH, Salhoff CR, McDonald JW. The NMDA receptor agonist DL-(tetrazol-5-yl)glycine is a highly potent excitotoxin. *Eur J Pharmacol*. 1994 Jan 3;270(1):67-72. doi: 10.1016/0926-6917(94)90081-7. PMID: 8157082.

Schorge S, Colquhoun D. Studies of NMDA receptor function and stoichiometry with truncated and tandem subunits. *J Neurosci*. 2003 Feb 15;23(4):1151-8. doi: 10.1523/JNEUROSCI.23-04-01151.2003. PMID: 12598603; PMCID: PMC6742241.

Schwenk J, Harmel N, Brechet A, Zolles G, Berkefeld H, Muller CS, Bildl W, Baehrens D, Huber B, Kulik A, Klocker N, Schulte U and Fakler B (2012) High-resolution proteomics unravel architecture and molecular diversity of native AMPA receptor complexes. *Neuron* **74**:621-633.

Schwenk J, Harmel N, Zolles G, Bildl W, Kulik A, Heimrich B, Chisaka O, Jonas P, Schulte U, Fakler B and Klocker N (2009) Functional proteomics identify cornichon proteins as auxiliary subunits of AMPA receptors. *Science* **323**:1313-1319.

Sekiguchi M, Fleck MW, Mayer ML, Takeo J, Chiba Y, Yamashita S and Wada K (1997) A novel allosteric potentiator of AMPA receptors: 4--2-(phenylsulfonylamino)ethylthio--2,6-difluoro-phenoxyaceta mide. *J Neurosci* **17**:5760-5771.

Sekiguchi M, Nishikawa K, Aoki S and Wada K (2002) A desensitization-selective potentiator of AMPA-type glutamate receptors. *Br J Pharmacol* **136**:1033-1041.

Shaffer CL, Patel NC, Schwarz J, Scialis RJ, Wei Y, Hou XJ, Xie L, Karki K, Bryce DK, Osgood SM, Hoffmann WE, Lazzaro JT, Chang C, McGinnis DF, Lotarski SM, Liu J, Obach RS, Weber ML, Chen L, Zasadny KR, Seymour PA, Schmidt CJ, Hajos M, Hurst RS, Pandit J and O'Donnell CJ (2015) The discovery and characterization of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor potentiator N-{(3S,4S)-4-[4-(5-cyano-2-thienyl)phenoxy]tetrahydrofuran-3-yl}propane-2-sulfona mide (PF-04958242). *J Med Chem* **58**:4291-4308.

Shanks NF, Savas JN, Maruo T, Cais O, Hirao A, Oe S, Ghosh A, Noda Y, Greger IH, Yates JR, 3rd and Nakagawa T (2012) Differences in AMPA and kainate receptor interactomes facilitate identification of AMPA receptor auxiliary subunit GSG1L. *Cell reports* **1**:590-598.

Sheardown MJ, Nielsen EO, Hansen AJ, Jacobsen P and Honore T (1990) 2,3-Dihydroxy-6-nitro-7-sulfamoyl-benzo(F)quinoxaline: a neuroprotectant for cerebral ischemia. *Science* **247**:571-574.

Shirai Y, Fujita Y, Hashimoto R, et al. Dietary Intake of Sulforaphane-Rich Broccoli Sprout Extracts during Juvenile and Adolescence Can Prevent Phencyclidine-Induced Cognitive Deficits at Adulthood. *PLoS One*. 2015;10(6):e0127244. Published 2015 Jun 24. doi:10.1371/journal.pone.0127244

Singh OV, Nagaraj NS. Transcriptomics, proteomics and interactomics: unique approaches to track the insights of bioremediation. *Brief Funct Genomic Proteomic*. 2006 Feb;4(4):355-62. doi: 10.1093/bfgp/eli006. Epub 2006 Feb 3. PMID: 17202126.

