·CASE ANALYSIS· ·临床病例讨论·

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# *NEXMIF* 基因突变导致智力障碍合并癫痫2例并文献复习

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[摘 要] 目前已发现超过100个位于X染色体上的基因与X连锁智力障碍(X-linked intellectual disability，XLID)相关。*NEXMIF*基因是一个XLID致病基因，该基因突变的患者除表现为智力障碍外，还可合并癫痫、行为异常、肌张力降低等其他神经系统症状，以及其他系统的异常。中南大学湘雅医院儿科2017年3月8日至2020年6月20日收治2例*NEXMIF*基因突变导致智力障碍合并癫痫的患儿。病例1，女，7岁8个月，因“发育落后6年”就诊，体格检查示右眼斜视、多动、注意力不集中。智力测试显示发育商为43.6，脑电图显示异常放电，头颅影像学无明显异常。全外显子测序发现*NEXMIF*基因(NM_001008537)存在新发c.2189delC(p. S730Lfs*17)杂合突变。随访期间患儿出现癫痫发作，表现为全身性发作、失神发作，目前使用左乙拉西坦联合拉莫三嗪治疗中，病情暂时得到控制。病例2，男，6个月，因“发育倒退3个月，抽搐2个月”就诊。出生后有喂养困难，既往有喉软骨发育不良病史。体格检查发现追光追物差，竖头不稳，四肢肌张力减低。脑电图监测到间断高度失律及痉挛发作，先后予托吡酯、促肾上腺皮质激素(adrenocorticotrophic hormone，ACTH)治疗。全外显子测序发现*NEXMIF*基因存在新发c.592C>T(Q198X)突变。随访过程中加用氨己烯酸片后患儿抽搐缓解，精神运动发育无明显进步，并出现斜视。目前国外报道91例*NEXMIF*基因突变患者，国内报道1例，外加本研究中的2例患儿，共94例。PubMed和HGMD共收录83个*NEXMIF*基因突变，加上本研究发现的2个未报道的突变，共85个突变。*NEXMIF*基因突变患者主要表现为轻到重度智力障碍，常常合并行为异常、癫痫、肌张力低下等其他神经系统症状。男性和女性患者临床表现互有重叠，男性患者常常表现为更严重的智力障碍、语言障碍、孤独症样症状，女性患者多合并难治性癫痫。目前报道的*NEXMIF*基因变异大多为导致NEXMIF蛋白质表达减少的功能缺失变异，其缺失程度可能与疾病的严重程度相关。

[关键词] *NEXMIF*基因；智力障碍；癫痫；婴儿痉挛

# *NEXMIF* mutations in intellectual disability and epilepsy: A report of 2 cases and literature review

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**ABSTRACT** More than 100 genes located on the X chromosome have been found to be associated with X-linked intellectual disability (XLID) to date, and *NEXMIF* is a pathogenic gene for XLID. In addition to intellectual disability, patients with *NEXMIF* gene mutation can also have other neurological symptoms, such as epilepsy, abnormal behavior, and hypotonia, as well as abnormalities of other systems. Two children with intellectual disability and epilepsy caused by *NEXMIF* gene mutation were treated in the Department of Pediatrics, Xiangya Hospital, Central South University from March 8, 2017 to June 20, 2020. Patient 1, a 7 years and 8 months old girl, visited our department because of the delayed psychomotor development. Physical examination revealed strabismus (right eye), hyperactivity, and loss of concentration. Intelligence test showed a developmental quotient of 43.6. Electroencephalogram showed abnormal discharge, and cranial imaging appeared normal. Whole exome sequencing revealed a *de novo* heterozygous mutation, c.2189delC (p.S730Lfs*17) in the *NEXMIF* gene (NM_001008537). During the follow-up period, the patient developed epileptic seizures, mainly manifested as generalized and absent seizures. She took the medicine of levetiracetam and lamotrigine, and the seizures were under control. Patient 2, a 6-months old boy, visited our department due to developmental regression and seizures. He showed poor reactions to light and sound, and was not able to raise head without aid. Hypotonia was also noticed. The electroencephalogram showed intermittent hyperarrhythmia, and spasms were monitored. He was given topiramate and adrenocorticotrophic hormone (ACTH). Whole exome sequencing detected a *de novo* c.592C>T (Q198X) mutation in *NEXMIF* gene. During the follow-up period, the seizures were reduced with vigabatrin. He had no obvious progress in the psychomotor development, and presented strabismus. There were 91 cases reported abroad, 1 case reported in China, and 2 patients were included in this study. A total of 85 variants in *NEXMIF* gene were found, involving 83 variants reported in PubMed and HGMD, and the 2 new variants presented in our patients. The patients with variants in *NEXMIF* gene all had mild to severe intellectual disability. Behavioral abnormalities, epilepsy, hypotonia, and other neurological symptoms are frequently presented. The phenotype of male partially overlaps with that of female. Male patients often have more severe intellectual disability, impaired language, and autistic features, while female patients often have refractory epilepsy. Most of the variants reported so far were loss-of-function resulted in the reduced protein expression of NEXMIF. The degree of NEXMIF loss appears to correlate with the severity of the phenotype.

