·癫痫及发作性疾病·

N-甲基-D-天冬氨酸受体*GRIN2A*基因变异与癫痫研究进展

唐薇婷 肖波

【摘要】 随着基因检测技术的发展，癫痫相关致病基因相继被发现，编码神经递质N-甲基-D-天冬氨酸受体（NMDAR）的*GRIN2A*基因变异与癫痫的发生密切相关，该基因变异导致的临床表型复杂多样，药物治疗效果不同。本文综述*GRIN2A*基因变异致NMDAR结构和功能改变与癫痫临床表型的关系，以为癫痫精准诊断与治疗提供依据。

【关键词】 癫痫； 受体，N-甲基-D-天冬氨酸； 基因； 突变； 综述

Research progress of N-methyl-D-aspartate receptor *GRIN2A* gene variations and epilepsy

TANG Wei-ting, XIAO Bo

Department of Neurology, Xiangya Hospital Central South University, Changsha 410008, Hu'nan, China

Corresponding author: XIAO Bo (Email: xiaobo_xy@126.com)

【Abstract】 In recent years, with the rapid development of gene sequencing technology, a variety of epilepsy pathogenic genes have been discovered, among which *GRIN2A* gene variations encoding the neurotransmitter N-methyl-D-aspartate receptor (NMDAR) are closely related to the occurrence of epilepsy. At present, there are relatively few studies on the function of epileptic related variations in *GRIN2A* gene. The resulting epilepsy phenotypes are complex and varied, and different patients have different therapeutic effects on different drugs. This paper briefly summarizes the possible relationship between the changes of NMDAR structure and function caused by *GRIN2A* gene variations and the clinical phenotype of epilepsy, providing clues for the precise treatment of epilepsy.

【Key words】 Epilepsy; Receptors, N-methyl-D-aspartate; Genes; Mutation; Review

This study was supported by National Key Research and Development Program of China (No. 2021YFC1005305), and the National Natural Science Foundation of China (No. 81974206).

Conflicts of interest: none declared

癫痫是神经系统常见疾病，被世界卫生组织（WHO）列为全球重点防治的神经精神疾病之一。癫痫以反复发作性中枢神经系统功能障碍为特征，主要表现为大脑神经元高度同步化异常放电。文献报道，有70%～80%的癫痫与遗传变异相关[1-3]。近年来，随着基因检测技术的发展，多种癫痫致病基因相继被发现，尤其是编码离子通道蛋白相关基因，如钾离子通道基因*KCNQ2*、*KCNQ3*、*KCNJ3*、*KCNT1*等，钠离子通道基因*SCN3B*、*SCN2A*、*SCN8A*等，钙离子通道基因*CACNA1H*等，以及编码神经递质受体相关基因*GRIN1*、*GRIN2A*、*GRIN2B*等[4-9]。局部神经网络兴奋-抑制失衡是癫痫的主要原因，谷氨酸作为中枢神经系统最主要的兴奋性神经递质，其受体结构和功能异常可能直接参与癫痫网络的形成[4-6,10]。谷氨酸受体（GluR）家族基因变异可导致患者出现癫痫临床表型，其中编码N-甲基-D-天冬氨酸受体（NMDAR）的*GRIN*基因变异占80%以上，尤其以*GRIN2A*显著[11-15]。本文拟综述*GRIN2A*基因变异致NMDAR结构和功能改变与癫痫临床表型的关系，以为癫痫的精准诊断与治疗提供依据。

