·神经肌肉病·

*DMD*基因新发错义突变致Becker型肌营养不良症一家系临床表型及基因突变分析

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【摘要】 **目的** 总结*DMD*基因新发错义突变导致的Becker型肌营养不良症一家系临床表型及基因突变特点。**方法与结果** 采用第二代测序技术对1例25岁男性Becker型肌营养不良症患者进行基因检测，Sanger测序进一步验证患者之母和妹*DMD*基因c.4449T>G(p.Asn1483Lys)位点，并结合患者及其家族成员的临床资料进行分析。结果显示，患者及其两位舅父具有相同的临床表型，双小腿肌肉呈假性肥大，双下肢近端肌萎缩和肌无力，血清肌酸激酶水平升高。患者基因检测*DMD*基因外显子34 c.4449T>G(p.Asn1483Lys)为错义突变，经检索为新发突变，其母和妹为携带者，结合患者两位舅父临床表现，确诊为Becker型肌营养不良症，该家系为Becker型肌营养不良症家系且存在该基因突变位点的共分离现象。**结论** *DMD*基因外显子34 c.4449T>G(p.Asn1483Lys)为新发错义突变，丰富了*DMD*基因突变谱，为该家系遗传咨询和产前诊断提供了有价值的信息。

【关键词】 肌营养不良，杜氏； 基因； 突变，误义； 系谱

Clinical phenotype and genotype analysis on a family of Becker muscular dystrophy caused by a novel missense mutation of *DMD* gene

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【**Abstract**】 **Objective** To summarize the phenotype and genotype of a family of Becker muscular dystrophy (BMD) caused by a novel missense mutation of *DMD* gene. **Methods and Results** Clinical data of one BMD proband and the family members were collected. Next-generation sequencing technology was used to detect possible gene mutation in the proband, a 25-year-old male BMD patient. Sanger sequencing technology was used to further detect possible mutation of c.4449T>G (p.Asn1483Lys) locus of *DMD* gene in the proband's mother and younger sister. The analysis was carried out combined with clinical data of the proband and other family members. Results showed the patient had the same phenotype as his two uncles (mother's brothers), who presented pseudohypertrophy of calf muscles, atrophy and weakness of proximal lower extremities and elevated serum creatine kinase (CK). Gene mutation analysis demonstrated a novel missense mutation c.4449T>G (p.Asn1483Lys) in exon 34 of *DMD* gene in the proband. The proband's mother and younger sister were carriers of mutated gene. Combined with the clinical manifestations of proband's uncles, the patient was clearly diagnosed as BMD, and the family was clearly diagnosed as BMD pedigree. Besides, there was a common separation phenomenon in the family. **Conclusions** The study described a novel missense mutation in exon 34 c.4449T>G (p.Asn1483Lys) of *DMD* gene which caused BMD. This enriches the mutation map of *DMD* gene, and also provides valuable

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information for genetic counseling and prenatal diagnosis.

【Key words】 Muscular dystrophy, Duchenne; Genes; Mutation, missense; Pedigree

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假肥大型肌营养不良症是一种较为常见的遗传性肌肉病，共分为两型，即Duchenne型肌营养不良症（DMD）和Becker型肌营养不良症（BMD）[1]；以进行性加重的对称性肌无力和肌萎缩为临床特点，主要累及骨骼肌，发病过程中可伴认知功能障碍和心肌损害。其中，Duchenne型患者大多症状严重，伴心肌损害，一般于12岁前即失去行走能力；而Becker型患者病情较轻，较少累及心脏，12岁时尚能行走，可以有正常的预期寿命[2]。两型肌营养不良症均为X连锁隐性遗传性疾病，是由于*DMD*基因突变引起的抗肌萎缩蛋白（dystrophin）结构和功能异常所致[3-5]。该基因位于染色体Xp21，其主要突变类型为外显子缺失或重复，占70%～80%，其次为点突变，占20%～30%[6-7]。而点突变导致的无义突变较为常见，错义突变则极为罕见[8-13]。笔者采用第二代高通量测序技术[简称第二代测序技术（NGS）]对一诊断明确的*DMD*基因非缺失和（或）重复突变的Becker型肌营养不良症家系进行基因检测，并进行共分离分析，经检索为新的致病性错义突变，可为该家系的遗传咨询和产前基因诊断提供一些具有临床价值的信息。

