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REVIEW ARTICLE

Role of Grina/Nmdara1 in the Central Nervous System Diseases

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Abstract: Glutamate receptor, ionotropic, N-methyl-D-aspartate associated protein 1 (GRINA) is a member of the NMDA receptors (NMDARs) and is involved in several neurological diseases, which governs the key processes of neuronal cell death or the release of neurotransmitters. Upregulation of GRINA has been reported in multiple diseases in human beings, such as major depressive disorder (MDD) and schizophrenia (SCZ), with which the underlying mechanisms remain elusive. In this review, we provide a general overview of the expression and physiological function of GRINA in the central nervous system (CNS) diseases, including stroke, depression ,epilepsy, SCZ, and Alzheimer's disease (AD).

Keywords: NMDARs, stroke, depression, epilepsy, SCZ, AD.

1. INTRODUCTION

NMDARs are one of three pharmacologically distinct subtypes of ionotropic receptors that mediate a majority of excitatory neurotransmissions in the brain [1]. Activation of NMDARs and downstream cellular signaling are important for neuronal development, synaptic plasticity, learning and memory [2], but also contribute to the pathogenesis of diverse neurological disorders, such as AD, epilepsy, stroke and SCZ [3-5]. NMDARs are highly permeable to Ca^{2+}, and Ca^{2+} influx, which is essential for synaptogenesis, experience-dependent synaptic remodelling and long-lasting changes in synaptic efficacy such as long-term potentiation (LTP) and long-term depression (LTD) [1]. GRINA is a glutamate receptor-associated protein and several studies have demonstrated its dysfunction in the brain which is linked to the occurrence of several CNS diseases. As summarized in Table **1**, the upregulation of GRINA has been reported in the depression and SCZ. Meanwhile, the neuroprotective function of GRINA has been shown to be involved in ischemic stroke and post-ischemic unfolded protein response. Herein, we reviewed the existing literature about GRINA, deciphered the functions of GRINA through its domains, and discussed its roles in the CNS diseases.

2. DOMAINS AND EXPRESSION OF GRINA

Human GRINA is located at the chromosome region 8q24.3, near the subtelomere [9], and encodes a 371 amino acid protein with a predicted molecular weight of 41.2 kDa. Protein domain prediction (DOMPRED) revealed a critical region which containing the seven-transmembrane α-helices (Fig. **1**). In order to understand the characterization of GRINA domains, we analyzed the NCBI's Conserved Domains Database (CDD) [13]. GRINA displayed two major domains: a Pro-rich domain (fragment 39-139) within an N-terminal tail and an LFG-like domain (fragment 151-367), belonging to the BI-1-like superfamily, across the transmembrane region [14].

Nielsen and colleagues measured the expression of GRINA by Northern blot in different murine tissues [15]. They observed a broad expression pattern, strongly expressed in the brain and kidney, and also in the cortex, cerebellum, hindbrain and basal ganglia, as well as other organs like the testes and spleen. GRINA is expressed throughout the brain but at the highest levels in the hippocampus, suggesting that GRINA is likely to play crucial roles in the hippocampus associated neurological diseases, as discussed in more detail.

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Table 1. Summary of studies describing alterations of GRINA in CNS diseases.

Disease Name	Study Models	Conclusions	References
Depression	Clinical patients	GRINA as novel factors associated with major depressive disorder	Goswami DB *et al*. [6]
Depression	Clinical patients	GRINA up-regulated among the suicides with major depression	Sequeira A *et al*. [7]
Schizophrenia	Clinical patients	Persons with schizophrenia had significantly increased levels of GRINA	Čiháková D *et al*. [8]
Epilepsy	*In-vitro* cell culture	GRINA mapped to the same region of chromosome 8 as BFNC	Lewis TB *et al*. [9]
Epilepsy	Clinical patients	GRINA associated with severe mental retardation and epilepsy	Bonaglia MC *et al*. [10]
Stroke	*In-vivo* mouse model *In-vitro* cell culture	GRINA involved in EPO-mediated neuroprotection after stroke	Habib P *et al*. [11]
Stroke	*In-vivo* mouse model *In-vitro* cell culture	GRINA plays a crucial role in post-ischemic unfolded protein response	Habib P *et al*. [12]

2.1. Grina in Major Depressive Disorder

Major depressive disorder (MDD) is one of the most prevalent mood disorders and ranks first among all neurological disorders in terms of disability-adjusted life years [16]. Although the principal cause of this disorder is largely unknown, some depressed patients show a remarkable improvement following the administration of NMDARs channel antagonist [17, 18]. A recent study indicated that an NMDAR antagonist ketamine enhances visual sensory evoked potential LTP in patients with MDD [19], and blocks bursting in the lateral habenula to rapidly relieve depression [20]. Similar to ketamine, other NMDAR antagonists, including MK-801 [21] and AP-5 [22] mimicked ketamine's effect in inducing AMPAR-mediated synaptic potentiation. This finding was hypothesized to indicate that ketamine, *via* blocking the NMDAR at rest, drives synaptic potentiation, leading to synaptic plasticity changes that might be relevant to the antidepressant actions of NMDAR antagonists [23].

Goswami DB *et al*., used brain samples from MDD patients and found that GRINA is increased in the prefrontal cortex of MDD subjects [6]. In the same study, a majority of the NMDA receptor subunits (GRINA, GRIN2A, GRINL1A) up-regulated among the suicides with major depression versus the controls or the suicides without history of major depression [7]. These results suggest that the expression of GRINA is associated with the pathophysiology of depression and is a critical approach for novel antidepressant treatments.

2.2. Grina in Schizophrenia

Schizophrenia (SCZ) is a chronic neuropsychiatric disorder associated with affective, cognitive, neuromorphological, and molecular abnormalities [24]. Even though the etiology of SCZ is uncertain, it is believed to be a neurodevelopmental disorder that results from a combination of environmental insults and genetic vulnerabilities [25]. NMDA receptor is a major subtype of glutamate receptor that mediates fast synaptic transmission in the CNS. Several studies have shown that NMDA hypofunction is tightly linked to SCZ [26-28]. One study demonstrated the differential effect of NMDA receptor GluN2C and GluN2D subunit ablation on behavior and channel blocker-induced SCZ phenotypes [29]. Notably, NMDA receptor antagonists induced SCZ-like behaviors in animal models [30] and psychosis impairment in normal human subjects [31]. Hao *et al*., reported that NMDARs may be potential therapeutic targets to prevent disease development during asymptomatic periods of SCZ and may serve as targets for preventive and/or therapeutic strategies for SCZ [32].