一、N-甲基-D-天冬氨酸受体结构和功能

NMDAR是离子型谷氨酸受体（iGluR）的重要

doi：10.3969/j.issn.1672-6731.2023.02.003

基金项目：国家重点研发计划项目（项目编号：2021YFC1005305）；国家自然科学基金资助项目（项目编号：81974206）

作者单位：410008 长沙，中南大学湘雅医院神经内科

通讯作者：肖波，Email：xiaobo_xy@126.com

亚型之一，属于电压配体双门控阳离子通道，广泛表达于中枢神经系统，介导相对缓慢的兴奋性突触传递[16-19]。NMDAR是由4个亚基组成的异四聚体结构，中间形成离子通道孔，与倒置的钾离子通道相似。功能性NMDAR由2个Glu N1亚基和2个Glu N2亚基组成，或由2个Glu N1亚基、1个Glu N2亚基、1个Glu N3亚基组成[19]。每个亚基由4个半独立结构域组成，即细胞外氨基末端结构域（ATD）、激动剂结合结构域（ABD）、跨膜结构域（TMD）和细胞内羧基末端结构域（CTD），其中，细胞外ABD是由2个多肽片段S1和S2组成的双叶蝶状结构，上叶和下叶共同构成激动剂配体结合区域，当甘氨酸结合Glu N1亚基和（或）Glu N3亚基、同时谷氨酸结合Glu N2亚基时，NMDAR通道被激活。多项基于ABD晶体结构的研究显示，NMDAR激动剂与细胞外ABD结合可导致ABD及其相邻TMD的空间重排，选择性开放阳离子通道，使大量钙离子内流，神经元胞膜去极化，进而产生动作电位和神经冲动传导[19-21]。

二、基因变异对N-甲基-D-天冬氨酸受体结构和功能的影响

Glu N1亚基由*GRIN1*基因编码，Glu N3A和Glu N3B亚基分别由*GRIN3A*和*GRIN3B*基因编码，Glu N2A、Glu N2B、Glu N2C、Glu N2D亚基分别由*GRIN2A*、*GRIN2B*、*GRIN2C*、*GRIN2D*基因编码[17,19]。尤以Glu N2亚基对NMDAR功能的影响最显著，可影响突触反应时程、突触强度和突触可塑性，进而影响神经元功能、电活动和神经系统发育[18-19]。

NMDAR不同亚基结构域的空间分布相对独立，功能各异，不同基因变异致NMDAR功能改变具有多样性[22-23]，部分引起NMDAR功能增强，称为功能获得突变（GoF），如*GRIN2A* A243V、V452M、P552R、N615K、F652V、K669N、P669S、L812M和L817V等；部分引起NMDAR功能降低或缺失，称为功能失去突变（LoF），如*GRIN2A* P79R、I184S、C231Y、C436R、G483R、R504W、V506A、R518H、T531M、A548T、V685G、I694T、M705V、E714K、A716T、A727T、D731N、V734L和K772E等；以及极少不引起NMDAR功能改变，例如*GRIN2A* R586K、I814T、D933N、N976S等。编码NMDAR结构域的基因变异通过影响N-甲基-D-天冬氨酸（NMDA）受体与配体结合、NMDAR通道门控、NMDAR生成、顺向转运等机制多维度调控NMDAR功能[17,23-24]。有文献报道，约70%的细胞外ABD突变为功能失去突变，56%的TMD突变为功能获得突变[11]，例如，ABD S2段及其邻近M3跨膜螺旋的*GluN2A* M817V、L812M突变为功能获得突变[25-27]；S1段和S2段*Glu2A* G483R、M705V突变则为功能失去突变，使Glu2A蛋白表达水平显著下降，谷氨酸和甘氨酸对此类突变NMDAR的激活能力随之下降[28-29]；S2段*Glu2A* E714K突变虽可显著下调Glu2A蛋白的表达，但对此类突变的NMDAR的激活无明显影响[29]。

三、*GRIN2A*基因变异与癫痫

NMDAR作为中枢神经系统最重要的兴奋性神经递质谷氨酸受体，在神经发育、记忆形成、兴奋性与抑制性神经网络平衡、突触可塑性等方面均发挥重要作用，因此，NMDAR功能异常与多种中枢神经系统疾病特别是癫痫的发生发展密切相关[11,23]，其中编码NMDAR的*GRIN*基因变异具有较高的致病性[10,30]。有研究对健康人群的NMDAR进行遗传耐受性分析，发现细胞外ABD和TMD最不耐受突变，提示编码这两个区域的基因变异易致病[11]。自2010年首个致病性突变——*GRIN2A* N615K被报道以来，已从不同临床表型的癫痫患者中鉴定出近200种变异，绝大多数为*GRIN2A*基因变异[11,15]。癫痫相关变异分布在NMDAR各结构域，主要位于细胞外ABD和TMD[11,23]。

