REVIEW ARTICLE

A negative regulator of synaptic development: MDGA and its links to neurodevelopmental disorders

Rui Wang[1] · Jia-Xian Dong[1] · Lu Wang[1] · Xin-Yan Dong[1] · Eitan Anenberg[1] · Pei-Fang Jiang[1] · Ling-Hui Zeng[2] ·
Yi-Cheng Xie[1]

Abstract

Background Formation of protein complexes across synapses is a critical process in neurodevelopment, having direct implications on brain function and animal behavior. Here, we present the understanding, importance, and potential impact of a newly found regulator of such a key interaction.

Data sources A systematic search of the literature was conducted on PubMed (Medline), Embase, and Central-Cochrane Database.

Results Membrane-associated mucin domain-containing glycosylphosphatidylinositol anchor proteins (MDGAs) were recently discovered to regulate synaptic development and transmission via suppression of neurexins–neuroligins trans-synaptic complex formation. MDGAs also regulate axonal migration and outgrowth. In the context of their physiological role, we begin to consider the potential links to the etiology of certain neurodevelopmental disorders. We present the gene expression and protein structure of MDGAs and discuss recent progress in our understanding of the neurobiological role of MDGAs to explore its potential as a therapeutic target.

Conclusion MDGAs play a key role in neuron migration, axon guidance and synapse development, as well as in regulating brain excitation and inhibition balance.

Keywords Adhesion molecule · E/I balance · Neurodevelopmental disorders · Synapse

Introduction

Neural circuits are considered to made up of all synapses which act as the connections or nodes for neurons throughout a vast network [1]. Following neuronal migration and axonal outgrowth, synaptic connections between the cells of a circuit are established with exceptionally high precision in the development and continuous reconstruction of synaptic circuits during the lifetime of an animal. The regulation of these processes is dependent on cell adhesion molecules [1, 2]. Membrane-associated mucin (MAM) domain-containing glycosylphosphatidylinositol (GPI) anchor proteins (MDGAs) belong to the immunoglobulin superfamily (IgSF)

of cell adhesion molecules and are known to be expressed in many vertebrates, notably humans [3]. Previous studies have revealed the involvement of MDGAs in fundamental and central events in the nervous system: neuron migration, axon guidance and synapse development [4–11]. Moreover, there is accumulating evidence emphasizing their pathophysiological significance based on their roles in synapse development and then neural circuit formation [4, 9, 11].

MDGAs have been reported, in multiple recent independent studies, to be susceptibility genes for neurological and neuropsychiatric disorders, specifically schizophrenia [12–14], bipolar disorder [13], epileptic encephalopathy [15], intellectual disability [16], neuroticism [17] and autism spectrum disorders (ASDs) [18] (Table 1). Meta-analysis of genome-wide linkage scans in patients with schizophrenia connected MDGA1 to schizophrenia and bipolar disorder both in Scandinavian and Chinese Han population [12–14], Consistently, some cognitive deficits (i.e., impaired long-term potentiation, altered hippocampus-dependent spatial learning and memory) were seen in MDGA1$^{-/-}$ mice [4].

✉ Yi-Cheng Xie
  ycxie@zju.edu.cn

[1] Children's Hospital, Zhejiang University School of Medicine, Hangzhou 310052, China

[2] Department of Clinical Medicine, Zhejiang University City College, Hangzhou 310015, China

Table 1 The MDGAs and associated disorders with genetic mutation

Gene	Associated disorders	Species	Genetic category	References	Note
MDGA1	Schizophrenia	Human	Genetic association analysis	[14]	From Scandinavian population
				[13]	From Chinese Han population
	Bipolar disorder	Human	Genetic association analysis	[13]	From Chinese Han population
	Cognitive deficits	Mouse	Gene mutation—homozygous MDGA1$^{-/-}$	[4]	
MDGA2	Epileptic encephalopathy	Human	Genetic association analysis	[15]	
	Intellectual disability	Human	Genetic association analysis	[16]	From Pakistani population
	Neuroticism	Human	Genetic association analysis	[17]	From a US national sampling frame and available from the National Institute of Mental Health genetics repository
	Autism	Human	Genetic association analysis	[18]	
	Autism-like behavior	Mouse	Gene mutation—heterozygous MDGA2$^{+/-}$	[9]	