Siu A, Drachtman R. Dextromethorphan: a review of N-methyl-d-aspartate receptor antagonist in the management of pain. *CNS Drug Rev*. 2007 Spring;13(1):96-106. doi: 10.1111/j.1527-3458.2007.00006.x. PMID: 17461892; PMCID: PMC6494157.

Skrenkova K, Hemelikova K, Kolcheva M, Kortus S, Kaniakova M, Krausova B, Horak M. Structural features in the glycine-binding sites of the GluN1 and GluN3A subunits regulate the surface delivery of NMDA receptors. *Sci Rep*. 2019 Aug 23;9(1):12303. doi: 10.1038/s41598-019-48845-3. PMID: 31444392; PMCID: PMC6707325.

Slutsky I, Abumaria N, Wu LJ, Huang C, Zhang L, Li B, Zhao X, Govindarajan A, Zhao MG, Zhuo M, Tonegawa S, Liu G. Enhancement of learning and memory by elevating brain magnesium. *Neuron*. 2010 Jan 28;65(2):165-77. doi: 10.1016/j.neuron.2009.12.026. PMID: 20152124.

Sobolevsky AI, Rosconi MP and Gouaux E (2009) X-ray structure, symmetry and mechanism of an AMPA-subtype glutamate receptor. *Nature* **462**:745-756.

Sofroniew MV. Molecular dissection of reactive astrogliosis and glial scar formation. *Trends Neurosci*. 2009 Dec;32(12):638-47. doi: 10.1016/j.tins.2009.08.002. Epub 2009 Sep 24. PMID: 19782411; PMCID: PMC2787735.

Sólyom S, Tarnawa I. Non-competitive AMPA antagonists of 2,3-benzodiazepine type. *Curr Pharm Des*. 2002;8(10):913-39. doi: 10.2174/1381612024607081. PMID: 11945139.

Sommer B, Keinanen K, Verdoorn TA, Wisden W, Burnashev N, Herb A, Kohler M, Takagi T, Sakmann B and Seeburg PH (1990) Flip and flop: a cell-specific functional switch in glutamate-operated channels of the CNS. *Science* **249**:1580-1585.

Soto D, Coombs ID, Renzi M, Zonouzi M, Farrant M and Cull-Candy SG (2009) Selective regulation of long-form calcium-permeable AMPA receptors by an atypical TARP, gamma-5. *Nat Neurosci* **12**:277-285.

Soto D, Olivella M, Grau C, Armstrong J, Alcon C, Gasull X, Santos-Gómez A, Locubiche S, Gómez de Salazar M, García-Díaz R, Gratacòs-Batlle E, Ramos-Vicente D, Chu-Van E, Colsch B, Fernández-Dueñas V, Ciruela F, Bayés À, Sindreu C, López-Sala García-Cazorla À, Altafaj X. L-Serine dietary supplementation is associated with clinical improvement of loss-of-function GRIN2B-related pediatric encephalopathy. *Sci Signal*. 2019 Jun 18;12(586):eaaw0936. doi: 10.1126/scisignal.aaw0936. PMID: 31213567.

Sproul A, Steele SL, Thai TL, Yu S, Klein JD, Sands JM, et al. (2011). N-methyl-D-aspartate receptor subunit NR3a expression and function in principal cells of the collecting duct. *Am. J. Physiol. Renal. Physiol.* 301 F44–F54. 10.1152/ajprenal.00666.2010

Stephenson JR, Wang X, Perfitt TL, Parrish WP, Shonesy BC, Marks CR, Mortlock DP, Nakagawa T, Sutcliffe JS, Colbran RJ. A Novel Human CAMK2A Mutation Disrupts Dendritic Morphology and Synaptic Transmission, and Causes ASD-Related Behaviors. *J Neurosci*. 2017 Feb 22;37(8):2216-2233. doi: 10.1523/JNEUROSCI.2068-16.2017. Epub 2017 Jan 27. PMID: 28130356; PMCID: PMC5338762.

Stone TW. Neuropharmacology of quinolinic and kynurenic acids. *Pharmacol Rev*. 1993 Sep;45(3):309-79. PMID: 8248282.