The region in the N terminal domain of GRINA (fragment 63-96) shows homology with the 33-mer gliadin peptide [33]. Based on this homology, the 33-mer gliadin peptide would act as a natural antagonist, interfering with GRINA and altering its functions. This biochemical mechanism would be relevant in the extraintestinal manifestations of SCZ [33]. Indeed, about one-third of people with SCZ have elevated IgG antibodies to gliadin (AGA IgG) [14]. Supporting this association, a recent study with 80 healthy controls and 160 patients with SCZ showed that GRINA IgG was higher in SCZ patients than in healthy controls, and that the presence of anti-GRINA antibodies was associated with anti-AGA antibodies [8]. These results support the possible role of GRINA in SCZ. However, further research works required to elucidate their exact mechanisms in SCZ.

2.3. Grina in Epilepsy

Epilepsy is one of the most common neurological disorders that are characterized by abrupt, recurrent, and synchronous discharges of the brain [34]. Previous studies have found a surprising number of NMDARs mutations in seizure disorders, causing various childhood epilepsy syndromes [35, 36]. Secondly, a sharp increase in the extracellular concentration of glutamate in the focal hemisphere has been observed immediately prior to the onset of an electrographic seizure [9]. Finally, glutamate antagonists selective for NMDARs act as potent anticonvulsants in a range of epilepsies [37, 38]. These findings suggest that NMDARs appear to be a locus for epilepsy.

A form of inherited epilepsy is benign familial neonatal convulsions (BFNC) localized to chromosome 8. GRINA mapped to 8q24 was considered as a candidate for the epileptic disorder [9]. Another recent study found that the

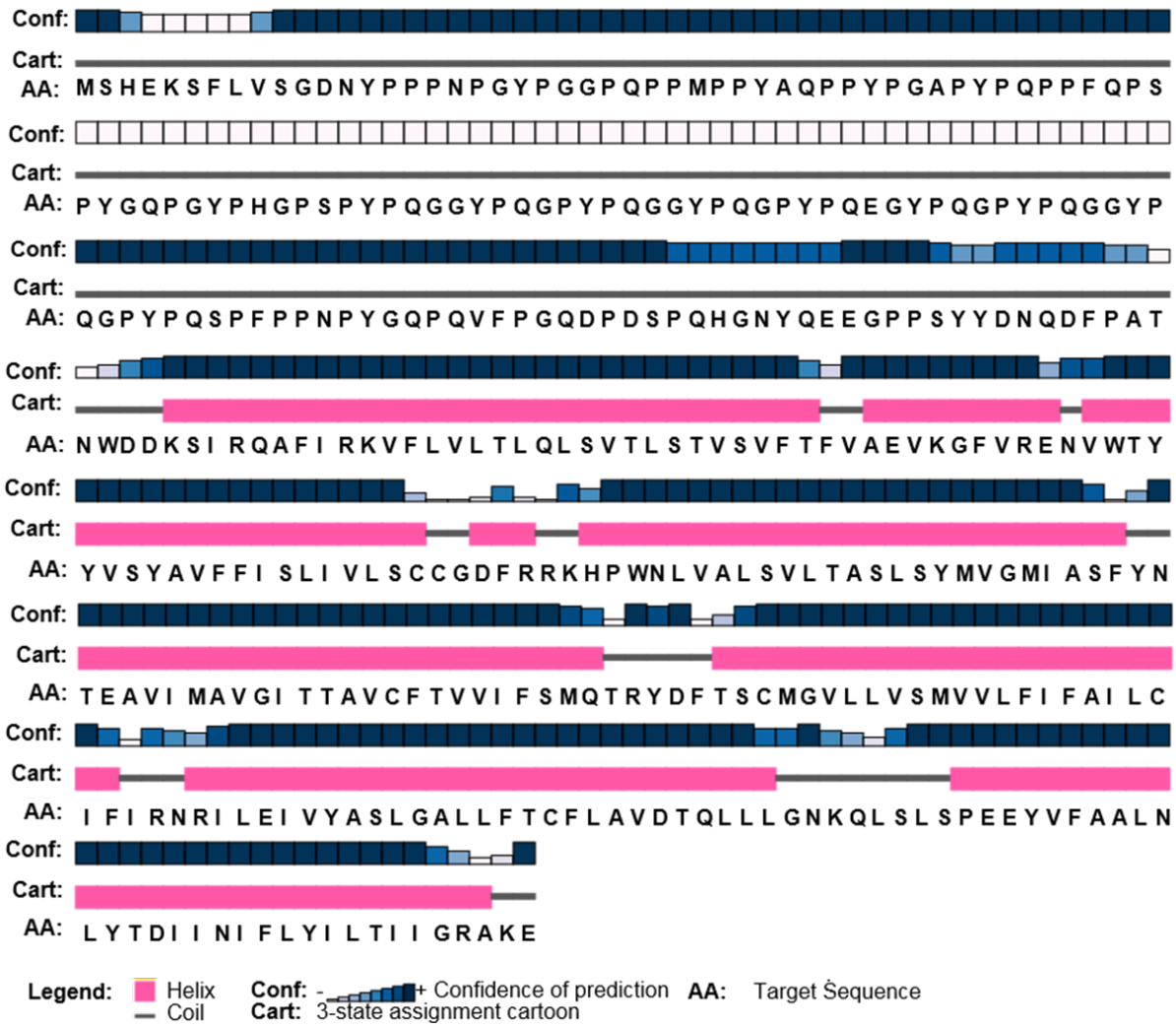

Fig. (1). Secondary structure prediction (PSIPRED) cartoon of human GRINA. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

GRINA within the 2.3Mb duplicated segment of chromosome 8q24.3 is associated with severe mental retardation and epilepsy [10]. These findings suggested the potential role of GRINA in ameliorating epilepsy *via* targeting the balance between inhibition and excitation.