Meanwhile, *MDGA2* was identified as a new candidate gene for epileptic encephalopathy [15], intellectual disability [16] and neuroticism [17] by genetic association analysis in a large number of samples. Additionally, MDGA2 was demonstrated to be associated with autism through ten independent and otherwise unrelated cases [18]. While, an autism-like behavior phenotype were also seen in MDGA2$^{+/-}$ mice, including impaired long-term potentiation, motor stereotypy and deficits in social interaction and hippocampus-dependent learning and memory [9]. In general, MDGA expression has functional consequences which, in animal models, are related to brain excitation and behavioral states that are associated with certain psychiatric disorders [4, 9]. Enhancing understanding of MDGAs regulation in synapses of different cell types and then brain circuits appears to be critical in revealing pharmaceutical targets for clinical intervention.

MDGA genes and proteins

There are two *MDGA* gene homologues, *MDGA1* and *MDGA2*, that encode two respective proteins. The human *MDGA1* gene, is located in 6p21.2, consists of 18 exons, and encodes the 955 amino acids long membrane-associated MDGA1 protein [3]. *MDGA1* was identified as the genomic organization of the human ortholog of Ig6M from cDNAs isolated from human cells, and was named GPIM (GPI and MAM protein) [3]. It is now more universally referred to as *MDGA1*. The human *MDGA2* gene spans 835 kb of DNA on the reverse strand of chromosome 14q21.3. It has 23 exons and is predicted to be comprised of two alternative first exons that give rise to two similarly sized mRNA isoforms [19].

The two homologous MDGA proteins, MDGA1 and MDGA2, possess a characteristic domain organization composed of a N-terminal signal peptide followed by six Ig domains, a MAM domain, and a C-terminal containing cleavage site for GPI to anchor to the cell membrane (Fig. 1) [8, 19]. There is a stretch of amino acids in MDGA1 with weak homology to an FNIII domain, while the corresponding stretch in MDGA2 lacks any such similarity but has a 47% identity to MDGA1 [19]. More than 40% of the amino acids within the structure of MDGA1 and MDGA2 are identical with more than 85% being conserved. MDGA characteristics are highly conserved across multiple vertebrate species, including mouse, rat, chicken, medaka and
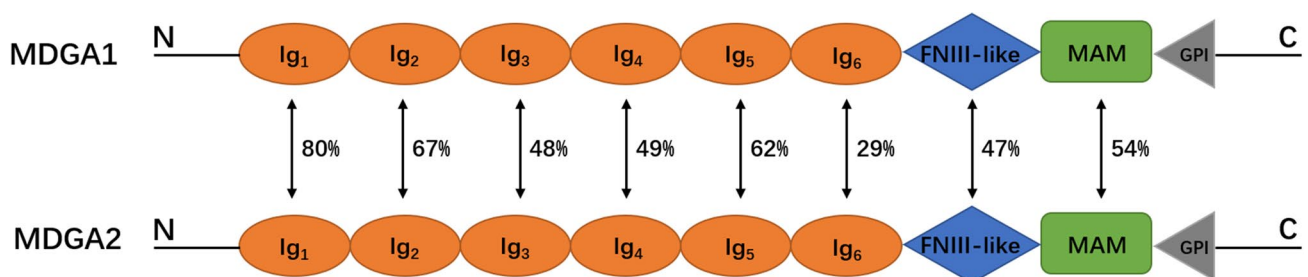

Fig. 1 Domain structure of MDGA1 and MDGA2 proteins. Domains of MDGAs are highlighted by distinct colors. *Ig* immunoglobulin domain, *FNIII* fibronectin type 3 repeat, *MAM* membrane-associated mucin domain, *GPI* glycosylphosphatidylinositol

zebrafish [3, 7, 19–21]. Importantly, for the study of disease through rodent models, there is a 94.5% and 97.9% equivalency between human and mouse MDGA1 and MDGA2 respective structures.