Strange M, Bräuner-Osborne H, Jensen AA (2006) Functional characterisation of homomeric ionotropic glutamate receptors GluR1-GluR6 in a fluorescence-based high throughput screening assay. *Comb Chem High Throughput Screen* **9**(2):147-58.

Strehlow V, Heyne HO, Vlaskamp DRM, Marwick KFM, Rudolf G, de Bellescize J, Biskup S, Brilstra EH, Brouwer OF, Callenbach PMC, Hentschel J, Hirsch E, Kind PC, Mignot C, Platzer K, Rump P, Skehel PA, Wyllie DJA, Hardingham GE, van Ravenswaaij-Arts CMA, Lesca G, Lemke JR; GRIN2A study group. GRIN2A-related disorders: genotype and functional consequence predict phenotype. *Brain*. 2019 Jan 1;142(1):80-92. doi: 10.1093/brain/awy304. PMID: 30544257; PMCID: PMC6308310.

Suryavanshi PS, Ugale RR, Yilmazer-Hanke D, Stairs DJ, Dravid SM. GluN2C/GluN2D subunit-selective NMDA receptor potentiator CIQ reverses MK-801-induced impairment in prepulse inhibition and working memory in Y-maze test in mice. *Br J Pharmacol*. 2014;171(3):799-809. doi:10.1111/bph.12518

Sutcu R, Yonden Z, Yilmaz A, Delibas N. Melatonin increases NMDA receptor subunits 2A and 2B concentrations in rat hippocampus. *Mol Cell Biochem*. 2006 Feb;283(1-2):101-5. doi: 10.1007/s11010-006-2385-4. PMID: 16444591.

Takahashi M, Kohara A, Shishikura J, Kawasaki-Yatsugi S, Ni JW, Yatsugi S, Sakamoto S, Okada M, Shimizu-Sasamata M and Yamaguchi T (2002) YM872: a selective, potent and highly water-soluble alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonist. *CNS Drug Rev* **8**:337-352.

Takahashi H, Shin Y, Cho SJ, Zago WM, Nakamura T, Gu Z, Ma Y, Furukawa H, Liddington R, Zhang D, Tong G, Chen HS, Lipton SA. Hypoxia enhances S-nitrosylation-mediated NMDA receptor inhibition via a thiol oxygen sensor motif. *Neuron*. 2007 Jan 4;53(1):53-64. doi: 10.1016/j.neuron.2006.11.023. PMID: 17196530; PMCID: PMC1855274.

Tang W, Liu D, Traynelis SF, Yuan H. Positive allosteric modulators that target NMDA receptors rectify loss-of-function GRIN variants associated with neurological and neuropsychiatric disorders. *Neuropharmacology*. 2020 Oct 15;177:108247. doi: 10.1016/j.neuropharm.2020.108247. Epub 2020 Jul 24. PMID: 32712275; PMCID: PMC7554152.

Tardiolo G, Bramanti P, Mazzon E. Overview on the Effects of *N*-Acetylcysteine in Neurodegenerative Diseases. *Molecules*. 2018;23(12):3305. Published 2018 Dec 13. doi:10.3390/molecules23123305

The UniProt Consortium, UniProt: a worldwide hub of protein knowledge, *Nucleic Acids Research*, Volume 47, Issue D1, 08 January 2019, Pages D506–D515, https://doi.org/10.1093/nar/gky1049

Timm DE, Benveniste M, Weeks AM, Nisenbaum ES and Partin KM (2011) Structural and functional analysis of two new positive allosteric modulators of GluA2 desensitization and deactivation. *Mol Pharmacol* **80**:267-280.

Ting K, Brew BJ, Guillemin GJ. (2009). Effect of quinolinic acid on human astrocytes morphology and functions: implications in Alzheimer's disease. *J. Neuroinflamm*. 6:36. 10.1186/1742-2094-6-36

Tingley WG, Ehlers MD, Kameyama K, Doherty C, Ptak JB, Riley CT, Huganir RL. Characterization of protein kinase A and protein kinase C phosphorylation of the N-methyl-D-aspartate receptor NR1 subunit using phosphorylation site-specific antibodies. *J Biol Chem*. 1997 Feb 21;272(8):5157-66. doi: 10.1074/jbc.272.8.5157. PMID: 9030583.