病例资料

患者 男性，25岁。主因进行性双下肢近端无力20年，进行性加重5年余，于2017年12月5日至我院神经科门诊就诊。患者自5岁（1997年）开始无明显诱因出现双下肢无力，自觉跑步比同龄人慢，平地行走和上楼轻松；但随年龄的增长肌无力症状逐渐加重，自2012年始出现上楼、蹲起困难，但尚可行走、慢跑，与此同时双侧上肢近端肌力减弱但远端肌力尚可，写字、打字如常。2013年至当地医院就诊，未给出明确诊断，为求进一步诊断与治疗，遂至我院就诊。患者自发病以来精神、睡眠尚可，饮食正常，大小便正常。

既往史、个人史及家族史 患者生长发育里程碑无明显异常，其父母及妹无类似症状，父母非近亲婚配，母亲（49岁）身体健康，父亲因意外事故于40岁（2006年）去世，生前身体健康。其妹（23岁）身体健康，无类似症状。患者大舅父（54岁）和三舅父（51岁）中学时运动能力均正常，于30岁后开始出现蹲起和上楼困难，目前尚能行走，外院实验室检查血清肌酸激酶（CK）水平升高、双侧小腿肥大。其余亲属无类似疾病病史，其他家族遗传性疾病无可述及。

体格检查 神志清楚，语言流利，高级智能正常，脑神经检查未见明显异常。双侧上肢近端肌力4^{+}级、远端5级，双侧下肢肌力4^{+}级；四肢肌张力均降低；双侧腓肠肌轻度肥大，触之坚硬；腰椎轻微前凸；无翼状肩胛、跟腱挛缩，可足尖行走，足跟行走欠佳，呈鸭步步态；Gowers征阳性；双上肢腱反射正常，双下肢膝反射和踝反射减弱，共济运动和深浅感觉未见明显异常，病理反射未引出。

辅助检查 实验室检查：血清乳酸脱氢酶（LDH）228 U/L（114～240 U/L）、肌酸激酶2554 U/L（25～200 U/L）、肌酐45 μmol/L（53～115 μmol/L），血常规、肝功能试验、水电解质各项指标均于正常值范围。电生理学检查：心电图呈窦性心动过速，心率107次/min，左心室高电压。心脏彩超提示主动脉窦部增宽，左心室收缩功能正常，射血分数（EF）56%（55%～80%）。

基因检测 征得患者同意，采用第二代测序技术对其进行*DMD*基因检测。根据北京智因东方转化医学研究中心检测结果，存在*BSCL2*基因外显子2 c.3G＞C（p.Met1Ile）错义突变（图1a）和*DMD*基因外显子34 c.4449T＞G（p.Asn1483Lys）错义突变（图1b）。鉴于患者近端肌无力与*BSCL2*基因突变导致的远端型遗传性运动神经病5型之临床表现不相符，推测其临床表型来自*DMD*基因突变。因此征得患者母亲和妹妹知情同意，对其母和妹*DMD*基因c.4449T＞G（p.Asn1483Lys）位点进行Sanger测序，结

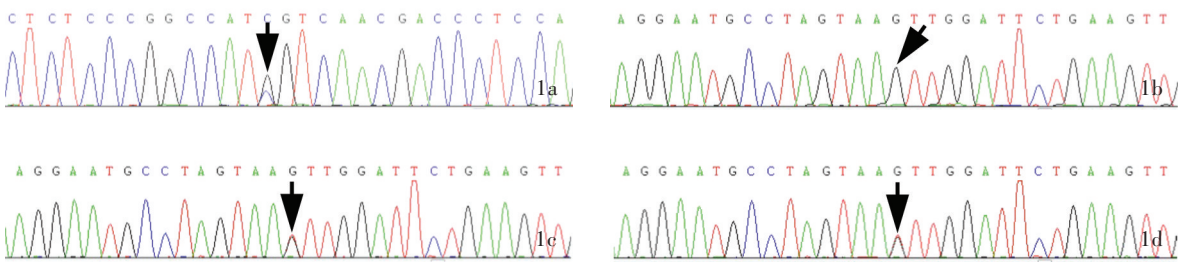

图1 基因检测结果 1a 患者*BSCL2*基因c.3G>C(p.Met1Ile)杂合突变(箭头所示) 1b 患者*DMD*基因c.4449T>G(p.Asn1483Lys)杂合突变(箭头所示) 1c 患者之母*DMD*基因c.4449T>G(p.Asn1483Lys)杂合突变(箭头所示),与患者一致 1d 患者之妹*DMD*基因c.4449T>G(p.Asn1483Lys)杂合突变(箭头所示),与患者一致