2.4. Grina in Stroke

Stroke is the second leading cause of death and the third most common cause of disability worldwide [39]. The two main types of stroke are ischemic and hemorrhagic. Ischemic strokes comprise about 87% of all strokes [40]. Ischemic stroke triggers a complex series of pathophysiological events, including the accumulation of synaptic and extrasynaptic glutamate, ion channel dysfunction, inflammation and so on, eventually leading to neuronal cell death and ischemic brain injury [41, 42]. NMDARs -mediated excitotoxicity is the leading cause of neuronal cell death in ischemic stroke [43]. It is well documented that DAPK1 interaction with NMDA receptor NR2B subunits mediates brain damage in stroke [44]. The genetic mutation of GluN2B protects brain cells against stroke damages [45]. Differential roles of NMDA receptor subtypes in ischemic neuronal cell death and ischemic tolerance were found in other recent research [46, 47]. GRINA is a glutamate receptor-associated protein and several studies have demonstrated that GRINA has a highly potent protective effect, preventing mice from cerebral ischemia-induced cell death [11] and post-ischemic unfolded protein response (UPR) [12].

The LFG-like domain gives GRINA an alternative name LFG1. As commented before, mammalian members of the BI-like superfamily include transmembrane proteins related to cell death and survival [48]. Previous studies have provided evidence for the critical role of TMBIM members in the transient brain ischemia. Endoplasmic reticulum protein BI-1 modulates unfolded protein response signaling and protects against traumatic brain injury and apoptotic cell death [49, 50]. Fas apoptotic inhibitory molecule 2 (Faim2) has been shown to modulate hippocampal neuroplasticity and is neuroprotection in cerebral ischemia [51-53].

Overall, these findings strongly suggest that TMBIM members GRINA, BI-1 and Faim2 could be new therapeutic approaches to decrease excitotoxicity-induced neuronal cell death in stroke.

2.5. Grina in Alzheimer's Disease

Alzheimer's disease (AD) is the most common neurodegenerative disease and is characterized by cognitive disorder and memory dysfunction in the elderly population, affecting almost 40 million people worldwide [54]. The pathophysiology of AD includes the appearance of senile plaques consisting of Aβ and neurofibrillary tangles containing phosphorylated tau, leading to the substantial loss of synaptic profiles [55]. Accumulating evidence has suggested that NMDARs dysfunction is tightly linked to AD [5, 56, 57]. In a recent study by Dong *et al*. [58], intracerebroventricularly injected IL-1β induced calcium overload and endoplasmic reticulum stress, and NMDAR antagonist MK801 pretreatment significantly attenuated neuronal apoptosis and NMDAR up-regulation [59]. Another recent study found that NMDARs activation mediated by Aβ is involved in Aβ-induced mitochondrial toxicity and neuronal dysfunction [60]. Overall, these findings strongly suggest the important function of NMDARs in AD.

Marked and sustained changes in intracellular calcium signaling occur prior to cognitive decline and extensive neuronal death in AD [61]. GRINA regulates intracellular calcium homeostasis by interaction with IP3R, modulation the ER Ca^{2+} release [62, 63]. Recent studies have found that GRINA modulates voltage-gated $Ca_V2.2$ Ca^{2+} channels in a G-protein-like manner [64]. Calcium entry through $Ca_V2.2$ channels is a major mechanism triggering transmitter release in certain synapses, indicating that GRINA-mediated cytosolic Ca^{2+} overload is associated with synaptic transmission in AD. In another study, GRINA was found to contain three potential ALG2-binding motifs (ABM1) that interact with the longest isoform of ALG2. Interestingly, ALG2 is among the top RAR-related orphan receptor A (RORA)-linked genes with an elevated expression in the hippocampus of patients with AD [65]. Furthermore, an alternative splice variant lacking the sequence PPPNPGYPGGPQPPMPPYAQ(fragment 15-34) has been found in AD patients' cortex (NCBI accession AK294127), but its relevance is still unknown [14]. Recent observations indicate a decreased cancer risk in patients with AD. GRINA modulates aerobic glycolysis and promotes tumor progression in gastric cancer [66]. Based on these findings, it is conceivable that GRINA plays a crucial role in AD.Moreover, further research is required to evaluate