Tomita S, Chen L, Kawasaki Y, Petralia RS, Wenthold RJ, Nicoll RA and Bredt DS (2003) Functional studies and distribution define a family of transmembrane AMPA receptor regulatory proteins. *J Cell Biol* **161**:805-816.

Traynelis SF, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK, et al. Glutamate receptor ion channels: structure, regulation, and function. *Pharmacol Rev*. 2010;62:405–496.

Trivisano M, Santarone ME, Micalizzi A, Ferretti A, Dentici ML, Novelli A, Vigevano F, Specchio N (2020) GRIA3 missense mutation is cause of an x-linked developmental and epileptic encephalopathy. *Seizure* **82**:1-6.

Tsai GE, Yang P, Chang YC, Chong MY. D-alanine added to antipsychotics for the treatment of schizophrenia. *Biol Psychiatry*. 2006 Feb 1;59(3):230-4. doi: 10.1016/j.biopsych.2005.06.032. Epub 2005 Sep 9. PMID: 16154544.

Tsai JJ, Wu T, Leung H, Desudchit T, Tiamkao S, Lim KS, Dash A. (2018) Perampanel, an AMPA receptor antagonist: From clinical research to practice in clinical settings. *Acta Neurol Scand*. **137**(4):378-391.

Turner SJ, Mayes AK, Verhoeven A, Mandelstam SA, Morgan AT, Scheffer IE. GRIN2A: an aptly named gene for speech dysfunction. *Neurology*. 2015a;84:586–93.

Turski L, Huth A, Sheardown M, McDonald F, Neuhaus R, Schneider HH, Dirnagl U, Wiegand F, Jacobsen P and Ottow E (1998) ZK200775: a phosphonate quinoxalinedione AMPA antagonist for neuroprotection in stroke and trauma. *Proc Natl Acad Sci U S A* **95**:10960-10965.

Udvardi PT, Föhr KJ, Henes C, Liebau S, Dreyhaupt J, Boeckers TM, Ludolph AG. Atomoxetine affects transcription/translation of the NMDA receptor and the norepinephrine transporter in the rat brain--an in vivo study. *Drug Des Devel Ther*. 2013 Dec 4;7:1433-46. doi: 10.2147/DDDT.S50448. PMID: 24348020; PMCID: PMC3857115.

Uemura T, Lee SJ, Yasumura M, Takeuchi T, Yoshida T, Ra M, Taguchi R, Sakimura K, Mishina M (2010) Trans-synaptic interaction of GluRdelta2 and Neurexin through Cbln1 mediates synapse formation in the cerebellum. *Cell*. **141**(6):1068-79.

Ulbrich MH, and Isacoff EY. 2007. Subunit counting in membrane-bound proteins. *Nat. Methods*. 4:319–321. 10.1038/nmeth1024

Urbano M, Okwara L, Manser P, Hartmann K, Deutsch SI. A trial of d-cycloserine to treat the social deficit in older adolescents and young adults with autism spectrum disorders. *J Neuropsychiatry Clin Neurosci*. 2015;27(2):133-8. doi: 10.1176/appi.neuropsych.13070155. PMID: 25923852.

Volgraf M, Sellers BD, Jiang Y, Wu G, Ly CQ, Villemure E, Pastor RM, Yuen PW, Lu A, Luo X, Liu M, Zhang S, Sun L, Fu Y, Lupardus PJ, Wallweber HJ, Liederer BM, Deshmukh G, Plise E, Tay S, Reynen P, Herrington J, Gustafson A, Liu Y, Dirksen A, Dietz MG, Liu Y, Wang TM, Hanson JE, Hackos D, Scearce-Levie K, Schwarz JB. Discovery of GluN2A-Selective NMDA Receptor Positive Allosteric Modulators (PAMs): Tuning Deactivation Kinetics via Structure-Based Design. *J Med Chem*. 2016 Mar 24;59(6):2760-79. doi: 10.1021/acs.jmedchem.5b02010. Epub 2016 Mar 8. PMID: 26919761.