Figure 1 The findings of gene sequencing The proband had a heterozygous mutation c.3G>C (p.Met1Ile) in *BSCL2* gene (arrow indicates, Panel 1a). The proband had a heterozygous mutation c.4449T>G (p.Asn1483Lys) in *DMD* gene (arrow indicates, Panel 1b). The proband's mother had the same heterozygous c.4449T>G (p.Asn1483Lys) mutation in *DMD* gene as the proband's (arrow indicates, Panel 1c). The proband's younger sister had the same heterozygous c.4449T>G (p.Asn1483Lys) mutation in *DMD* gene as the proband's (arrow indicates, Panel 1d).

果显示,患者之母和妹均携带与其相同的突变基因(图1c,1d),证实其母和妹携带与患者相同的错义突变。根据美国医学遗传学和基因组学会(ACMG)和美国分子病理学会(AMP)制定的基因变异解读标准和指南[14],提示c.4449T>G(p.Asn1483Lys)错义突变可能致病。该基因突变位点在dbSNP(http://www.ncbi.nlm.nih.gov/SNP/)、ExAC(http://exac.broadinstitute.org/)、千人基因组(http://www.internationalgenome.org/)等数据库中均未收录,为新发突变,目前国内外未见文献报道。结合患者两位舅父具有类似的临床表现,且*DMD*基因位于X染色体,可以推测患者基因突变遗传自母系,而其母及两位舅父的*DMD*基因则均遗传自其外祖母;患者母亲、妹妹及其外祖母均为携带者。结合患者临床表现,以及实验室和基因检测结果确诊为Becker型肌营养不良症,该家系确定为X连锁隐性遗传性Becker型肌营养不良症家系(图2)。

治疗与随访 确诊后患者在我院门诊接受药物治疗,予糖皮质激素醋酸泼尼松(15 mg/d)联合改善线粒体功能之药物艾地苯醌(30 mg/次、3次/d)治疗,除定期在门诊复查血清心肌酶谱变化和心脏超声外,同时嘱患者如出现肢体乏力症状加重或有明显肌肉疼痛时须及时就诊。至今已随访6个月,病情无明显变化。

讨 论

假肥大型肌营养不良症为等位基因疾病,无论是Duchenne型或Becker型其致病基因均为*DMD*基因,该基因定位于X染色体短臂2区1带(Xp21),长度约为2.40×10^3 bp,是目前发现的人类最大的基因之一,占整个X染色体的2%以及人类基因组的0.5‰[4]。*DMD*基因共有79个外显子,所编码的蛋白质产物被命名为dystrophin蛋白。Duchenne型肌营养不良症患者病情较为严重,12岁前即失去行走能力,需坐轮椅,大多数患者可于20~30岁死于呼吸道感染或心力衰竭。Becker型肌营养不良症的临床表现与Duchenne型相似,但进展缓慢,程度较轻,12岁尚可行走且较少累及心脏。本文患者年龄为25岁,至今尚能行走,双侧小腿肥大坚硬,上楼困难,Gowers征阳性,心脏仅轻度受累,符合Becker型肌营养不良症的诊断。

根据可读框(ORF)假说[15],Duchenne型肌营养不良症患者绝大多数是由移码突变所致,即可读框中插入或缺失1~2个或多个碱基打断*DMD*基因中正常的三联密码子排列,使变化点下游的碱基出现位移,导致可读框发生移码突变,致使*DMD*基因蛋白质合成产物——dystrophin蛋白的合成停止,从而诱发Duchenne型肌营养不良症;若缺失或插入的碱基仅使一个三联密码子发生异常改变,可读框仍保留,尚有部分dystrophin蛋白表达,则临床症状较轻,表现为Becker型肌营养不良症。Bladen等[8]对Duchenne型和(或)Becker型肌营养不良症患者的基因检测资料进行统计,7149例患者中错义突变者仅为30例,占0.42%;Okubo等[9]共统计1167例Duchenne型和295例Becker型肌营养不良症患者,在发生错义突变者中Duchenne型3例(0.26%)、Becker型5例(1.69%);而Juan-Mateu等[10]统计的176例Becker型肌营养不良症患者中错义突变者仅