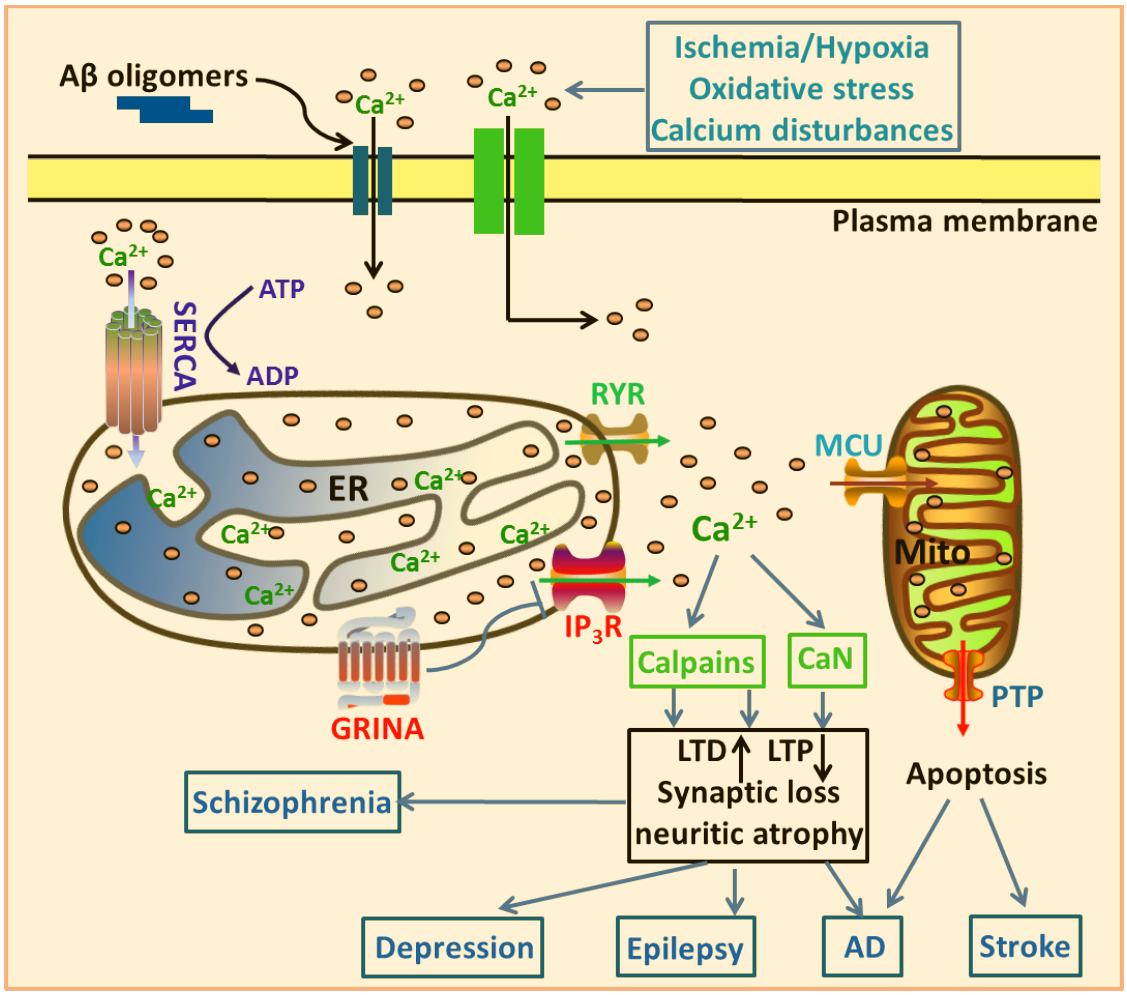

Fig. (2). The role of GRINA in central nervous system diseases. ER: Endoplasmic reticulum; Mito: mitochondrial; CaN: calcineurin; MCU:mitochondrial Ca^{2+} uniporter; PTP: permeability-transition pore; RYR: ryanodine receptor; IP_3R: inositol-1,4,5- triphosphate receptor; LTD: long-term depression; LTP: long-term potentiation; AD: Alzheimer's disease. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

whether the overexpression of GRINA can be neuroprotective against Aβ-induced cytosolic Ca^{2+} overload in animal models.

CONCLUSION

Currently available data indicate the significant regulatory roles of GRINA in the pathogenesis of glutamate receptor-dependent neurological disorders (Fig. **2**). It has been reviewed here that the GRINA contributes to neuroprotection, synaptic transmission and plasticity due to its two conserved domains (Pro-rich domain and LFG-like domain). Such data provide new insights into the GRINA in neurological diseases, suggesting that the modulation of GRINA will hopefully lead to the development of therapeutically effective drugs. While the focus of this review was the role of GRINA in CNS diseases, more research should be directed towards the DNA binding and vesicle transport, or the pathologic function of GRINA in many other human diseases (gastric cancer, osteoarthritis and celiac disease).

LIST OF ABBREVIATIONS

AD	=	Alzheimer's disease
BFNC	=	Benign familial neonatal convulsions
CDD	=	Conserved domains database
CNS	=	Central nervous system
Faim2	=	Fas apoptotic inhibitory molecule 2
GRINA	=	Glutamate receptor, ionotropic, N-methyl-D-aspartate associated protein 1
LTD	=	Long-term depression
LTP	=	Long-term potentiation
MDD	=	Major depressive disorder
NMDARs	=	NMDA receptors
SCZ	=	Schizophrenia
UPR	=	Unfolded protein response

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Collingridge, G.L.; Isaac, J.T.R.; Wang, Y.T. Receptor trafficking and synaptic plasticity. *Nat. Rev. Neurosci.,* **2004**, *5*(12), 952-962. http://dx.doi.org/10.1038/nrn1556 PMID: 15550950

[2] Bliss, T.V.P.; Collingridge, G.L. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature,* **1993**, *361*(6407), 31-39. http://dx.doi.org/10.1038/361031a0 PMID: 8421494

[3] Di Maio, R.; Mastroberardino, P.G.; Hu, X.; Montero, L.M.; Greenamyre, J.T. Thiol oxidation and altered NR2B/NMDA receptor functions in *in vitro* and *in vivo* pilocarpine models: implications for epileptogenesis. *Neurobiol. Dis.,* **2013**, *49*(1), 87-98. http://dx.doi.org/10.1016/j.nbd.2012.07.013 PMID: 22824136

[4] Fan, X.; Jin, W.Y.; Wang, Y.T. The NMDA receptor complex: a multifunctional machine at the glutamatergic synapse. *Front. Cell. Neurosci.,* **2014**, *8*, 160-160. http://dx.doi.org/10.3389/fncel.2014.00160 PMID: 24959120

[5] Wang, R.; Reddy, P.H. Role of Glutamate and NMDA Receptors in Alzheimer's Disease. *J. Alzheimers Dis.,* **2017**, *57*(4), 1041-1048. http://dx.doi.org/10.3233/JAD-160763 PMID: 27662322

[6] Goswami, D.B.; Jernigan, C.S.; Chandran, A.; Iyo, A.H.; May, W.L.; Austin, M.C.; Stockmeier, C.A.; Karolewicz, B. Gene expression analysis of novel genes in the prefrontal cortex of major depressive disorder subjects. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2013**, *43*, 126-133. http://dx.doi.org/10.1016/j.pnpbp.2012.12.010 PMID: 23261523

[7] Sequeira, A.; Mamdani, F.; Ernst, C.; Vawter, M.P.; Bunney, W.E.; Lebel, V.; Rehal, S.; Klempan, T.; Gratton, A.; Benkelfat, C.; Rouleau, G.A.; Mechawar, N.; Turecki, G. Global brain gene expression analysis links glutamatergic and GABAergic alterations to suicide and major depression. *PLoS One,* **2009**, *4*(8), e6585. http://dx.doi.org/10.1371/journal.pone.0006585 PMID: 19668376