Studies have shown that each component in the structure of MDGAs plays a role in their function. The MAM domain of MDGA1 and MDGA2 is a specialized protein structure on the cell-surface that interacts with its environment to mediate protein dimerization [8]. Fujimura et al. [20] reported such an interaction in axonal rich regions and suggested a role of MDGA in synapse-selectivity during development. Membrane attachment via a GPI anchor makes MDGAs unique among all MAM-containing proteins as offering it the capability to interact directly with key synapse-organizing proteins and wherein it can modulate specific synaptic events [8]. MDGA1, via the GPI anchor, is localized to lipid rafts to mediate the chemotropic guidance of nerve growth cones [22]. Similarly to other GPI-anchored proteins, the extracellular domain of MDGAs can shed to extracellular space (unpublished data), this suggests it may act like other adhesion molecules (e.g., neuroligin-1 and calsyntenin-3), plays a role in modulation of synaptic function [23, 24]. The presence of six Ig domains and an FNIII-like domain gives it a structural similarity to IgSFs, the largest families of axon guidance molecules that are involved in various aspects of the formation and maintenance of neural circuits [25]. This is functionally in accordance with other genes responsible for formation of Ig and/or FNIII domains such as CADM1 [26], IL1RAPL1, LRFN5 [27], and PTPRD [28] which are linked to neurological disorders. Three seminal studies of the six Ig domains and the FNIII-like domains revealed that these structures are connected into a compact triangular arrangement to mediate MDGAs binding to neuroligins (NLs) [8, 29, 30]. Our initial understanding of MDGA1 and MDGA2 has shown their involvement in synaptic formation [4, 9, 10]. However, there remains a plethora of undiscovered information regarding specific biochemical interaction critical to understand synaptic formation and neurodevelopmental disorders.

MDGAs: cell adhesion regulates neuronal migration and axonal outgrowth during nervous development

The formation of functional neuronal circuits is dependent on accurate neuronal migration, proper axonal outgrowth and synaptic connection; this relies on adhesive interactions mediated by extracellular matrix molecules such as MDGAs. Study of the time course and localization of MDGA expression is critical for understanding formation of neural circuits. High levels of MDGA1 and MDGA2 expression, as found through examination of mRNA, are mainly restricted

to central and peripheral nervous system [19]. MDGA2 in zebrafish is expressed in a subset of motor neurons, notably in the cranial, trigeminal and facial nerves; its knockdown resulted in migration defects in trigeminal neurons, aberrant axonal growth and defasciculation of facial branchiomotor axons [31]. In rats, MDGA1-positive cells were found in the pontine migratory stream from the dorsal raphe nucleus to the basilar pontine nuclei and in a subpopulation of dorsal spinal interneurons as they migrate ventrolaterally away from the roofplate [19]. MDGA1 knockdown in mice blocked radial migration of superficial layer cortical neurons [7] and MDGA2 knockdown in chicken-induced strong axon outgrowth phenotypes in MDGA2-expressing commissural interneurons [32]. These observations demonstrate how MDGA1 and MDGA2, each with their distinct functions, are necessary for proper neuron migration and axon outgrowth.

MDGAs: the suppressors of synapse development

Recently MDGAs were identified as binding partners of NLs, competing directly with neurexins (NRXs) (Fig. 2) [4, 8–10]. NRXs and NLs are pre-synaptic and post-synaptic adhesion molecules that form trans-synaptic complexes which promote development and function of the synapse [1]. NRXs and NLs are arguably the most extensively studied synaptic adhesion molecules being fundamental synaptic organizers in the central nervous system [1, 33]. Importantly, the disfunction of NRXs and NLs is strongly associated with neurodevelopmental disorders [33]. There are four NLs in rodents (NL1–NL4) that have unique synaptic localizations and function [1]; MDGAs bind to all four NLs but with a distinct affinity [4, 5, 8–10]. NL1 is found in excitatory synapses [34] and NL2 in inhibitory, cholinergic, and dopaminergic synapses [35–38]. NL3 is localized in both excitatory and inhibitory synapses [39, 40], and NL4 is found in glycinergic synapses [40]. MDGAs bind in a cis configuration with high affinity to NL1 and NL2 and to NL3 and NL4 with a 10- to 20-fold lower affinity [8], giving unique modes for regulating different neuronal populations during synaptic development and in normal synaptic transmission [4, 5, 9–11].