*GRIN2A*基因变异致癫痫表型多样，尤以获得性癫痫性失语[AEA，亦称Landau-Kleffner综合征（LKS）]最常见，还包括特发性局灶性癫痫（IFE）、伴中央颞区棘波的儿童自限性癫痫、非典型儿童良性部分性癫痫（ABPE）、儿童自限性癫痫、伴中央颞区棘波的非典型儿童癫痫、慢波睡眠中持续棘慢复合波癫痫（ECSWS）、早发性癫痫性脑病（EOEE）及首诊无法明确分类的儿童癫痫[28,31]。然而迄今未发现*GRIN2A*基因变异致NMDAR功能改变与临床表型之间的确切关系：一方面，携带相同变异的患者临床表型可能相似或完全不同，有文献报道3例携带*GRIN2A* D731N突变的患者临床表现为癫痫伴发育迟滞、Landau-Kleffner综合征和伴中央颞区棘波的儿童自限性癫痫并发语言障碍[28,32-34]，推测与氨基酸或核苷酸突变方式、突变位点以及患者性别、遗传背景和环境因素等有关；另一方面，携带不同变异的患者表现为同一表型，如携带*GRIN2A* G483R、R518H、T531M、F652V、E714K突变的患者临床表型均为慢波睡眠中持续棘慢复合波癫痫[23,28-29]；携带

GRIN2A P31T、A243V、A290V、R370W、P699S、A727T突变的患者临床表型均为伴中央颞区棘波的儿童自限性癫痫[28-29]，推测可能是由于上述变异导致的NMDAR功能改变相似。此外，还发现*GRIN2A*基因变异致NMDAR功能改变与临床表型严重程度较一致：临床症状相对较轻的患者（如伴中央颞区棘波的儿童自限性癫痫、非典型儿童良性部分性癫痫），其所携带变异对NMDAR功能的影响相对较小；临床症状严重患者（如伴智力障碍的慢波睡眠中持续棘慢复合波癫痫、早发性癫痫性脑病），其所携带的变异对NMDAR功能的影响较大。例如，携带*GRIN2A* A243V突变患者的临床表型是预后相对良好的伴中央颞区棘波的儿童自限性癫痫，进一步分析显示，该突变可降低NMDAR对锌离子的敏感性，使NMDAR功能轻微增强；携带*GRIN2A* N615K突变患者的临床表型为伴严重智力障碍的早发性癫痫性脑病，该突变使镁离子对NMDAR的阻滞作用完全丧失，导致NMDAR功能显著增强[29,35]。总之，癫痫相关NMDAR功能失去突变均导致预后较差的临床表型，通常伴发智力障碍、发育迟滞等，这些突变通过减弱NMDAR对谷氨酸和（或）甘氨酸的敏感性，减少突触反应时间、单通道开放时间和开放概率，降低NMDAR动作电位或NMDAR蛋白[总蛋白和（或）表面蛋白]表达水平等，阻碍NMDAR下游信号传导，减弱γ-氨基丁酸（GABA）能神经元抑制效应，使神经回路兴奋性与抑制性失衡，导致癫痫的发生[32-33,36]；功能获得突变则通过改变NMDAR功能，例如，增强NMDAR对谷氨酸和（或）甘氨酸的敏感性以及降低对镁离子、锌离子、质子的敏感性，增加单通道开放时间和开放概率等，使NMDAR功能增强，引起中枢神经系统过度兴奋，导致癫痫的发生[36]。

四、*GRIN2A*基因变异相关癫痫的药物治疗

NMDAR作为癫痫药物治疗的靶分子已获得共识[9,37-39]。*GRIN2A*基因变异可以导致NMDAR功能增强或者功能降低或缺失，从而为癫痫药物治疗提供一种新的思路，即通过特异性NMDAR阻断剂或正向变构调节剂（PAM）减弱NMDAR功能改变，达到临床控制发作和减轻脑损伤的目的。