[8] Čiháková, D.; Eaton, W.W.; Talor, M.V.; Harkus, U.H.; Demyanovich, H.; Rodriguez, K.; Feldman, S.; Kelly, D.L. Gut permeability and mimicry of the glutamate ionotropic receptor NMDA type Subunit Associated with protein 1 (GRINA) as potential mechanisms related to a subgroup of people with schizophrenia with elevated antigliadin antibodies (AGA IgG). *Schizophr. Res.,* **2019**, *208*, 414-419. http://dx.doi.org/10.1016/j.schres.2019.01.007 PMID: 30685393

[9] Lewis, T.B.; Wood, S.; Michaelis, E.K.; DuPont, B.R.; Leach, R.J. Localization of a gene for a glutamate binding subunit of a NMDA receptor (GRINA) to 8q24. *Genomics,* **1996**, *32*(1), 131-133. http://dx.doi.org/10.1006/geno.1996.0088 PMID: 8786101

[10] Bonaglia, M.C.; Giorda, R.; Tenconi, R.; Pessina, M.; Pramparo, T.; Borgatti, R.; Zuffardi, O. A 2.3 Mb duplication of chromosome 8q24.3 associated with severe mental retardation and epilepsy detected by standard karyotype. *Eur. J. Hum. Genet.,* **2005**, *13*(5), 586-591. http://dx.doi.org/10.1038/sj.ejhg.5201369 PMID: 15657611

[11] Habib, P.; Stamm, A.S.; Zeyen, T.; Noristani, R.; Slowik, A.; Beyer, C.; Wilhelm, T.; Huber, M.; Komnig, D.; Schulz, J.B.; Reich, A. EPO regulates neuroprotective Transmembrane BAX Inhibitor-1 Motif-containing (TMBIM) family members GRINA and FAIM2 after cerebral ischemia-reperfusion injury. *Exp. Neurol.,* **2019**, *320*, 112978. http://dx.doi.org/10.1016/j.expneurol.2019.112978 PMID: 31211943

[12] Habib, P.; Stamm, A.S.; Schulz, J.B.; Reich, A.; Slowik, A.; Capellmann, S.; Huber, M.; Wilhelm, T. EPO and TMBIM3/GRINA Promote the activation of the adaptive arm and counteract the terminal arm of the unfolded protein response after murine transient cerebral ischemia. *Int. J. Mol. Sci.,* **2019**, *20*(21), 5421. http://dx.doi.org/10.3390/ijms20215421 PMID: 31683519

[13] Marchler-Bauer, A.; Derbyshire, M.K.; Gonzales, N.R.; Lu, S.; Chitsaz, F.; Geer, L.Y.; Geer, R.C.; He, J.; Gwadz, M.; Hurwitz, D.I.; Lanczycki, C.J.; Lu, F.; Marchler, G.H.; Song, J.S.; Thanki, N.; Wang, Z.; Yamashita, R.A.; Zhang, D.; Zheng, C.; Bryant, S.H. CDD: NCBI's conserved domain database. *Nucleic Acids Res.,* **2015**, *43*(Database issue), D222-D226. http://dx.doi.org/10.1093/nar/gku1221 PMID: 25414356

[14] Jiménez-González, V.; Ogalla-García, E.; García-Quintanilla, M.; García-Quintanilla, A. Deciphering GRINA/Lifeguard1: nuclear

location, ca^{2+} homeostasis and vesicle transport. *Int. J. Mol. Sci.,* **2019**, *20*(16), 4005. http://dx.doi.org/10.3390/ijms20164005 PMID: 31426446

[15] Nielsen, J.A.; Chambers, M.A.; Romm, E.; Lee, L.Y.; Berndt, J.A.; Hudson, L.D. Mouse transmembrane BAX inhibitor motif 3 (Tmbim3) encodes a 38 kDa transmembrane protein expressed in the central nervous system. *Mol. Cell. Biochem.,* **2011**, *357*(1-2), 73-81. http://dx.doi.org/10.1007/s11010-011-0877-3 PMID: 21614515

[16] Murrough, J.W.; Abdallah, C.G.; Mathew, S.J. Targeting glutamate signalling in depression: progress and prospects. *Nat. Rev. Drug Discov.,* **2017**, *16*(7), 472-486. http://dx.doi.org/10.1038/nrd.2017.16 PMID: 28303025

[17] Zarate, C.A., Jr; Singh, J.B.; Carlson, P.J.; Brutsche, N.E.; Ameli, R.; Luckenbaugh, D.A.; Charney, D.S.; Manji, H.K. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch. Gen. Psychiatry,* **2006**, *63*(8), 856-864. http://dx.doi.org/10.1001/archpsyc.63.8.856 PMID: 16894061

[18] Berman, R.M.; Cappiello, A.; Anand, A.; Oren, D.A.; Heninger, G.R.; Charney, D.S.; Krystal, J.H. Antidepressant effects of ketamine in depressed patients. *Biol. Psychiatry,* **2000**, *47*(4), 351-354. http://dx.doi.org/10.1016/S0006-3223(99)00230-9 PMID: 10686270

[19] Sumner, R.L.; Mcmillan, R.; Spriggs, M.J.; Campbell, D.; Malpas, G.; Maxwell, E.; Deng, C.; Hay, J.; Ponton, R.; Kirk, I.J. Ketamine enhances visual sensory evoked potential long-term potentiation in patients with major depressive disorder. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging,* **2020**, *5*(1),45-55 PMID: 31495712

[20] Yang, Y.; Cui, Y.; Sang, K.; Dong, Y.; Ni, Z.; Ma, S.; Hu, H. Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. *Nature,* **2018**, *554*(7692), 317-322. http://dx.doi.org/10.1038/nature25509 PMID: 29446381

[21] Nosyreva, E.; Szabla, K.; Autry, A.E.; Ryazanov, A.G.; Monteggia, L.M.; Kavalali, E.T. Acute suppression of spontaneous neurotransmission drives synaptic potentiation. *J. Neurosci.,* **2013**, *33*(16), 6990-7002. http://dx.doi.org/10.1523/JNEUROSCI.4998-12.2013 PMID: 23595756

[22] Nosyreva, E.; Autry, A.E.; Kavalali, E.T.; Monteggia, L.M. Age dependence of the rapid antidepressant and synaptic effects of acute NMDA receptor blockade. *Front. Mol. Neurosci.,* **2014**, *7*, 94-94. http://dx.doi.org/10.3389/fnmol.2014.00094 PMID: 25520615