MDGAs were initially reported to bind to NL2 at a site where they would compete with NRXs to thereby suppress inhibitory synapse development [5, 10]. MDGA1 binds selectively and directly to NL2 through Ig domains; no cell adhesion has been observed between cells expressing NL2 and MDGA1, suggesting a cis configuration binding between MDGA1 and NL2 [5, 10]. RNAi-mediated knockdown of MDGA1 increased the amount of inhibitory synapses cultured from rat hippocampal neurons without affecting the number of excitatory synapses, and MDGA1 overexpression
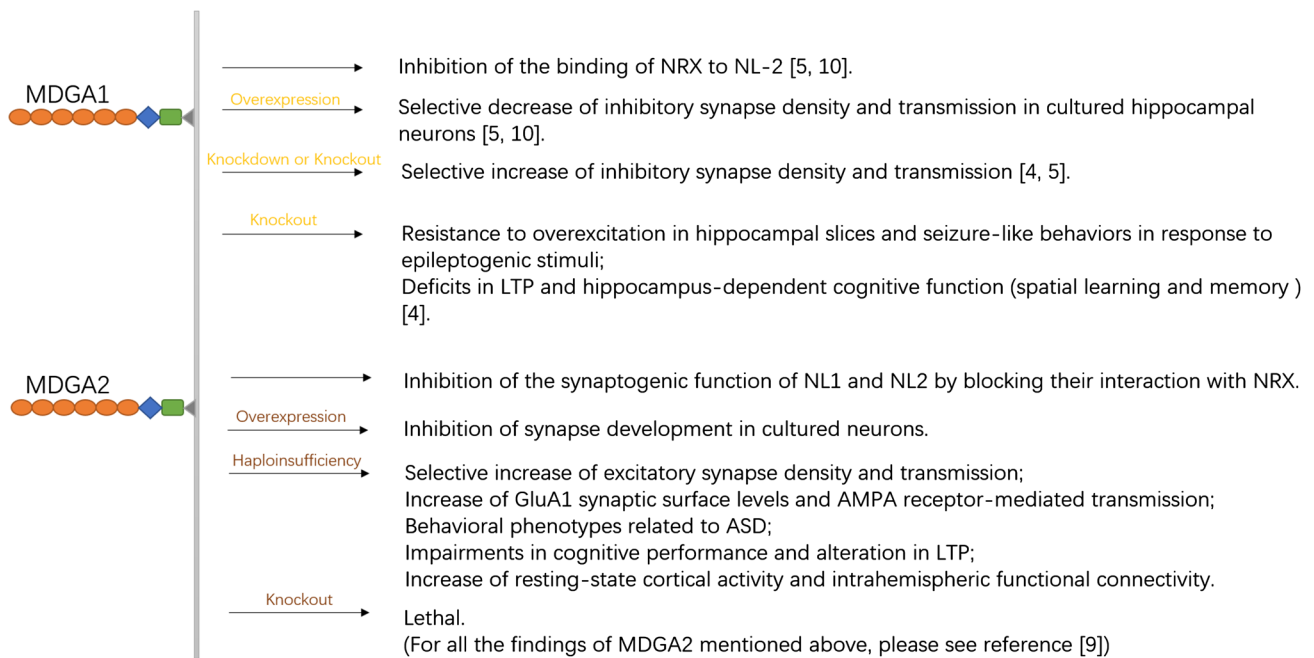
Fig. 2 The function of MDGAs in synaptic development

led to opposite results [5, 10]. Connor et al. [9] proposed that MDGA2 binds to both NL1 and NL2 and selectively inhibits excitatory synapse development. This idea comes from the observation that MDGA2$^{+/-}$ mice have increased excitatory synapse density and excitatory transmission with no changes in inhibitory synapses [9].

Recent proteomic study showed contrary results, where MDGA1 was detected in the excitatory synaptic cleft and MDGA2 was found in the inhibitory synaptic cleft of cultured cortical neurons [11]. Imaging of recombinant MDGAs expressed in cortical neuron showed the recombinant MDGA2 in inhibitory synapses [11], while the recombinant MDGA1 was found in both excitatory and inhibitory synapses [11, 24]. The discrepancy between findings in the proteomic study and recombinant MDGA imaging study could be due to the incomplete coverage of the inhibitory proteome in the proteomic study [11]. Overall, MDGA1 is likely localized to both inhibitory and excitatory synapses, while MDGA2 is specific to inhibitory synapses [11]. Additionally, the study also found, based on the synaptogenic activity of NL2, when MDGA1 was co-overexpressed with NL2, the NL2-enhanced recruitment of both inhibitory and excitatory vesicles were suppressed; however, co-overexpression of MDGA2 selectively suppressed excitatory vesicle recruitment [11]. Reaffirming the above observations, MDGA1 knockdown by shRNA increased immunocytochemical signals for the vesicular GABA transporter [5, 11]. Conversely, MDGA2 knockdown had no notable effects, but when combined with MDGA1 knockdown it caused an

increase in immunocytochemical signals for both glutamic acid decarboxylase and vesicular GABA transporter [11]. This is analogous to the effects of attenuated NL2 activity [41, 42]. These results showed that MDGA2 functions to downregulate excitatory vesicle recruitment.

