

·论著·

LPIN1 基因突变所致先天性肌病 1 例报道并文献复习

高华杰, 季苏琼, 马雪, 毕抓劲, 张清, 杨梦歌, 卜碧涛

作者单位
华中科技大学同济医学院附属同济医院神经内科
武汉 430000
收稿日期
2021-05-09
通讯作者
卜碧涛
bubitao@tjh.tjmu.edu.cn

摘要 **目的:**报道 1 例 LPIN1 基因突变引起的先天性肌病,加强对常染色体隐性遗传的 LPIN1 基因突变相关表型的认识。**方法:**收集 1 例先天性肌病患者的临床表现、实验室检查、影像学表现、肌肉病理以及基因检测结果,结合文献复习进行分析讨论。**结果:**患者为男性儿童,自幼肢体肌力差。体格检查见肌张力低下,肢体肌力差,Gower(+)。血肌酸激酶升高。肌电图示肌源性损害。肌肉核磁见双侧大、小腿肌群广泛受累。肌肉病理见 I 型纤维占明显优势,约 70%~80%。Sanger 测序示 LPIN1 基因纯合突变(c.357_358insCT)。搜索既往报道的 LPIN1 基因相关肌病患者 66 例,所有患者均表现为横纹肌溶解(肌酸激酶显著增高、肌痛、血红蛋白尿),肌肉核磁表现无特异性,最常见合并心肌受累。**结论:**本病例系国内首次报道 LPIN1 基因突变所致的先天性肌病。肌肉活检有助于病理诊断,基因检测对遗传方式确定具有决定意义。

关键词 先天性肌病;横纹肌溶解;LPIN1 基因

中图分类号 R741;R741.02;R741.05;R746 **文献标识码** A **DOI** 10.16780/j.cnki.sjssgncj.20210034

本文引用格式:高华杰, 季苏琼, 马雪, 毕抓劲, 张清, 杨梦歌, 卜碧涛. LPIN1 基因突变所致发作性肌痛和肌红蛋白尿症 1 例报道并文献复习[J]. 神经损伤与功能重建, 2021, 16(10): 572-575.

LPIN1 Mutation-related Congenital Myopathy: A Case Report and Literature Review GAO Hua-jie, JI Su-qiong, MA Xue, BI Zhua-Jin, ZHANG Qing, YANG Meng-Ge, BU Bi-tao. Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

Abstract Objective: Report a case of LPIN1 mutation-related congenital myopathy, and investigate the phenotypes associated with the autosomal recessive LPIN1 mutation. **Methods:** A patient with congenital myopathy was described. The clinical data, laboratory test results, muscle pathology, and gene screening were reported. Relevant literature was reviewed for further analysis. **Results:** The patient was a male child who had suffered poor muscle strength since young. Physical examination revealed hypotonia, poor limb muscle strength, and Gower's sign. Serum creatine kinase (CK) level was increased. Electromyogram (EMG) showed myogenic damage. Muscle MRI showed the thigh and calf muscles on both sides were extensively damaged. Muscle pathology demonstrated that type I fibers were dominant at about 70%~80%. Homozygous mutation of the LPIN1 gene (c.357_358insCT) was identified by Sanger sequencing. We collected data of 66 cases of LPIN1 gene-related myopathy from MEDLINE. All patients presented with rhabdomyolysis (significant increase in creatine kinase, myalgia, and hemoglobinuria). Muscle MRI manifestation was largely normal. Myocardial involvement was the most common combined type of congenital myopathy. **Conclusion:** This is the first report in the country of congenital myopathy due to an autosomal recessive inheritance of a LPIN1 mutation. Muscle biopsy is useful for diagnosis, and gene analysis is crucial in confirming the inherited pattern.

Key words congenital myopathy; rhabdomyolysis; LPIN1 gene

先天性肌病是一组临床和遗传异质性肌肉疾病^[1,2],其临床表现为出生时或出生后肌张力低下、肌无力、先天性骨骼畸形,伴或不伴运动发育迟滞,可有心肌、呼吸肌及眼肌异常但较少见,病情相对稳定或呈缓慢进展^[3-5]。现报道 1 例先天性肌病并对相关进展进行文献回顾。