**KEY WORDS** *NEXMIF* gene; intellectual disability; epilepsy; infantile spasm

智力障碍是一类临床异质性很高的神经发育障碍性疾病，常共患注意力缺陷多动障碍、癫痫等疾病。5%~10%的男性智力障碍患者由X染色体上的基因突变导致[1]，携带这些基因突变的女性也可因X染色体非选择性失活而表现为智力障碍及其他症状[2]。X连锁智力障碍(X-linked intellectual disability，

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XLID)具有很大的遗传异质性，目前已有100多个位于X染色体上的基因被报道与XLID相关[3]。*NEXMIF*基因是一个XLID致病基因，该基因突变的患者除了表现为智力障碍，还可合并癫痫、行为异常、肌张力降低等其他神经系统症状，以及其他系统的异常。笔者报告2例在中南大学湘雅医院儿科(以下简称我科)就诊的*NEXMIF*基因突变的患儿，结合文献总结其临床表型、基因型特点。本研究已通过中南大学湘雅医院医学伦理委员会审批(审批号：201605585)。

## 1 病例资料

病例1，女，7岁8个月时因“发育落后6年”于2017年3月8日就诊于我科门诊。患儿1岁前发育正常，1岁后被发现发育落后。患儿2个月追光追物，3个月笑出声、竖头，8个月发音，12个月叫人，18个月独走，24个月说句子。患儿就诊时可以独走、跑、跳，易摔跤；能正常日常交流，偶有回答不切题；上小学一年级，不会数数、写字，可以背诵简单诗句、唱歌；生活部分自理；性格急躁，好动，喜玩手指甲，上课无法集中注意力，不能完成考试。患儿系第1胎第1产，其母孕22周时因先兆流产，予黄体酮治疗，足月顺产。出生情况好，否认缺氧、窒息等病史。体格检查：体重35.5 kg，身高126 cm，头围55.0 cm，左眼向右斜视，可以简单对答，注意力不集中，精细动作较差。四肢肌力、肌张力、神经反射等正常。EEG：醒睡期双侧额极、额区、颞区为主弥漫性β波，多灶性或广泛性棘波、多棘波、棘慢波发放，双侧后头部更明显。采用0~6岁儿童神经心理发育量表行智力测试：大运动发育商46，精细动作发育商36，语言发育商52，适应能力发育商39，社交行为发育商46，综合发育商43.6，心理年龄40.2月。头颅MRI未见异常。遗传学检测：染色体、拷贝数变异检测未发现异常。全外显子测序检测到患儿*NEXMIF*基因存在1个c.2189delC (p.S730Lfs*17) (NM_001008537)杂合突变，Sanger测序结果提示父母均未携带此突变(图1)。依据美国医学遗传学与基因组学学会(American College of Medical Genetics and Genomics，ACMG)变异分类指南，该突变评级为致病性突变(PVS1+PS2+PM2)。患儿10岁时出现2次睡眠时抽搐，表现为眼神呆滞、口角流涎，持续数秒后缓解。11岁再发抽搐，可表现为突然跌倒或突然失语、流涎，每次持续数秒。EEG示大量广泛性快节律多棘(慢)波阵发或散发，全脑快波增多。头颅MRI：平扫、增强及弥散加权成像未见明显异常；双侧颞叶海马波谱提示可能存在右侧海马神经元损伤。患儿开始服用左乙拉西坦，癫痫发作控制3个月后复发，后加用拉莫三嗪，目前(2021年8月，投稿后更新数据)服用左乙拉西坦(0.75 g，每天2次)、拉莫三嗪(12.5 mg，每天2次)，已有4个月无抽搐。末次随访时(2021年8月，投稿后更新数据)患儿12岁，体重60 kg，身高140 cm，虽日常生活不需要协助，但学习能力差，不会写自己的名字。