Similarly to MDGAs, γ-protocadherin physically interacts with NL1 via their ectodomains to disrupt NL1 binding to NRX1β [43]. This process is competitive with MDGAs, given they have similar protein structure [8, 43]. Nuanced interpretation of slight discrepancies among all these findings along with the discovery of other regulatory genes (i.e., γ-protocadherin) suggests a complex, unexplored, and multifaceted role for MDGAs in synapse development.
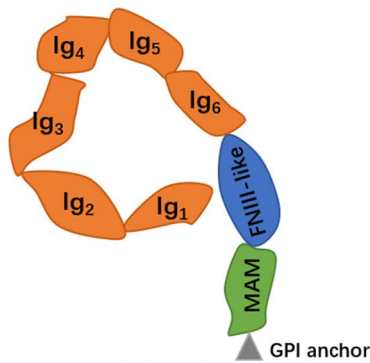
The structure of MDGA–NL complexes

Crystal structure of MDGA1–NL1 and MDGA1–NL2 complexes shows sites for MDGAs and NLs interactions and reveals how MDGAs can suppress NRX–NL interactions [8]. Elegheert et al. described the crystal structure of MDGA1–NL1 complex along with a comprehensive series of descriptive biochemistry and cell biology data [8]. The long MDGA1 ectodomain is constrained into a compact triangular arrangement locked up by intramolecular interactions between Ig1 and FNIII-like domain (Fig. 3). Two of these triangular assemblies cradle an entire NL1 dimer in cis on the post-synaptic membrane. There are two separate interaction sites (site I and II) that bind MDGA1 to NL1, site
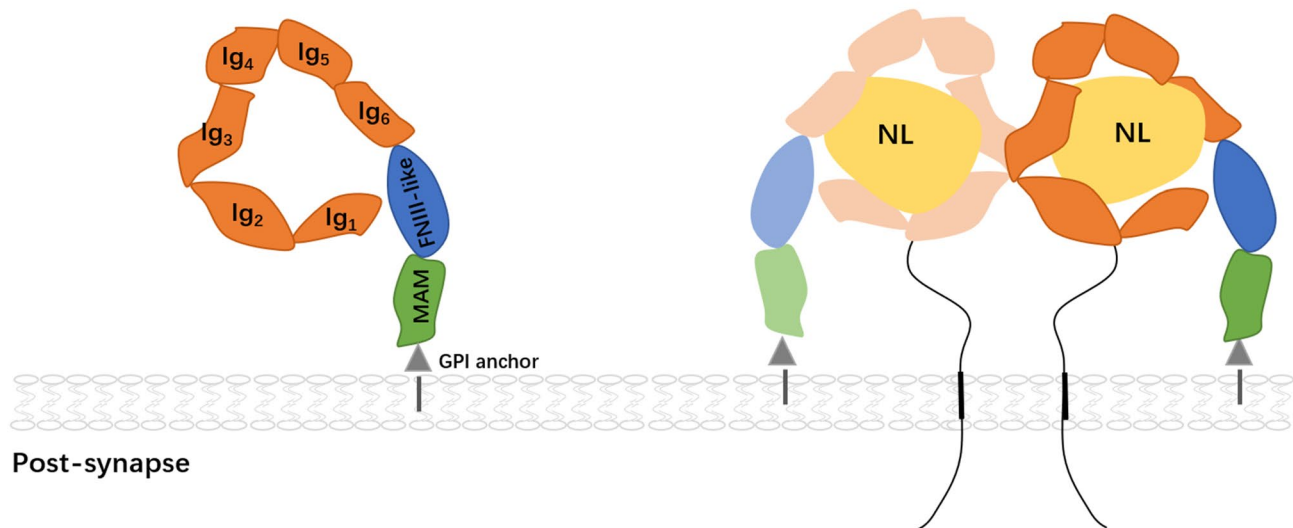
Fig. 3 Structure of MDGA and MDGA–NL complex. Schematic representation of MDGA and NL–MDGA complex. The Ig1 and FNIII-like domain are linked by intramolecular interactions to form the specific triangular pattern. The MDGA triangle binds to the NL dimer in a cis-interaction between their post-synaptically anchored ectodomains