1 资料与方法

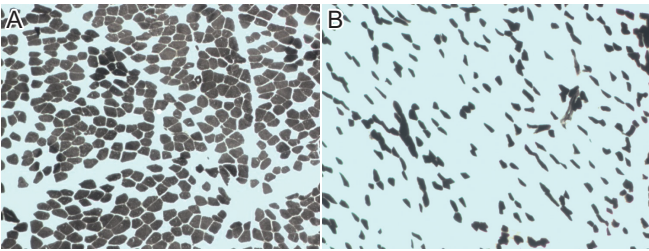
1.1 病例资料

患者,男,9 岁 7 个月,主因“四肢无力 9 年余,加重伴右侧肢体阵发性疼痛不适 3 天”

于 2017 年 3 月 28 日入院。患者自幼肢体肌力差,2 岁时才能自行行走,伴明显的行走不稳,反复就医。3 岁时肌活检结果提示先天性肌病可能,电镜示脂质沉积性肌病。给予营养神经、改善肌肉代谢等对症支持治疗,患者病情反复波动-好转。3 天前无明显诱因逐渐出现右侧肢体阵发性疼痛,以右侧肘关节及小腿为甚,伴右肘关节曲伸受限,左侧手指间断不自主呈爪形捏合,动作笨拙,行走不利,易摔跤。既往史:患儿顺产,自幼体弱,体型偏瘦,体力较同龄人差,智力发育尚可。否认肝炎、结核等传染病接触史,

否认药物及食物过敏史。家族史:父母近亲婚配,弟弟无类似病史。

入院查体:神志清楚,吐词清晰,双瞳孔等大等圆,直径3 mm,对光反射灵敏,眼球活动自如;行走不稳,四肢肌力4级,肌张力减低,腱反射可,深浅感觉未见明显异常,病理征(-);颈软、无抵抗,克氏征(-),Gower(+)。胸部、腹部查体未见明显异常。入院前辅助检查:2011年我院右侧腓肠肌肌肉活检:HE示肌纤维大小形态基本正常,未见坏死及再生,未见核内移,未见异常空泡或包涵体,未见炎症细胞浸润,未见小血管炎症,结缔组织增生不明显;ATP未见群组,I型纤维占明显优势,约70%~80%,II型纤维较少,大小形态基本正常,未见肯定萎缩纤维,见图1。电镜有串珠样脂质沉积。2011年外院查DMD基因未见异常。

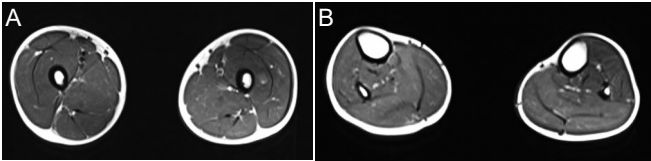


注:(A)Ph 4.3;(B)Ph 10.8
图1 患者右侧腓肠肌肌肉活检ATP酶染色(×100)

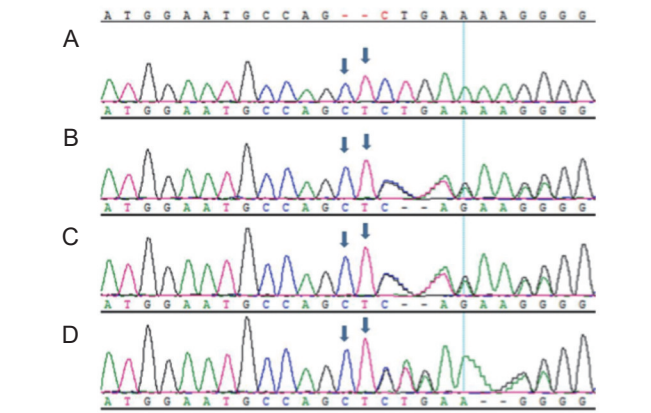
入院后辅助检查:血常规、甲状腺功能全套、甲状腺免疫全套、葡萄糖、糖化血红蛋白、凝血四项未见明显异常。心梗三项:肌红蛋白>1200 ng/mL、肌酸激酶MB型同工酶>300 ng/mL。生化全套(含血糖):谷丙转氨酶 684 U/L、谷草转氨酶 1479 U/L、肌酸激酶>20000 U/L、乳酸脱氢酶>1867 U/L。尿常规:茶色,红细胞29.6/μL。心电图:窦性心律,心电图正常范围。彩超心脏:心脏形态结构及瓣膜活动未见明显异常,EF67%。磁共振-大、小腿平扫:双侧股二头肌下段、双侧股直肌、双小腿腓肠肌、比目鱼肌、胫骨前肌、胫骨后肌、腓骨长短肌走行区异常信号,见图2。考虑诊断为先天性肌病。