癫痫模型显示，*GRIN2A* S644G纯合突变小鼠通常出生3周内死亡，予以NMDAR阻断剂或负向变构调节剂（FITM）右美沙芬、右美沙芬+奎尼丁、美金刚，可延迟致命性癫痫发作的发生[40]。在非洲爪蟾卵母细胞构建的细胞模型和癫痫小鼠模型中发现，NMDAR正向变构调节剂内源性神经类固醇24S-羟基胆固醇以及氨基糖苷类或甘氨酸结合位点的共激动剂D-丝氨酸、L-丝氨酸和脱环丝氨酸等对NMDAR功能降低或缺失的细胞或动物均有效，在细胞上可增强突变型受体的电流反应，在动物模型上可减少癫痫发作[9,41-46]。上述动物实验和体外研究为携带*GRIN2A*基因变异的癫痫患者精准药物治疗提供了理论依据。有文献报道1例携带*GRIN2A* L812M突变的早发性癫痫性脑病患者，对多种抗癫痫发作药物（ASM）耐药，但对NMDAR非竞争性阻断剂美金刚反应良好[24,46]；1例携带*GRIN2A* S664G突变的癫痫患者加用美金刚和右美沙芬后，发作频率显著减少[40]。亦有研究显示，携带*GRIN2A* N615K突变的癫痫患者对美金刚耐药，究其原因，美金刚作用于NMDAR镁离子结合位点，*GRIN2A* N615K突变导致镁离子对NMDAR的抑制作用完全丧失[46]。由此可见，*GRIN2A*基因突变位点不同，导致的NMDAR功能改变各异，临床表型复杂多样，NMDAR阻断剂反应亦不尽一致。因此，应从药理学、生物物理学、NMDAR在细胞膜表面的表达和转运等多维度探究*GRIN*基因变异导致的NMDAR结构和功能改变，明确基因型-临床表型-药物疗效的关系，以实现癫痫的精准诊断与治疗；此外，基因变异导致其编码蛋白结构和功能改变的精准药物治疗研究病例数较少，尚无法提供全面的药物疗效和安全性证据，有待大样本双盲对照临床试验进一步验证精准药物治疗的有效性和安全性。

综上所述，编码NMDAR的*GRIN*基因变异与癫痫密切相关，迄今已报道相关突变200余个，其功能各异、临床表型复杂多样，仅不足1/3完善基因功能评估，但该基因变异导致癫痫的作用机制尚未明确，且缺乏针对性强、不良反应轻微的特异性治疗药物。未来将进一步填补癫痫相关*GRIN*基因变异的临床数据库，完善其编码的NMDAR结构和功能研究，探寻更具针对性的变构调节剂，构建*GRIN*基因变异、NMDAR结构和功能改变、癫痫临床表型、药物精准治疗的标准化流程，推动癫痫的个体化诊断与治疗。

利益冲突 无

参 考 文 献

[1] Thakran S, Guin D, Singh P, Singh P, Kukal S, Rawat C, Yadav S, Kushwaha SS, Srivastava AK, Hasija Y, Saso L,