I is the exact location that NRX1β interacts with NL1; from this we can infer a binding competition between MDGA1 and NRXs. In accordance with this, Gangwar et al., and Kim et al., independently described crystalline complexes of the MDGA1 Ig1–Ig2 tandem or Ig1–Ig2–Ig3 triplet with the NL2 ectodomain [29, 30], with high similarity to MDGA1–NL1 complex. Interestingly, although the binding affinity between MDGA1 and NL1 or NL2 showed only mild discrepancy investigated using surface plasmon resonance (SPR) assays [8], MDGA1 was shown, using tagged pull down assays in the mouse brain, to selectively form complexes with NL2 and not with NL1 [29]. This evidence further supports the existence of a specific in vivo mechanism that inhibits the formation of MDGA1–NL1 complexes. Collectively, the study of MDGA structure supports its role in negatively modulating synaptic development by disrupting previously characterized NRX–NL interactions.

Conclusions

MDGAs are a newly discovered family of synaptic adhesion proteins that regulate and interact directly with NRX–NL synaptic complexes. MDGAs are essential to synaptic function with the full knockout of MDGA2 in mice being perinatally lethal and with constitutive deletion

of MDGA1 resulting in cognitive deficits [9]. To explore the function of MDGAs in nervous system, one must perturb the system selectively at different developmental stage. Moreover, double knockout of MDGA1 and MDGA2 could be used to study the function of MDGAs without functional compensation from each other that possibly occurred in single knockout mouse lines, particularly in the brain regions where express both MDGA1 and MDGA2 (e.g., hippocampal CA1 [4, 9]). NL point mutation [8] knock in mice could be used to selectively interrupt MDGA–NL without affecting other potential function of MDGA that could be resulted from MDGA knockout. Given that MDGAs selectively control inhibitory and excitatory synapse development [4, 9–11], one could tune the excitation and inhibition balance in the brain by developing small molecules or peptides to specifically interfere the interaction of MDGAs and NLs. Moreover, MDGA expression is synaptic and cell-type specific [4, 9, 11], thus MDGAs conditional KO mice can be crossed with specific Cre-driver lines (e.g., PV-Cre/VGAT-Cre or CamKII-Cre) to explore the contribution of MDGAs on formation of specific neuronal circuits. MDGAs bind to NLs mainly via their Ig1–Ig2 tandem or Ig1–Ig2–Ig3 triplet [8, 10], and other large interaction domains suggesting they have additional unexplored functions. The involvement of MDGAs in relating growth processes of neurons in the mammal is

far reaching and not well understood, and offers an additional avenue of study for the development of treatments to related neurodevelopmental disorders.

Compliance with ethical standards

Ethical approval No ethnical approval is required for this review article.