Walker CS, Jensen S, Ellison M, Matta JA, Lee WY, Imperial JS, Duclos N, Brockie PJ, Madsen DM, Isaac JT, Olivera B and Maricq AV (2009) A novel Conus snail polypeptide causes excitotoxicity by blocking desensitization of AMPA receptors. *Curr Biol* **19**:900-908.

Wang TM, Brown BM, Deng L, Sellers BD, Lupardus PJ, Wallweber HJA, Gustafson A, Wong E, Volgraf M, Schwarz JB, Hackos DH, Hanson JE. A novel NMDA receptor positive allosteric modulator that acts via the transmembrane domain. *Neuropharmacology*. 2017 Jul 15;121:204-218. doi: 10.1016/j.neuropharm.2017.04.041. Epub 2017 Apr 27. PMID: 28457974.

Ward SE, Harries MH, Aldegheri L, Bradford AM, Ballini E, Dawson L, Lacroix L, Pardoe J, Starr K, Weil A, Waters K, Atack JR and Woolley M (2020) Pharmacological characterisation of MDI-222, a novel AMPA receptor positive allosteric modulator with an improved safety profile. *J Psychopharmacol* 34:93-102.

Weaver CD, Yao TL, Powers AC, Verdoorn TA. Differential expression of glutamate receptor subtypes in rat pancreatic islets. *Journal of Biological Chemistry*. 1996;271:12977–12984.

Weickert CS, Fung SJ, Catts VS, Schofield PR, Allen KM, Moore LT, et al. Molecular evidence of N-methyl-D-aspartate receptor hypofunction in schizophrenia. *Mol Psychiatry* (2013) 18:1185–92. doi: 10.1038/mp.2012.137

Welters A, Lammert E, Mayatepek E, Meissner T. Need for Better Diabetes Treatment: The Therapeutic Potential of NMDA Receptor Antagonists. *Klin Padiatr*. 2017 Jan;229(1):14-20. English. doi: 10.1055/s-0042-117831. Epub 2016 Dec 14. PMID: 27975343.

Wenthold RJ, Petralia RS, Blahos J, II and Niedzielski AS (1996) Evidence for multiple AMPA receptor complexes in hippocampal CA1/CA2 neurons. *J Neurosci* **16**:1982-1989.

Whittemore ER, Ilyin VI, Konkoy CS and Woodward RM (1997a) Subtype-selective antagonism of NMDA receptors by nylidrin. *Eur J Pharmacol* 337:197-208.

Whittemore ER, Ilyin VI and Woodward RM (1997b) Antagonism of N-methyl-D-aspartate receptors by sigma site ligands: potency, subtype-selectivity and mechanisms of inhibition. *J Pharmacol Exp Ther* 282:326-338.

Wilding TJ and Huettner JE (1995) Differential antagonism of alpha-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid-preferring and kainate-preferring receptors by 2,3-benzodiazepines. *Mol Pharmacol* **47**:582-587.

Williams K. Ifenprodil, a novel NMDA receptor antagonist: site and mechanism of action. *Curr Drug Targets*. 2001 Sep;2(3):285-98. doi: 10.2174/1389450013348489. PMID: 11554553.

Williams K. Subunit-specific potentiation of recombinant N-methyl-D-aspartate receptors by histamine. *Mol Pharmacol*. 1994;46:531–541.

Williams K, Kashiwagi K, Fukuchi J, Igarashi K (1995). An acidic amino acid in the N-methyl-D-aspartate receptor that is important for spermine stimulation. *Mol Pharmacol* 48: 1087–1098.