Ramachandran S, Kukreti R. Genetic landscape of common epilepsies: advancing towards precision in treatment[J]. Int J Mol Sci, 2020, 21:7784.
[2] Hildebrand MS, Dahl HH, Damiano JA, Smith RJ, Scheffer IE, Berkovic SF. Recent advances in the molecular genetics of epilepsy[J]. J Med Genet, 2013, 50:271-279.
[3] Perucca P, Bahlo M, Berkovic SF. The genetics of epilepsy[J]. Annu Rev Genomics Hum Genet, 2020, 21:205-230.
[4] Allen AS, Berkovic SF, Cossette P, Delanty N, Dlugos D, Eichler EE, Epstein MP, Glauser T, Goldstein DB, Han Y, Heinzen EL, Hitomi Y, Howell KB, Johnson MR, Kuzniecky R, Lowenstein DH, Lu YF, Madou MR, Marson AG, Mefford HC, Esmaeeli Nieh S, O'Brien TJ, Ottman R, Petrovski S, Poduri A, Ruzzo EK, Scheffer IE, Sherr EH, Yuskaitis CJ, Abou-Khalil B, Alldredge BK, Bautista JF, Berkovic SF, Boro A, Cascino GD, Consalvo D, Crumrine P, Devinsky O, Dlugos D, Epstein MP, Fiol M, Fountain NB, French J, Friedman D, Geller EB, Glauser T, Glynn S, Haut SR, Hayward J, Helmers SL, Joshi S, Kanner A, Kirsch HE, Knowlton RC, Kossoff EH, Kuperman R, Kuzniecky R, Lowenstein DH, McGuire SM, Motika PV, Novotny EJ, Ottman R, Paolicchi JM, Parent JM, Park K, Poduri A, Scheffer IE, Shellhaas RA, Sherr EH, Shih JJ, Singh R, Sirven J, Smith MC, Sullivan J, Lin Thio L, Venkat A, Vining EP, Von Allmen GK, Weisenberg JL, Widdess-Walsh P, Winawer MR; Epi4K Consortium, Epilepsy Phenome/Genome Project. De novo mutations in epileptic encephalopathies[J]. Nature, 2013, 501:217-221.
[5] Symonds JD, Zuberi SM, Johnson MR. Advances in epilepsy gene discovery and implications for epilepsy diagnosis and treatment[J]. Curr Opin Neurol, 2017, 30:193-199.
[6] Oyrer J, Maljevic S, Scheffer IE, Berkovic SF, Petrou S, Reid CA. Ion channels in genetic epilepsy: from genes and mechanisms to disease-targeted therapies[J]. Pharmacol Rev, 2018, 70:142-173.
[7] Talwar D, Hammer MF. SCN8A epilepsy, developmental encephalopathy, and related disorders[J]. Pediatr Neurol, 2021, 122:76-83.
[8] Verma IC, Bhatia S, Arora V. Genetic testing in pediatric epilepsy[J]. Indian J Pediatr, 2021, 88:1017-1024.
[9] Perucca P, Perucca E. Identifying mutations in epilepsy genes: impact on treatment selection[J]. Epilepsy Res, 2019, 152:18-30.
[10] Hanada T. Ionotropic glutamate receptors in epilepsy: a review focusing on AMPA and NMDA receptors[J]. Biomolecules, 2020, 10:464.
[11] XiangWei W, Jiang Y, Yuan H. *De Novo* mutations and rare variants occurring in NMDA receptors[J]. Curr Opin Physiol, 2018, 2:27-35.
[12] Myers SJ, Yuan H, Kang JQ, Tan FCK, Traynelis SF, Low CM. Distinct roles of *GRIN2A* and *GRIN2B* variants in neurological conditions[J]. F1000Res, 2019, 8:F1000 Faculty Rev-1940.
[13] Mangano GD, Riva A, Fontana A, Salpietro V, Mangano GR, Nobile G, Orsini A, Iacomino M, Battini R, Astrea G, Striano P, Nardello R. De novo GRIN2A variants associated with epilepsy and autism and literature review[J]. Epilepsy Behav, 2022, 129:108604.
[14] Lesca G, Møller RS, Rudolf G, Hirsch E, Hjalgrim H, Szepetowski P. Update on the genetics of the epilepsy-aphasia spectrum and role of GRIN2A mutations[J]. Epileptic Disord, 2019, 21(S1):41-47.
[15] Benke TA, Park K, Krey I, Camp CR, Song R, Ramsey AJ, Yuan H, Traynelis SF, Lemke J. Clinical and therapeutic significance of genetic variation in the GRIN gene family encoding NMDARs[J]. Neuropharmacology, 2021, 199:108805.
[16] Lalo U, Koh W, Lee CJ, Pankratov Y. The tripartite glutamatergic synapse[J]. Neuropharmacology, 2021, 199:108758.
[17] Amin JB, Moody GR, Wollmuth LP. From bedside-to-bench: what disease-associated variants are teaching us about the NMDA receptor[J]. J Physiol, 2021, 599:397-416.
[18] Pagano J, Giona F, Beretta S, Verpelli C, Sala C. N-methyl-D-aspartate receptor function in neuronal and synaptic development and signaling[J]. Curr Opin Pharmacol, 2021, 56:93-101.
[19] 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 CM, Dell'Acqua ML, Diamond JS, Camp CR, Perszyk RE, Yuan H, Traynelis SF. Structure, function, and pharmacology of glutamate receptor ion channels[J]. Pharmacol Rev, 2021, 73:298-487.
[20] Lee CH, Lü W, Michel JC, Goehring A, Du J, Song X, Gouaux E. NMDA receptor structures reveal subunit arrangement and pore architecture[J]. Nature, 2014, 511:191-197.
[21] Karakas E, Furukawa H. Crystal structure of a heterotetrameric NMDA receptor ion channel[J]. Science, 2014, 344:992-997.
[22] Vieira MM, Jeong J, Roche KW. The role of NMDA receptor and neuroligin rare variants in synaptic dysfunction underlying neurodevelopmental disorders[J]. Curr Opin Neurobiol, 2021, 69:93-104.
[23] Xu XX, Luo JH. Mutations of N-methyl-D-aspartate receptor subunits in epilepsy[J]. Neurosci Bull, 2018, 34:549-565.
[24] Swanger SA, Chen W, Wells G, Burger PB, Tankovic A, Bhattacharya S, Strong KL, Hu C, Kusumoto H, Zhang J, Adams DR, Millichap JJ, Petrovski S, Traynelis SF, Yuan H. Mechanistic insight into NMDA receptor dysregulation by rare variants in the GluN2A and GluN2B agonist binding domains[J]. Am J Hum Genet, 2016, 99:1261-1280.
[25] Yuan H, Hansen KB, Zhang J, Pierson TM, Markello TC, Fajardo KV, Holloman CM, Golas G, Adams DR, Boerkoel CF, Gahl WA, Traynelis SF. Functional analysis of a de novo GRIN2A missense mutation associated with early-onset epileptic encephalopathy[J]. Nat Commun, 2014, 5:3251.
[26] 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[J]. Mol Pharmacol, 2017, 91:317-330.
[27] Venkateswaran S, Myers KA, Smith AC, Beaulieu CL, Schwartzentruber JA, Majewski J, Bulman D, Boycott KM, Dyment DA; FORGE Canada Consortium. Whole-exome sequencing in an individual with severe global developmental delay and intractable epilepsy identifies a novel, de novo GRIN2A mutation[J]. Epilepsia, 2014, 55:e75-79.
[28] 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[J]. Nat Genet, 2013, 45:1061-1066.
[29] 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 [J]. Nat Genet, 2013, 45:1067-1072.