Conflict of interest No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

References

1. Südhof TC. Synaptic neurexin complexes: a molecular code for the logic of neural circuits. Cell. 2017;171:745–69.
2. Dityatev A, Bukalo O, Schachner M. Modulation of synaptic transmission and plasticity by cell adhesion and repulsion molecules. Neuron Glia Biol. 2008;4:197–209.
3. De Juan C, Iniesta P, González-Quevedo R, Morán A, Sánchez-Pernaute A, Torres AJ, et al. Genomic organization of a novel glycosylphosphatidylinositol MAM gene expressed in human tissues and tumors. Oncogene. 2002;21:3089–94.
4. Connor SA, Ammendrup-Johnsen I, Kishimoto Y, Karimi Tari P, Cvetkovska V, Harada T, et al. Loss of synapse repressor MDGA1 enhances perisomatic inhibition, confers resistance to network excitation, and impairs cognitive function. Cell Rep. 2017;21:3637–45.
5. Lee K, Kim Y, Lee S-JJ, Qiang Y, Lee D, Lee HW, et al. MDGAs interact selectively with neuroligin-2 but not other neuroligins to regulate inhibitory synapse development. Proc Natl Acad Sci. 2013;110:336–41.
6. Takeuchi A, Hamasaki T, Litwack ED, O'Leary DDM. Novel IgCAM, MDGA1, expressed in unique cortical area- and layer-specific patterns and transiently by distinct forebrain populations of cajal-retzius neurons. Cereb Cortex. 2007;17:1531–41.
7. Takeuchi A, O'Leary DD. Radial migration of superficial layer cortical neurons controlled by novel Ig cell adhesion molecule MDGA1. J Neurosci. 2006;26:4460–4.
8. Elegheert J, Cvetkovska V, Clayton AJ, Heroven C, Vennekens KM, Smukowski SN, et al. Structural mechanism for modulation of synaptic neuroligin-neurexin signaling by MDGA proteins. Neuron. 2017;95:896–913.
9. Connor SA, Ammendrup-Johnsen I, Chan AW, Kishimoto Y, Murayama C, Kurihara N, et al. Altered cortical dynamics and cognitive function upon haploinsufficiency of the autism-linked excitatory synaptic suppressor MDGA2. Neuron. 2016;91:1052–68.
10. Pettem KL, Yokomaku D, Takahashi H, Ge Y, Craig AM. Interaction between autism-linked MDGAs and neuroligins suppresses inhibitory synapse development. J Cell Biol. 2013;200:321–36.
11. Loh KH, Stawski PS, Draycott AS, Udeshi ND, Lehrman EK, Wilton DK, et al. Proteomic analysis of unbounded cellular compartments: synaptic clefts. Cell. 2016;166:1295–307.
12. Lewis CM, Levinson DF, Wise LH, Delisi LE, Straub RE, Hovatta I, et al. Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: schizophrenia. Am J Hum Genet. 2003;73:34–48.
13. Li J, Liu J, Feng G, Li T, Zhao Q, Li Y, et al. The MDGA1 gene confers risk to schizophrenia and bipolar disorder. Schizophr Res. 2011;125:194–200.
14. Kähler AK, Djurovic S, Kulle B, Jönsson EG, Agartz I, Hall H, et al. Association analysis of schizophrenia on 18 genes involved in neuronal migration: MDGA1 as a new susceptibility gene. Am J Med Genet Part B Neuropsychiatr Genet. 2010;147B:1089–100.
15. Lesca G, Rudolf G, Labalme A, Hirsch E, Arzimanoglou A, Genton P, et al. Epileptic encephalopathies of the Landau-Kleffner and continuous spike and waves during slow-wave sleep types: genomic dissection makes the link with autism. Epilepsia. 2012;53:1526–38.
16. Riazuddin S, Hussain M, Razzaq A, Iqbal Z, Shahzad M, Polla DL, et al. Exome sequencing of Pakistani consanguineous families identifies 30 novel candidate genes for recessive intellectual disability. Mol Psychiatry. 2017;22:1604–14.
17. Van EDO, Kuo PH, Hartmann AM, Webb BT, Möller HJ, Hettema JM, et al. Genomewide association analysis followed by a replication study implicates a novel candidate gene for neuroticism. Arch Gen Psychiatry. 2008;65:1062–71.
18. Bucan M, Abrahams BS, Wang K, Glessner JT, Herman EI, Sonnenblick LI. Genome-wide analyses of exonic copy number variants in a family-based study point to novel autism susceptibility genes. PLoS Genet. 2009;5:e1000536.
19. David Litwack E, Babey R, Buser R, Gesemann M, O'Leary D. Identification and characterization of two novel brain-derived immunoglobulin superfamily members with unique structural organization. Mol Cell Neurosci. 2004;25:263–74.
20. Fujimura Y, Iwashita M, Matsuzaki F, Yamamoto T. MDGA1, an IgSF molecule containing a MAM domain, heterophilically associates with axon- and muscle-associated binding partners through distinct structural domains. Brain Res. 2006;1101:12–9.
21. Sano S, Takashima S, Niwa H, Yokoi H, Shimada A, Arenz A, et al. Characterization of teleost Mdga1 using a gene-trap approach in medaka (*Oryzias latipes*). Genesis. 2010;47:505–13.
22. Díaz-López A, Rivas C, Iniesta P, Morán A, García-Aranda C, Megías D, et al. Characterization of MDGA1, a novel human glycosylphosphatidylinositol-anchored protein localized in lipid rafts. Exp Cell Res. 2005;307:91–9.
23. Suzuki K, Hayashi Y, Nakahara S, Kumazaki H, Prox J, Horiuchi K, et al. Activity-dependent proteolytic cleavage of neuroligin-1. Neuron. 2012;76:410–22.
24. Pettem KL, Yokomaku D, Luo L, Linhoff MW, Prasad T, Connor SA, et al. The specific α-neurexin interactor calsyntenin-3 promotes excitatory and inhibitory synapse development. Neuron. 2013;80:113–28.
25. Sonderegger P. Ig superfamily molecules in the nervous system. CRC Press, 1999.
26. Zhiling Y, Fujita E, Tanabe Y, Yamagata T, Momoi T. Momoi MY Mutations in the gene encoding CADM1 are associated with autism spectrum disorder. Biochem Biophys Res Commun. 2008;377:926–9.
27. Piton A, Michaud JL, Peng H, Aradhya S, Gauthier J, Mottron L, et al. Mutations in the calcium-related gene IL1RAPL1 are associated with autism. Hum Mol Genet. 2008;17:3965–74.