Williams S, Chen L, Savignac HM, Tzortzis G, Anthony DC, Burnet PW. Neonatal prebiotic (BGOS) supplementation increases the levels of synaptophysin, GluN2A-subunits and BDNF proteins in the adult rat hippocampus. *Synapse*. 2016 Mar;70(3):121-4. doi: 10.1002/syn.21880. Epub 2016 Jan 9. PMID: 26682524.

Wolosker H. (2011). Serine racemase and the serine shuttle between neurons and astrocytes. *Biochim. Biophys. Acta* 1814, 1558–1566 10.1016/j.bbapap.2011.01.001

Wu FS, Gibbs TT, Farb DH. Pregnenolone sulfate: a positive allosteric modulator at the N-methyl-D-aspartate receptor. *Mol Pharmacol*. 1991 Sep;40(3):333-6. PMID: 1654510.

Wu LJ, Toyoda H, Zhao MG, Lee YS, Tang J, Ko SW, Jia YH, Shum FW, Zerbinatti CV, Bu G, Wei F, Xu TL, Muglia LJ, Chen ZF, Auberson YP, Kaang BK, Zhuo M. Upregulation of forebrain NMDA NR2B receptors contributes to behavioral sensitization after inflammation. *J Neurosci*. 2005 Nov 30;25(48):11107-16. doi: 10.1523/JNEUROSCI.1678-05.2005. PMID: 16319310; PMCID: PMC6725642.

Wu Y, Arai AC, Rumbaugh G, Srivastava AK, Turner G, Hayashi T, Suzuki E, Jiang Y, Zhang L, Rodriguez J, Boyle J, Tarpey P, Raymond FL, Nevelsteen J, Froyen G, Stratton M, Futreal A, Gecz J, Stevenson R, Schwartz CE, Valle D, Huganir RL and Wang T (2007) Mutations in ionotropic AMPA receptor 3 alter channel properties and are associated with moderate cognitive impairment in humans. *Proc Natl Acad Sci U S A* **104**:18163-18168.

Xiang Wei W, Kannan V, Xu Y, Kosobucki GJ, Schulien AJ, Kusumoto H, Moufawad El Achkar C, Bhattacharya S, Lesca G, Nguyen S, Helbig KL, Cuisset JM, Fenger CD, Marjanovic D, Schuler E, Wu Y, Bao X, Zhang Y, Dirkx N, Schoonjans AS, Syrbe S, Myers SJ, Poduri A, Aizenman E, Traynelis SF, Lemke JR, Yuan H, Jiang Y. Heterogeneous clinical and functional features of GRIN2D-related developmental and epileptic encephalopathy. *Brain*. 2019 Oct 1;142(10):3009-3027. doi: 10.1093/brain/awz232. PMID: 31504254; PMCID: PMC6763743.

Xue JG, Masuoka T, Gong XD, Chen KS, Yanagawa Y, Law SK, Konishi S. NMDA receptor activation enhances inhibitory GABAergic transmission onto hippocampal pyramidal neurons via presynaptic and postsynaptic mechanisms. *J Neurophysiol*. 2011 Jun;105(6):2897-906. doi: 10.1152/jn.00287.2010. Epub 2011 Apr 6. PMID: 21471392.

Yao Y, Mayer ML. Characterization of a soluble ligand binding domain of the NMDA receptor regulatory subunit NR3A. *J. Neurosci.* 2006;26:4559–4566.

Yelshanskaya MV, Singh AK, Narangoda C, Williams RSB, Kurnikova MG and Sobolevsky AI (2020) Structural basis of AMPA receptor inhibition by trans-4-butylcyclohexane carboxylic acid. *Br J Pharmacol*.

Yelshanskaya MV, Singh AK, Sampson JM, Narangoda C, Kurnikova M and Sobolevsky AI (2016b) Structural Bases of Noncompetitive Inhibition of AMPA-Subtype Ionotropic Glutamate Receptors by Antiepileptic Drugs. *Neuron* **91**:1305-1315.