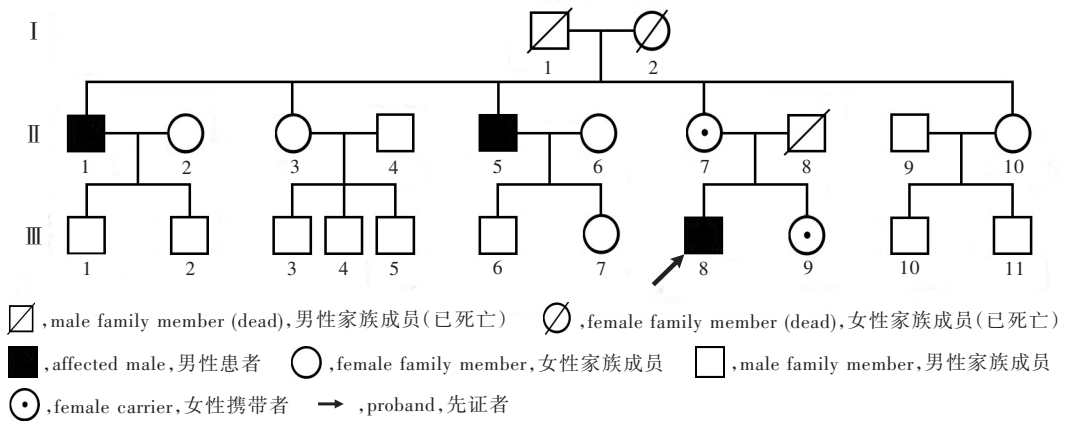

图2 BMD家系图

Figure 2 The pedigree of BMD.

1例,占0.57%。由此可见,错义突变在*DMD*基因突变形式中较为罕见。本文患者为*DMD*基因外显子34 c.4449T > G(p.Asn1483Lys)错义突变,为新发突变,目前国内外尚无文献报道,是第1483位甲硫氨酸突变为赖氨酸;其外显子34位于杆状区,参与编码Dp427蛋白,该蛋白主要表达于脑、肌肉等组织中,本文患者外显子34的错义突变可导致Dp427蛋白结构或功能异常,从而出现相应临床表型;其两位舅父亦有类似临床表现,患者基因突变遗传自其母亲,而母亲及两位舅父的*DMD*基因均遗传自其外祖母,提示患者母亲和外祖母均为携带者,患者之妹经基因检测证实亦为携带者。

与无义突变、移码突变、剪接位点突变等致病性突变相比,确定错义突变是否为致病性突变的难度更大,因为前者可通过影响基因结构而改变编码氨基酸顺序,继而导致其所组成蛋白质的功能异常;而错义突变则不然,其致病性需视顺序发生异常改变的编码氨基酸的位置而定,唯有位于重要活性区域的编码氨基酸顺序改变才会影响蛋白质的功能,从而产生致病性。从基因学角度而言,判断某一错义突变是否具有致病性,需确定其是否引起剪接位点的变化而致异位剪接、是否在家系中共分离?若其家系中仅有患者才存在错义突变,而正常表型者无此特定错义突变,则提示此特定错义突变可能是致病性突变。如果在其他无血缘关系的相同疾病家系中也发现了相同的基因和错义突变,则可以确定该错义突变即为致病性突变。如果无两个以上家系,则可通过敲除小鼠等动物该基因位点的方法,建立动物模型,观察基因缺失动物是否出现与患者相似的临床表型,如果有,则可以确定该错义突变为致病性突变。

本文家系中患者及其两位舅父具有相似临床表型,提示存在相同的基因突变,但患者两位舅父拒绝接受基因检测,为了解家系中其他成员的基因突变情况,对患者母亲和妹妹进行了基因检测,二者均存在*DMD*基因外显子34 c.4449T > G(p.Asn1483Lys)错义突变,在家系中存在共分离现象。十分遗憾,未能获得患者两位姨母和舅父的基因检测信息。