[23] Zanos, P.; Gould, T.D. Mechanisms of ketamine action as an antidepressant. *Mol. Psychiatry,* **2018**, *23*(4), 801-811. http://dx.doi.org/10.1038/mp.2017.255 PMID: 29532791

[24] Alsharafi, W.A.; Luo, Z.; Long, X.; Xie, Y.; Xiao, B. MicroRNA in glutamate receptor-dependent neurological diseases. *Clin. Sci. (Lond.),* **2017**, *131*(14), 1591-1604. http://dx.doi.org/10.1042/CS20170964 PMID: 28667061

[25] Balu, D.T. The NMDA Receptor and Schizophrenia: From Pathophysiology to Treatment. *Adv. Pharmacol.,* **2016**, *76*, 351-382. http://dx.doi.org/10.1016/bs.apha.2016.01.006 PMID: 27288082

[26] Ross, C.A.; Margolis, R.L.; Reading, S.A.J.; Pletnikov, M.; Coyle, J.T. Neurobiology of schizophrenia. *Neuron,* **2006**, *52*(1), 139-153. http://dx.doi.org/10.1016/j.neuron.2006.09.015 PMID: 17015232

[27] DeVito, L.M.; Balu, D.T.; Kanter, B.R.; Lykken, C.; Basu, A.C.; Coyle, J.T.; Eichenbaum, H. Serine racemase deletion disrupts memory for order and alters cortical dendritic morphology. *Genes Brain Behav.,* **2011**, *10*(2), 210-222. http://dx.doi.org/10.1111/j.1601-183X.2010.00656.x PMID: 21029376

[28] Gunduz-Bruce, H.; Kenney, J.; Changlani, S.; Peixoto, A.; Gueorguieva, R.; Leone, C.; Stachenfeld, N. A translational approach for NMDA receptor profiling as a vulnerability biomarker for depression and schizophrenia. *Exp. Physiol.,* **2017**, *102*(5), 587-597. http://dx.doi.org/10.1113/EP086212 PMID: 28294453

[29] Shelkar, G.P.; Pavuluri, R.; Gandhi, P.J.; Ravikrishnan, A.; Gawande, D.Y.; Liu, J.; Stairs, D.J.; Ugale, R.R.; Dravid, S.M. Differential effect of NMDA receptor GluN2C and GluN2D subunit ablation on behavior and channel blocker-induced schizophrenia phenotypes. *Sci. Rep.,* **2019**, *9*(1), 7572. http://dx.doi.org/10.1038/s41598-019-43957-2 PMID: 31110197

[30] Ghotbi Ravandi, S.; Shabani, M.; Bashiri, H.; Saeedi Goraghani, M.; Khodamoradi, M.; Nozari, M. Ameliorating effects of berberine on MK-801-induced cognitive and motor impairments in a neonatal rat model of schizophrenia. *Neurosci. Lett.,* **2019**, *706*, 151-157. http://dx.doi.org/10.1016/j.neulet.2019.05.029 PMID: 31103726

[31] Buchanan, R.W.; Javitt, D.C.; Marder, S.R.; Schooler, N.R.; Gold, J.M.; McMahon, R.P.; Heresco-Levy, U.; Carpenter, W.T. The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST): the efficacy of glutamatergic agents for negative symptoms and cognitive impairments. *Am. J. Psychiatry,* **2007**, *164*(10), 1593-1602. http://dx.doi.org/10.1176/appi.ajp.2007.06081358 PMID: 17898352

[32] Hao, K.; Su, X.; Luo, B.; Cai, Y.; Chen, T.; Yang, Y.; Shao, M.; Song, M.; Zhang, L.; Zhong, Z.; Li, W.; Lv, L. Prenatal immune activation induces age-related alterations in rat offspring: Effects upon NMDA receptors and behaviors. *Behav. Brain Res.,* **2019**, *370*, 111946. http://dx.doi.org/10.1016/j.bbr.2019.111946 PMID: 31112730

[33] Garcia-Quintanilla, A.; Miranzo-Navarro, D. Extraintestinal manifestations of celiac disease: 33-mer gliadin binding to glutamate receptor GRINA as a new explanation. *BioEssays,* **2016**, *38*(5), 427-439. http://dx.doi.org/10.1002/bies.201500143 PMID: 26990286

[34] Xu, X.X.; Luo, J.H. Mutations of N-Methyl-D-Aspartate receptor subunits in epilepsy. *Neurosci. Bull.,* **2018**, *34*(3), 549-565. http://dx.doi.org/10.1007/s12264-017-0191-5 PMID: 29124671

[35] Gao, K.; Tankovic, A.; Zhang, Y.; Kusumoto, H.; Zhang, J.; Chen, W.; XiangWei, W.; Shaulsky, G.H.; Hu, C.; Traynelis, S.F.; Yuan, H.; Jiang, Y. A de novo loss-of-function GRIN2A mutation associated with childhood focal epilepsy and acquired epileptic aphasia. *PLoS One,* **2017**, *12*(2), e0170818. http://dx.doi.org/10.1371/journal.pone.0170818 PMID: 28182669

[36] Frasca, A.; Aalbers, M.; Frigerio, F.; Fiordaliso, F.; Salio, M.; Gobbi, M.; Cagnotto, A.; Gardoni, F.; Battaglia, G.S.; Hoogland, G.; Di Luca, M.; Vezzani, A. Misplaced NMDA receptors in epileptogenesis contribute to excitotoxicity. *Neurobiol. Dis.,* **2011**, *43*(2), 507-515. http://dx.doi.org/10.1016/j.nbd.2011.04.024 PMID: 21575722

[37] Rothan, H.A.; Amini, E.; Faraj, F.L.; Golpich, M.; Teoh, T.C.; Gholami, K.; Yusof, R. NMDA receptor antagonism with novel indolyl, 2-(1,1-Dimethyl-1,3-dihydro-benzo[e]indol-2-ylidene)-malonaldehyde, reduces seizures duration in a rat model of epilepsy. *Sci. Rep.,* **2017**, *7*(1), 45540. http://dx.doi.org/10.1038/srep45540 PMID: 28358047