Yi F, Rouzbeh N, Hansen KB, Xu Y, Fanger CM, Gordon E, Paschetto K, Menniti FS, Volkmann RA. PTC-174, a positive allosteric modulator of NMDA receptors containing GluN2C or GluN2D subunits. Neuropharmacology. 2020 Aug 15;173:107971. doi: 10.1016/j.neuropharm.2020.107971. Epub 2020 Jan 25. PMID: 31987864; PMCID: PMC7293934.

Yu J, Rao P, Clark S, Mitra J, Ha T, Gouaux E. Hippocampal AMPA receptor assemblies and mechanism of allosteric inhibition. *Nature*. 2021 May 12. doi: 10.1038/s41586-021-03540-0. Epub ahead of print. PMID: 33981040.

Yu SY, Wu DC, Zhan RZ. GluN2B subunits of the NMDA receptor contribute to the AMPA receptor internalization during long-term depression in the lateral amygdala of juvenile rats. *Neuroscience*. 2010 Dec 29;171(4):1102-8. doi: 10.1016/j.neuroscience.2010.09.038. Epub 2010 Sep 25. PMID: 20884329.

Yuen EY, Jiang Q, Chen P, Gu Z, Feng J, Yan Z. Serotonin 5-HT1A receptors regulate NMDA receptor channels through a microtubule-dependent mechanism. *J Neurosci*. 2005 Jun 8;25(23):5488-501. doi: 10.1523/JNEUROSCI.1187-05.2005. PMID: 15944377; PMCID: PMC6724987.

Yuen EY, Jiang Q, Feng J, Yan Z. Microtubule regulation of N-methyl-D-aspartate receptor channels in neurons. *J Biol Chem*. 2005 Aug 19;280(33):29420-7. doi: 10.1074/jbc.M504499200. Epub 2005 Jun 23. PMID: 15975919.

Yuen EY, Jiang Q, Chen P, Feng J, Yan Z. Activation of 5-HT2A/C receptors counteracts 5-HT1A regulation of n-methyl-D-aspartate receptor channels in pyramidal neurons of prefrontal cortex. *J Biol Chem*. 2008 Jun 20;283(25):17194-204. doi: 10.1074/jbc.M801713200. Epub 2008 Apr 28. PMID: 18442977; PMCID: PMC2427346.

Zhang HX, Lyons-Warren A, Thio LL. The glycine transport inhibitor sarcosine is an inhibitory glycine receptor agonist. *Neuropharmacology*. 2009;57(5-6):551-555. doi:10.1016/j.neuropharm.2009.07.019

Zhao Y, Chen S, Swensen AC, Qian WJ and Gouaux E (2019) Architecture and subunit arrangement of native AMPA receptors elucidated by cryo-EM. *Science* **364**:355-362.

Zhang Z, Sun QQ. Development of NMDA NR2 subunits and their roles in critical period maturation of neocortical GABAergic interneurons. *Dev Neurobiol*. 2011 Mar;71(3):221-45. doi: 10.1002/dneu.20844. PMID: 20936660; PMCID: PMC3103948.

Zhu Z, Yi F, Epplin MP, Liu D, Summer SL, Mizu R, Shaulsky G, XiangWei W, Tang W, Burger PB, Menaldino DS, Myers SJ, Liotta DC, Hansen KB, Yuan H, Traynelis SF. Negative allosteric modulation of GluN1/GluN3 NMDA receptors. Neuropharmacology. 2020 Oct 1;176:108117. doi: 10.1016/j.neuropharm.2020.108117. Epub 2020 May 7. PMID: 32389749; PMCID: PMC7530031.

Zorumski CF, Izumi Y, Mennerick S. Ketamine: NMDA Receptors and Beyond. *J Neurosci*. 2016 Nov 2;36(44):11158-11164. doi: 10.1523/JNEUROSCI.1547-16.2016. PMID: 27807158; PMCID: PMC5148235.

Zuo J, De Jager PL, Takahashi KA, Jiang W, Linden DJ and Heintz N (1997) Neurodegeneration in Lurcher mice caused by mutation in delta2 glutamate receptor gene. *Nature* **388**:769-773.