药物治疗、基因治疗和康复疗法是Duchenne型和Becker型肌营养不良症患者的主要治疗手段。其中,糖皮质激素、血管紧张素转换酶抑制剂(ACEI)、艾地苯醌、沙丁胺醇等药物为首选治疗药物,尤其是口服糖皮质激素是标准治疗方法[16-18]。但治疗过程中,应考虑激素治疗的不良反应,如行为改变、骨质疏松、白内障、体重增加、库欣样外观等[19]。基因治疗主要包括外显子跳跃、无义突变通读和腺相关病毒介导的微小抗肌萎缩蛋白(AAV *micro-dystrophin*)基因替代治疗等,这些治疗方法已取得一定成果,具有较好的应用前景[20-22]。此外,运动疗法或物理治疗等康复疗法对于提高患者的生活质量、延缓疾病进展也具有一定作用[2]。上述治疗方法虽然具有较好的应用前景,然而目前均未能达到有效控制病情的目的,做好产前诊断、控制患病胎儿的出生方为重要的预防措施。因为该病是X连锁隐性遗传性疾病,已知母亲为携带者,其男胎患病的可能性约为50%[4],通过产前诊断可明确胎儿*DMD*基因情况。目前,取胎儿绒毛细胞样本进行

*DMD*基因检测的时间，最早可于妊娠第11～13周进行，亦可以于妊娠18周后行羊膜腔穿刺术抽取羊水标本进行检测，必要时可在妊娠24周后抽取脐血进行检测[23-24]。

Duchenne型和Becker型肌营养不良症为临床常见的X连锁隐性遗传性肌肉病，目前临床上尚无有效的治疗方法，遗传咨询及产前诊断至关重要。本研究通过第二代测序技术和生物信息学分析，明确诊断1例*DMD*基因外显子34错义突变引起的Becker型肌营养不良症，并发现一新发突变的基因位点，丰富了*DMD*基因突变谱，同时也为该家系进行准确的遗传咨询及产前诊断提供参考依据。

利益冲突 无

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American Epilepsy Society (AES) 2019 Annual Meeting

Time: December 6–10, 2019

Venue: Baltimore Convention Center, Baltimore MD, USA

Website: https://meeting.aesnet.org/

American Epilepsy Society (AES) 2019 Annual Meeting will take place in Baltimore Convention Center, Baltimore MD, USA on December 6–10, 2019. From best practices to breakthrough research, the AES 2019 Annual Meeting offers the most extensive education on everything epilepsy and an unparalleled opportunity to network with the brightest minds in the field.

The AES Annual Meeting offers high-quality educational programming across diverse work settings, professional roles, and experience levels. Whether you are just starting with the specialty, have a limited background in epilepsy, or are highly fluent with complex topics, you will find sessions and content relevant to your needs.

Symposia provide the major educational activities at the meeting. Topics range from clinically-oriented presentations, reviewing common issues in epilepsy to more complex topics combining basic sciences and clinical neurology. While target audiences differ, all symposia include discussion of clinically-relevant information.

Special Interest Groups (SIG) offer information and networking for attendees with similar interests, in sessions organized by AES members. Although the sizes of SIG sessions vary, all lend themselves to active participation and dialogue.

Special Lectures recognize the accomplishments of the distinguished leaders in clinical epilepsy and research. The Judith Hoyer Lecture in Epilepsy is delivered by an AES President Emeritus. The Lombroso Lecture is given by an invited member who has greatly advanced the collective understanding of epilepsy.

The Annual Course encourages in-depth exploration of important topics related to epilepsy, focused on clinical care, including review of the science underlying the topics, reviews of clinical research, and discussion of the associated clinical implications. The Annual Course includes a mixture of educational lectures, clinical vignettes, and panel discussions.

Investigators Workshops highlight exciting developments in basic, translational, and clinical epilepsy research in a format promoting interactive discussion. Speakers include established and junior epilepsy investigators, as well as researchers from other fields.

Skills Workshops deliver hands-on and interactive learning opportunities in focused clinical areas or basic science research skills. Attendance at each workshop is limited to a small number of participants to allow optimal interaction. Advanced registration and an additional fee are required.

As the world´s largest educational and scientific event for epilepsy professionals, the AES Annual Meeting is an ideal venue for clinicians and scientists to present research results to a global audience. Take advantage of this great opportunity to share your knowledge with fellow colleagues.