[30] Petrovski S, Wang Q, Heinzen EL, Allen AS, Goldstein DB. Genic intolerance to functional variation and the interpretation of personal genomes[J]. PLoS Genet, 2013, 9:e1003709.

[31] 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[J]. Brain, 2019, 142: 80-92.

[32] Samanta D. GRIN2A-related epilepsy and speech disorders: a comprehensive overview with a focus on the role of precision therapeutics[J]. Epilepsy Res, 2023, 189:107065.

[33] Gao K, Tankovic A, Zhang Y, Kusumoto H, Zhang J, Chen W, XiangWei W, Shaulsky GH, Hu C, Traynelis SF, Yuan H, Jiang Y. A de novo loss-of-function GRIN2A mutation associated with childhood focal epilepsy and acquired epileptic aphasia [J]. PLoS One, 2017, 12:e0170818.

[34] Tascón-Arcila J, Rojas-Jiménez S, Cornejo-Sánchez D, Gómez-Builes P, Ucroz-Benavides A, Holguín BM, Restrepo-Arbeláez D, Gómez-Castillo C, Solarte-Mia R, Cornejo-Ochoa W, Pineda-Trujillo N. Differential clinical features in colombian patients with rolandic epilepsy and suggestion of unlikely association with *GRIN2A*, *RBFOX1*, or *RBFOX3* gene variants[J]. J Child Neurol, 2021, 36:875-882.

[35] Endele S, Rosenberger G, Geider K, Popp B, Tamer C, Stefanova I, Milh M, Kortüm F, Fritsch A, Pientka FK, Hellenbroich Y, Kalscheuer VM, Kohlhase J, Moog U, Rappold G, Rauch A, Ropers HH, von Spiczak S, Tönnies H, Villeneuve N, Villard L, Zabel B, Zenker M, Laube B, Reis A, Wieczorek D, Van Maldergem L, Kutsche K. Mutations in GRIN2A and GRIN2B encoding regulatory subunits of NMDA receptors cause variable neurodevelopmental phenotypes[J]. Nat Genet, 2010, 42:1021-1026.