病例2，男，6个月时因“发育倒退3个月，抽搐2个月”来我科就诊。患儿3个月时在一次“支气管肺炎”后出现发育倒退，表现为起病前可以竖头、追光追物，起病后出现竖头不稳，并逐渐不能追光追物。4个月时出现抽搐，表现为四肢上抬抱球样动作，成串发作，每天发作3~7串/天，每串2~10下，持续约1 min后缓解。完善EEG，发现间断高度失律及暴发抑制图形，全脑多灶持续放电，予托吡酯治疗，未见明显好转。患儿系第1胎第1产，出生体重3.9 kg，出生时无窒息、抢救史，3个月以前生长发育正常，1~2个月可追光追物，可逗笑，2个月时抬头，3个月时竖头稳，后出现倒退。出生后有喂养困难，肌张力减低，呼吸时有喉鸣，诊断为喉软骨发育不良。入院体格检查：体重7.9 kg，身长67 cm，头围41.5 cm，前囟0.5 cm×0.5 cm，追声、追光、追物差，竖头不稳，未发现明显面容异常，不能翻身，不能独坐，四肢活动正常，肌张力降低，病理征阴性。心脏彩色多普勒超声检查示卵圆孔未闭；头颅MRI未发现明显异常；脑电图示多灶性及广泛性尖波、棘波、棘慢波、多棘慢波发放，监测到2次孤立及2次成串痉挛发作；心电图、腹部彩色多普勒超声检查、听觉诱发电位、视觉诱发电位、血尿筛查等正常。遗传学检测：染色体、拷贝数变异检测及线粒体基因检测均正常。全外显子测序发现*NEXMIF*基因有1个c.592C>T (p.Q198X)突变，Sanger测序显示父母均未携带此突变(图2)。依据ACMG变异分类指南，该突变评级为致病性突变(PVS1+PS2+PM2)。入院后托吡酯加量至18.75 mg，每天2次，并予促肾上腺皮质激素(adrenocorticotrophic hormone，ACTH) (16 U/d，24 d)治疗，患儿抽搐症状缓解，复查EEG提示发作间期多灶性棘波、棘慢波、尖慢波、多棘慢波发放。出院后在予泼尼松移行减量治疗中，患儿再次出现频繁抽搐，成串发作，每天发作5~6串，托吡酯加量至25 mg，每天2次，并加用氨己烯酸片(0.375 g，每天2次)治疗。患儿仍有抽搐，每月发作1~2次，并且双眼出现内斜视。末次随访时(2021年8月，投稿后更新数据)患儿1岁7个月，仍然竖头不稳，可以翻身，可以无意识发音，不能喊人。

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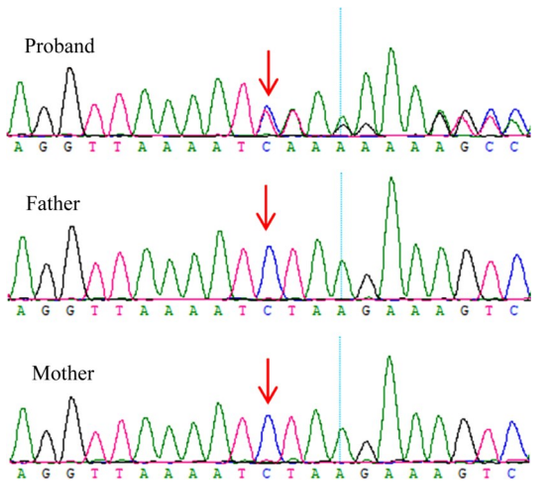