28. Chen H, He Z, Bagri A, Tessier-Lavigne M. Semaphorin–neuropilin interactions underlying sympathetic axon responses to class III semaphorins. Neuron. 1998;21:1283–90.

29. Kim JA, Kim D, Won SY, Han KA, Park D, Cho E, et al. Structural insights into modulation of neurexin-neuroligin trans-synaptic adhesion by MDGA1/neuroligin-2 complex. Neuron. 2017;94:1121–1131.e6.

30. Gangwar SP, Zhong X, Seshadrinathan S, Chen H, Machius M. Rudenko G Molecular mechanism of MDGA1: regulation of neuroligin 2: neurexin trans-synaptic bridges. Neuron. 2017;94:1132–41.

31. Ingold E, vom Berg-Maurer CM, Burckhardt CJ, Lehnherr A, Rieder P, Keller PJ, et al. Proper migration and axon outgrowth of zebrafish cranial motoneuron subpopulations require the cell adhesion molecule MDGA2A. Biol Open. 2015;4:146–54.

32. Joset P, Wacker A, Babey R, Ingold EA, Andermatt I, Stoeckli ET, et al. Rostral growth of commissural axons requires the cell adhesion molecule MDGA2. Neural Dev. 2011;6:22.

33. Südhof TC. Neuroligins and neurexins link synaptic function to cognitive disease. Nature. 2008;455:903–11.

34. Song JY, Ichtchenko K, Südhof TC, Brose N. Neuroligin 1 is a postsynaptic cell-adhesion molecule of excitatory synapses. Proc Natl Acad Sci USA. 1999;96:1100–5.

35. Varoqueaux F, Jamain S. Brose N Neuroligin 2 is exclusively localized to inhibitory synapses. Eur J Cell Biol. 2004;83:449–56.

36. Graf ER, Zhang XZ, Jin SX, Linhoff MW. Craig AM Neurexins induce differentiation of GABA and glutamate postsynaptic specializations via neuroligins. Cell. 2004;119:1013–26.

37. Takács VT, Freund TF. Nyiri G Neuroligin 2 is expressed in synapses established by cholinergic cells in the mouse brain. PLoS One. 2013;8:e72450.

38. Uchigashima M, Ohtsuka T, Kobayashi K. Watanabe M Dopamine synapse is a neuroligin-2-mediated contact between dopaminergic presynaptic and GABAergic postsynaptic structures. Proc Natl Acad Sci USA. 2016;113:4206–11.

39. Budreck EC, Scheiffele P. Neuroligin-3 is a neuronal adhesion protein at GABAergic and glutamatergic synapses. Eur J Neurosci. 2010;26:1738–48.

40. Hoon M, Südhof TC. Neuroligin-4 is localized to glycinergic postsynapses and regulates inhibition in the retina. Proc Natl Acad Sci USA. 2011;108:3053–8.

41. Poulopoulos A, Aramuni G, Meyer G, Soykan T, Hoon M, Papadopoulos T, et al. Neuroligin 2 drives postsynaptic assembly at perisomatic inhibitory synapses through gephyrin and collybistin. Neuron. 2009;63:628–42.

42. Gibson JR, Huber KM, Sudhof TC. Neuroligin-2 deletion selectively decreases inhibitory synaptic transmission originating from fast-spiking but not from somatostatin-positive interneurons. J Neurosci. 2009;29:13883–97.

43. Molumby MJ, Anderson RM, Newbold DJ, Koblesky NK, Garrett AM, Schreiner D, et al. γ-Protocadherins interact with neuroligin-1 and negatively regulate dendritic spine morphogenesis. Cell Rep. 2017;18:2702–14.