[38] Walker, M. Neuroprotection in epilepsy. *Epilepsia,* **2007**, *48*(Suppl. 8), 66-68. http://dx.doi.org/10.1111/j.1528-1167.2007.01354.x PMID: 18330004

[39] Ovbiagele, B.; Nguyen-Huynh, M.N. Stroke epidemiology: advancing our understanding of disease mechanism and therapy. *Neurotherapeutics,* **2011**, *8*(3), 319-329. http://dx.doi.org/10.1007/s13311-011-0053-1 PMID: 21691873

[40] Feigin, V.L.; Forouzanfar, M.H.; Krishnamurthi, R.; Mensah, G.A.; Connor, M.; Bennett, D.A.; Moran, A.E.; Sacco, R.L.; Anderson, L.; Truelsen, T.; O'Donnell, M.; Venketasubramanian, N.; Barker-Collo, S.; Lawes, C.M.; Wang, W.; Shinohara, Y.; Witt, E.; Ezzati, M.; Naghavi, M.; Murray, C. Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) and the GBD Stroke Experts Group. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet,* **2014**, *383*(9913), 245-254. http://dx.doi.org/10.1016/S0140-6736(13)61953-4 PMID: 24449944

[41] Tymianski, M. Emerging mechanisms of disrupted cellular signaling in brain ischemia. *Nat. Neurosci.,* **2011**, *14*(11), 1369-1373. http://dx.doi.org/10.1038/nn.2951 PMID: 22030547

[42] Wu, Q.J.; Tymianski, M. Targeting NMDA receptors in stroke: new hope in neuroprotection. *Mol. Brain,* **2018**, *11*(1), 15. http://dx.doi.org/10.1186/s13041-018-0357-8 PMID: 29534733

[43] Lai, T.W.; Zhang, S.; Wang, Y.T. Excitotoxicity and stroke: identifying novel targets for neuroprotection. *Prog. Neurobiol.,* **2014**, *115*, 157-188. http://dx.doi.org/10.1016/j.pneurobio.2013.11.006 PMID: 24361499

[44] Tu, W.; Xu, X.; Peng, L.; Zhong, X.; Zhang, W.; Soundarapandian, M.M.; Balel, C.; Wang, M.; Jia, N.; Zhang, W.; Lew, F.; Chan, S.L.; Chen, Y.; Lu, Y. DAPK1 interaction with NMDA receptor NR2B subunits mediates brain damage in stroke. *Cell,* **2010**, *140*(2), 222-234. http://dx.doi.org/10.1016/j.cell.2009.12.055 PMID: 20141836

[45] Tang, N.; Wu, J.; Zhu, H.; Yan, H.; Guo, Y.; Cai, Y.; Yan, H.; Shi, Y.; Shu, S.; Pei, L.; Lu, Y. Genetic mutation of glun2b protects

brain cells against stroke damages. *Mol. Neurobiol.,* **2018**, *55*(4), 2979-2990.
http://dx.doi.org/10.1007/s12035-017-0562-y PMID: 28456939

[46] Chen, M.; Lu, T.J.; Chen, X.J.; Zhou, Y.; Chen, Q.; Feng, X.Y.; Xu, L.; Duan, W.H.; Xiong, Z.Q. Differential roles of NMDA receptor subtypes in ischemic neuronal cell death and ischemic tolerance. *Stroke,* **2008**, *39*(11), 3042-3048.
http://dx.doi.org/10.1161/STROKEAHA.108.521898 PMID: 18688011

[47] Lau, D.; Bengtson, C.P.; Buchthal, B.; Bading, H. BDNF Reduces Toxic Extrasynaptic NMDA Receptor Signaling *via* Synaptic NMDA Receptors and Nuclear-Calcium-Induced Transcription of inhba/Activin A. *Cell Rep.,* **2015**, *12*(8), 1353-1366.
http://dx.doi.org/10.1016/j.celrep.2015.07.038 PMID: 26279570

[48] Lisak, D.A.; Schacht, T.; Enders, V.; Habicht, J.; Kiviluoto, S.; Schneider, J.; Henke, N.; Bultynck, G.; Methner, A. The transmembrane Bax inhibitor motif (TMBIM) containing protein family: Tissue expression, intracellular localization and effects on the ER CA^{2+}-filling state. *Biochim. Biophys. Acta,* **2015**, *1853*(9), 2104-2114.
http://dx.doi.org/10.1016/j.bbamcr.2015.03.002 PMID: 25764978

[49] Krajewska, M.; Xu, L.; Xu, W.; Krajewski, S.; Kress, C.L.; Cui, J.; Yang, L.; Irie, F.; Yamaguchi, Y.; Lipton, S.A.; Reed, J.C. Endoplasmic reticulum protein BI-1 modulates unfolded protein response signaling and protects against stroke and traumatic brain injury. *Brain Res.,* **2011**, *1370*, 227-237.
http://dx.doi.org/10.1016/j.brainres.2010.11.015 PMID: 21075086

[50] Kim, J.H.; Lee, E.R.; Jeon, K.; Choi, H.Y.; Lim, H.; Kim, S.J.; Chae, H.J.; Park, S.H.; Kim, S.; Seo, Y.R.; Kim, J.H.; Cho, S.G. Role of BI-1 (TEGT)-mediated ERK1/2 activation in mitochondria-mediated apoptosis and splenomegaly in BI-1 transgenic mice. *Biochim. Biophys. Acta,* **2012**, *1823*(4), 876-888.
http://dx.doi.org/10.1016/j.bbamcr.2012.01.016 PMID: 22309999

[51] Tauber, S.C.; Harms, K.; Falkenburger, B.; Weis, J.; Sellhaus, B.; Nau, R.; Schulz, J.B.; Reich, A. Modulation of hippocampal neuroplasticity by Fas/CD95 regulatory protein 2 (Faim2) in the course of bacterial meningitis. *J. Neuropathol. Exp. Neurol.,* **2014**, *73*(1), 2-13.
http://dx.doi.org/10.1097/NEN.0000000000000020 PMID: 24335530