**图1 病例1及其父母Sanger测序结果**

**Figure 1 Sanger sequences of patient 1 and her parents**

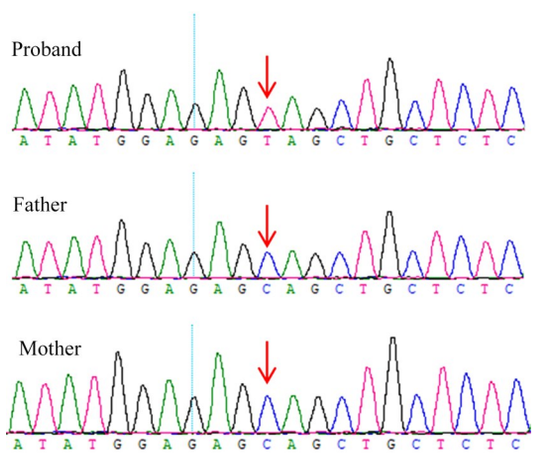


**图2 病例2及其父母Sanger测序结果**

**Figure 2 Sanger sequences of patient 2 and his parents**

## 2 讨 论

2004年Cantagrel等[4]首次发现X染色体臂间倒位inv(X)(p22.3;q13.2)导致*NEXMIF*基因被打断而致病的XLID家系。此后，有关*NEXMIF*基因突变所致智力障碍患者的报道逐渐增多，男女均有，其相关表型被定义为X连锁智力障碍98型(X-linked mental retardation 98，XLMR98)。*NEXMIF*基因，也称*KIAA2022*基因，位于Xq13.2，共192 kb，其开放阅读框包含4个外显子。编码的NEXMIF蛋白质有1 516个氨基酸，在胎儿大脑高表达，成人的大脑皮层、小脑表达高，心、肾、肺等器官表达相对较少[4]。NEXMIF在小鼠胚胎期的表达水平随着胎龄的增大而逐渐上升，并参与神经突起的延伸和神经回路形成[5-7]。*NEXMIF*基因敲除小鼠的突触密度以及突触蛋白表达明显下降，基因敲除的雄性小鼠还有海马突触功能异常的表现[8]，提示NEXMIF可能参与调节突触的生长和功能。行为学分析发现：基因敲除小鼠有孤独症样表现，如社交和沟通减少、重复的行为及学习和记忆能力下降，这些都与人类患者的表型相似[8]。

*NEXMIF*基因突变所致的XLMR98表型复杂，智力障碍是其主要临床表现，可合并癫痫、行为异常、肌张力降低等其他神经系统症状，以及胃食管反流、斜视、生长发育迟缓等其他系统异常。分别以“NEXMIF”和“KIAA2022”为检索词查阅中国知网(CNKI)数据库、万方数据库、在线人类孟德尔遗传数据库(OMIM)、人类基因突变数据库(HGMD)及PubMed数据库(建库至2021年8月，投稿后更新数据)，检索到1篇相关中文文献，48篇相关英文文献，共报道了92例*NEXMIF*基因变异的患者[4, 9-25]。在包括本组2例的94例患者中，男性30例，女性64例，年龄分布从孕$28^{+6}$周胎儿到53岁成人。主要临床表现包括：1)智力障碍(89/90，98.9%)，女性多表现为轻-中度智力障碍(41/61，67.2%)，男性则多为重-极重度智力障碍(19/28，67.9%)。2)癫痫(75/92，81.5%)，发作类型包括失神(47/73，64.4%)、肌阵挛(46/73，63.0%)、强直阵挛(30/73，41.1%)、失张力(30/73，41.1%)、眼睑肌阵挛(17/73，23.3%)、局灶性发作(7/73，9.6%)、痉挛发作(7/73，9.6%)、肌阵挛-失神(5/73，6.8%)，其中女性癫痫患者以肌阵挛更常见(40/57，70.2%)；仅13/74(17.6%)的患者癫痫完全控制，且女性控制情况(5/56，8.9%)较男性差(8/18，44.4%)。3)行为异常(64/90，71.1%)，如孤独症样症状(49/90，54.4%)、注意缺陷多动障碍(23/90，25.6%)、攻击行为(21/90，23.3%)，其中孤独症样症状在男性患者中更常见(21/28，75.0%)。4)其他系统异常包括面容异常(40/91，44.0%)、肌张力降低(35/90，38.9%)、共济失调/协调性差(15/90，16.7%)、小头畸形(17/89，19.1%)、胃食管反流(20/91，22.0%)、斜视(13/91，14.3%)、宫内/生后生长发育迟缓(14/91，15.4%)等。以上数据仅包含相关临床资料详细的患者。男性患者和女性患者临床表现互有重叠，但仍有不同。女性患者多合并难治性癫痫，发作形式以肌阵挛发作、失神发作更常见，其表型多与肌阵挛-失张力癫痫(myoclonia-atonic epilepsy，MAE)及眼睑肌阵挛伴失神(eyelid myoclonia with absence，EMA)这两类综合征重叠[20, 25]，而男性患者常表现为更严重的智力障碍、语言障碍、孤独症样症状。在文献[13]报道的14例女性*NEXMIF*基因突变患者中，12例表现为难治性癫痫，发作形式多为肌阵挛和/或失神发作。本组病例1为女性患儿，该患儿首先出现发育落