[36] Helbig I, Ellis CA. Personalized medicine in genetic epilepsies: possibilities, challenges, and new frontiers [J]. Neuropharmacology, 2020, 172:107970.

[37] Sivakumar S, Ghasemi M, Schachter SC. Targeting NMDA receptor complex in management of epilepsy [J]. Pharmaceuticals (Basel), 2022, 15:1297.

[38] Suvekbala V, Ramachandran H, Veluchamy A, Mascarenhas MAB, Ramprasath T, Nair MKC, Garikipati VNS, Gundamaraju R, Subbiah R. The promising epigenetic regulators for refractory epilepsy: an adventurous road ahead[J]. Neuromolecular Med, 2022.[Epub ahead of print]

[39] Ahmad MA, Pottoo FH, Akbar M. Gene therapy repairs for the epileptic brain: potential for treatment and future directions[J]. Curr Gene Ther, 2020, 19:367-375.

[40] 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[J]. Brain, 2020, 143:2039-2057.

[41] 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[J]. Neuropharmacology, 2020, 177: 108247.

[42] Sarigecili E, Direk MC, Komur M, Bozdogan ST, Okuyaz C. Identification of a novel mutation in *GRIN2A* gene with global developmental delay and refractory epilepsy [J]. Ann Indian Acad Neurol, 2020, 23:696-699.

[43] Xu XX, Liu XR, Fan CY, Lai JX, Shi YW, Yang W, Su T, Xu JY, Luo JH, Liao WP. Functional investigation of a GRIN2A variant associated with rolandic epilepsy [J]. Neurosci Bull, 2018, 34:237-246.

[44] Krey I, von Spiczak S, Johannesen KM, Hikel C, Kurlemann G, Muhle H, Beysen D, Dietel T, Møller RS, Lemke JR, Syrbe S. L-serine treatment is associated with improvements in behavior, EEG, and seizure frequency in individuals with GRIN-related disorders due to null variants[J]. Neurotherapeutics, 2022, 19: 334-341.

[45] Tang W, Beckley JT, Zhang J, Song R, Xu Y, Kim S, Quirk MC, Robichaud AJ, Diaz ES, Myers SJ, Doherty JJ, Ackley MA, Traynelis SF, Yuan H. Novel neuroactive steroids as positive allosteric modulators of NMDA receptors: mechanism, site of action, and rescue pharmacology on GRIN variants associated with neurological conditions [J]. Cell Mol Life Sci, 2023, 80:42.

[46] 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, Tifft CJ, Toro C, Boerkoel CF, Traynelis SF, Gahl WA; PhD for the NISC Comparative Sequencing Program. *GRIN2A* mutation and early-onset epileptic encephalopathy: personalized therapy with memantine[J]. Ann Clin Transl Neurol, 2014, 1:190-198.

（收稿日期：2023-02-07）
（本文编辑：彭一帆）

下期内容预告 本刊2023年第3期报道专题为癫痫及相关疾病，重点内容包括：2022年癫痫领域十大研究进展；皮质下结构与癫痫；单细胞转录组测序技术在癫痫及其他神经系统疾病研究中的进展；7T超高场强MRI在癫痫诊断与治疗中的应用进展；脑卒中后癫痫药物修饰治疗进展；脑深部电刺激术治疗耐药性癫痫研究进展；抑制miRNA-193a-5p表达对癫痫大鼠海马神经元损伤的影响；伴中央颞区棘波的儿童自限性癫痫临床特征及共病分析；钾离子通道基因变异相关儿童癫痫性脑病临床特征及基因变异分析；基于立体定向脑电图记录恐惧情绪的神经网络研究；快速低温对癫痫患者癫痫灶神经元的差异性影响研究；出血性卒中后癫痫患者生活质量及其影响因素分析；抗富亮氨酸胶质瘤失活基因1抗体相关脑炎相关发作临床-脑电特征；伴癫痫发作的自身免疫性脑炎临床特征分析