[52] Reich, A.; Spering, C.; Gertz, K.; Harms, C.; Gerhardt, E.; Kronenberg, G.; Nave, K.A.; Schwab, M.; Tauber, S.C.; Drinkut, A.; Harms, K.; Beier, C.P.; Voigt, A.; Göbbels, S.; Endres, M.; Schulz, J.B. Fas/CD95 regulatory protein Faim2 is neuroprotective after transient brain ischemia. *J. Neurosci.,* **2011**, *31*(1), 225-233.
http://dx.doi.org/10.1523/JNEUROSCI.2188-10.2011 PMID: 21209208

[53] Komnig, D.; Gertz, K.; Habib, P.; Nolte, K.W.; Meyer, T.; Brockmann, M.A.; Endres, M.; Rathkolb, B.; Hrabě de Angelis, M.; Schulz, J.B.; Falkenburger, B.H.; Reich, A. German Mouse Clinic Consortium. Faim2 contributes to neuroprotection by erythropoietin in transient brain ischemia. *J. Neurochem.,* **2018**, *145*(3), 258-270. http://dx.doi.org/10.1111/jnc.14296 PMID: 29315561

[54] Mota, S.I.; Ferreira, I.L.; Rego, A.C. Dysfunctional synapse in Alzheimer's disease - A focus on NMDA receptors. *Neuropharmacology,* **2014**, *76*(Pt A), 16-26.
http://dx.doi.org/10.1016/j.neuropharm.2013.08.013 PMID: 23973316

[55] Perl, D.P. Neuropathology of Alzheimer's disease. *Mt. Sinai J. Med.,* **2010**, *77*(1), 32-42.
http://dx.doi.org/10.1002/msj.20157 PMID: 20101720

[56] Zhang, Y.; Li, P.; Feng, J.; Wu, M. Dysfunction of NMDA receptors in Alzheimer's disease. *Neurol. Sci.,* **2016**, *37*(7), 1039-1047.
http://dx.doi.org/10.1007/s10072-016-2546-5 PMID: 26971324

[57] Hanson, J.E.; Pare, J.F.; Deng, L.; Smith, Y.; Zhou, Q. Altered GluN2B NMDA receptor function and synaptic plasticity during early pathology in the PS2APP mouse model of Alzheimer's disease. *Neurobiol. Dis.,* **2015**, *74*, 254-262.
http://dx.doi.org/10.1016/j.nbd.2014.11.017 PMID: 25484285

[58] Dong, Y.; Kalueff, A.V.; Song, C. N-methyl-d-aspartate receptor-mediated calcium overload and endoplasmic reticulum stress are involved in interleukin-1beta-induced neuronal apoptosis in rat hippocampus. *J. Neuroimmunol.,* **2017**, *307*, 7-13.
http://dx.doi.org/10.1016/j.jneuroim.2017.03.005 PMID: 28495142

[59] Ma, S.H.; Zhuang, Q.X.; Shen, W.X.; Peng, Y.P.; Qiu, Y.H. Interleukin-6 reduces NMDAR-mediated cytosolic Ca^{2+} overload and neuronal death *via* JAK/CaN signaling. *Cell Calcium,* **2015**, *58*(3), 286-295.
http://dx.doi.org/10.1016/j.ceca.2015.06.006 PMID: 26104917

[60] Ferreira, I.L.; Ferreiro, E.; Schmidt, J.; Cardoso, J.M.R.; Pereira, C.M.; Carvalho, A.L.; Oliveira, C.R.; Rego, A.C. Aβ and NMDAR activation cause mitochondrial dysfunction involving ER calcium release. *Neurobiol. Aging,* **2015**, *36*(2), 680-692.
http://dx.doi.org/10.1016/j.neurobiolaging.2014.09.006 PMID: 25442114

[61] Supnet, C.; Bezprozvanny, I. The dysregulation of intracellular calcium in Alzheimer disease. *Cell Calcium,* **2010**, *47*(2), 183-189.
http://dx.doi.org/10.1016/j.ceca.2009.12.014 PMID: 20080301

[62] Rojas-Rivera, D.; Armisén, R.; Colombo, A.; Martínez, G.; Eguiguren, A.L.; Díaz, A.; Kiviluoto, S.; Rodríguez, D.; Patron, M.; Rizzuto, R.; Bultynck, G.; Concha, M.L.; Sierralta, J.; Stutzin, A.; Hetz, C. TMBIM3/GRINA is a novel unfolded protein response (UPR) target gene that controls apoptosis through the modulation of ER calcium homeostasis. *Cell Death Differ.,* **2012**, *19*(6), 1013-1026.
http://dx.doi.org/10.1038/cdd.2011.189 PMID: 22240901

[63] Chen, K.; Li, X.; Song, G.; Zhou, T.; Long, Y.; Li, Q.; Zhong, S.; Cui, Z. Deficiency in the membrane protein Tmbim3a/Grinaa initiates cold-induced ER stress and cell death by activating an intrinsic apoptotic pathway in zebrafish. *J. Biol. Chem.,* **2019**, *294*(30), 11445-11457.
http://dx.doi.org/10.1074/jbc.RA119.007813 PMID: 31171717

[64] Mallmann, R.T.; Moravcikova, L.; Ondacova, K.; Lacinova, L.; Klugbauer, N. Grina/TMBIM3 modulates voltage-gated $Ca_V2.2$ Ca^{2+} channels in a G-protein-like manner. *Cell Calcium,* **2019**, *80*, 71-78.
http://dx.doi.org/10.1016/j.ceca.2019.04.002 PMID: 30991297

[65] Acquaah-Mensah, G.K.; Agu, N.; Khan, T.; Gardner, A. A regulatory role for the insulin- and BDNF-linked RORA in the hippocampus: implications for Alzheimer's disease. *J. Alzheimers Dis.,* **2015**, *44*(3), 827-838.
http://dx.doi.org/10.3233/JAD-141731 PMID: 25362032

[66] Xu, D.H.; Li, Q.; Hu, H.; Ni, B.; Liu, X.; Huang, C.; Zhang, Z.Z.; Zhao, G. Transmembrane protein GRINA modulates aerobic glycolysis and promotes tumor progression in gastric cancer. *J. Exp. Clin. Cancer Res.,* **2018**, *37*(1), 308.
http://dx.doi.org/10.1186/s13046-018-0974-1 PMID: 30541591