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后，7岁时EEG显示异常放电，无抽搐发作。10岁开始出现抽搐，发作形式包括全面性发作、失神发作以及可疑肌阵挛/失张力发作，这与已报道的女性患者表型相似。该患儿使用左乙拉西坦治疗后有3个月的短暂缓解期，后再次出现发作，加用拉莫三嗪后暂时未再发作。后续是否会再次出现抽搐，以及对抗癫痫药物治疗的反应还需继续随访。本组病例2为男性患者，表现为重度发育落后、无语言、婴儿痉挛、四肢肌张力降低，合并喂养困难、喉软骨发育不良、卵圆孔未闭、斜视，与文献[20]报道的男性患者表型相似。既往有少数*NEXMIF*基因突变导致男性癫痫脑病的报道。2013年Van Maldergem等[23]报道了1个携带*NEXMIF*基因突变的家系，该家系中兄弟2人均表现为重度智力障碍、婴儿痉挛、孤独症谱系障碍疾病。哥哥1月龄开始出现痉挛发作、高度失律，对药物的反应不明确。弟弟4岁时出现痉挛发作、高度失律，抗癫痫治疗有效。本组病例2在托吡酯治疗无效后使用ACTH冲击治疗，癫痫控制20余天。在予泼尼松移行减量治疗的过程中再次出现抽搐，加用氨己烯酸片治疗后发作减少，但未完全控制，目前每月仍发作1~2次。

PubMed和HGMD共收录83个*NEXMIF*基因突变，加上本研究发现的2个未报道的突变，一共85个突变。其中无义突变43个，框移突变32个，错义突变2个，拷贝数变异5个，框内缺失突变1个，以及染色体倒位、染色体平衡易位各1个。目前报道的*NEXMIF*基因变异大多为导致NEXMIF蛋白质表达减少的功能缺失变异，其缺失程度可能与疾病的严重程度相关。无义突变、框移突变以及染色体平衡易位、染色体倒位等导致的NEXMIF蛋白质表达减少是*NEXMIF*基因突变致病的原因。值得一提的是，*NEXMIF*基因重复也可能导致NEXMIF蛋白质表达减少。2015年Charzewska等[12]报道了1个XLMR家系，该家系中患者的X染色体13.3区域有一个364 kb大小的重复变异，*NEXMIF*基因就包含在其中。通常完整串联复制将造成基因表达加倍，但研究者[12]通过功能实验发现患者淋巴细胞和成纤维细胞中NEXMIF表达分别减少66%和96%。这个重复变异可能通过诱导阻遏物的表达或改变染色质构象影响基因的转录[26]。*NEXMIF*基因型和表型的关系并没有明显的联系，男性和女性患者表型不同是其主要特点。此外，NEXMIF蛋白质缺失的多少可能与表型的严重程度相关。以女性患者为例，X染色体100%失活的女性患者表型较重，而X染色体失活比例小的患者表型相对较轻[13]。本研究中1个为框移突变，1个为无义突变，预测均可导致蛋白质表达减少。病例1为女性，表型较轻，可能与X染色体非选择性失活比例低有关。

尽管*NEXMIF*基因突变患者临床表现多样，多个系统受累，部分患者表型严重，但还没有证据证实*NEXMIF*基因突变会严重影响患者的寿命。目前已知的年龄最大的患者男性为40岁，女性为53岁，因此携带*NEXMIF*基因突变的患者至少能生存至中年[13, 23]。*NEXMIF*基因突变患者常常有多种系统的症状，需要多学科合作，积极对症治疗。研究[25]报道丙戊酸单用或联用左乙拉西坦、拉莫三嗪、乙琥胺对*NEXMIF*基因突变导致的癫痫有效，但仅有17.6%的患者癫痫可以被完全控制。此外托吡酯、氯巴占、氨己烯酸片及生酮饮食也对部分患者有效，因此临床医生需要根据患者的个人反应进行个体化治疗。

综上，对于不明原因XLID合并孤独症样症状的男性患者，以及表现为智力障碍合并难治性癫痫的女性患者需要考虑*NEXMIF*基因突变的可能，尽早完善基因检测，为遗传咨询提供依据。

**作者贡献声明：**陈施梦　设计并实施研究、起草文章；邓小鹿、彭镜　对文章的知识性内容作批评性审阅；熊娟、陈柏谕　采集数据；何芳、杨丽芬、羊鑫　分析、解释数据；尹飞　对文章的知识性内容作批评性审阅，指导研究、文章撰写。

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