为缓解患者疼痛症状,经患者家属同意后给予甲基强的松龙120 mg静滴,1次/d,同时给予护胃、补钾、补钙等对症治疗;患者及其父母、弟弟抽血查遗传性肌病基因。基因检测结果显示:患者LPIN1基因c.357_358insCT纯合突变,见图3。第1次复查血心梗三项:肌红蛋白57.3 ng/mL、肌酸激酶MB型同工酶7.9 ng/mL;生化全套(含血糖):谷丙转氨酶312 U/L、谷草转氨酶107 U/L、肌酸激酶1291 U/L、乳酸脱氢酶1413U/L。甲基强的松龙改60 mg静滴,1次/d,余治疗不变。第2次

复查血心梗三项:肌红蛋白34.8 ng/mL、肌酸激酶MB型同工酶4.5 ng/mL;生化全套(含血糖):谷丙转氨酶169 U/L、谷草转氨酶57 U/L、肌酸激酶261 U/L、乳酸脱氢酶751 U/L。激素由静脉滴注改为强的松30 mg口服,1次/d,维持治疗。激素治疗后患者肌酸激酶水平显著降低,疼痛症状明显减轻。



注:(A)双侧大腿;(B)双侧小腿;
图2 患者大、小腿肌肉核磁影像(2017年4月)



注:(A)患者本人;(B)患者母亲;(C)患者父亲;(D)患者弟弟
图3 患者家系遗传性神经肌肉病基因检测(2017年6月)

1.2 方法

收集资料并分析。通过Pubmed数据库,输入关键词“LPIN1”和“myopathy”或“Rhabdomyolysis”,收集所有相关文献(检索时间截止2021年03月15日),得到所有关于先天性肌病和LPIN1基因的相关病例报道。采用描述性统计对符合条件的所有病例从临床表现、影像学表现、病理类型和基因结果进行分析。

2 结果

共检索文献31篇(不包含综述)。共搜索到LPIN1基因相关肌病患者66例,91%为儿童,9%为成人(≥18岁)。所有患者均表现为横纹肌溶解(肌酸激酶显著增高、肌痛、血红蛋白尿),15%的患者心肌受累(其中40%猝死),呼吸肌受累未见。14%患者做过病理检查(其中57%为尸检)。所有患者均做了基因检测(其中纯合突变占72%,杂合突变占28%)。

3 讨论

先天性肌病是由遗传决定的肌肉结构蛋白缺陷引

起的异质性疾病^[2]。患者发病年龄早,主要表现为肌张力水平低下、肢体无力,病情相对稳定或呈缓慢进展。发病率估计约为1:25000^[6]。先天性肌病患者肌肉核磁提示肢体近端骨骼肌脂肪化,以臀大肌、股直肌外的股四头肌为重^[2]。肌电图呈肌源性损害或者正常。肌酸激酶水平通常正常或升高。根据肌肉活检特征,先天性肌病通常分为5类:轴空性肌病、中心核肌病、杆状体肌病、肌球蛋白储积病和先天性肌纤维类型不均^[1,7]。先天性肌病的诊断要点包括临床评估(症状、体征、详细的家族史),肌肉核磁检查,血清肌酸激酶测定,肌电图。但鉴于肌酸激酶水平通常正常或轻度升高,对于先天性肌病的诊断并不是特别有帮助,而肌电图也可以是正常的。因此,肌肉活检(包括组织学、免疫组织化学和电子显微镜检查)、基因检测作为一种新兴的检查手段越来越多的应用于临床诊断。该病例患者表现为横纹肌溶解(肌酸激酶显著增高、肌痛、血红蛋白尿症)。横纹肌溶解症的病因可分为创伤性和非创伤性因素^[8-11]。其中,创伤性因素有运动过量、挤压;非创伤性因素有药物(他汀类、贝特类、中药甘草制剂)、内分泌疾病(低钾血症、糖尿病、原发性醛固酮增多症、甲状腺机能减退症等)、中毒(食物、百草枯等毒物),其他原因如感染、遗传性和自身免疫性疾病等^[12,13]。

本次报告的患者自幼以肢体无力起病,此次发病伴有肌痛,茶色尿,肌酸激酶水平增高,神经电生理提示肌源性损害,肌肉核磁示双侧大、小腿肌肉异常信号,考虑提示肌炎或肌病可能,肌肉活检提示本患者考虑先天性肌病伴I型纤维优势,诊断为先天性肌病。患者LPIN1基因c.357_358insCT纯合突变(图2),为常染色体隐性遗传,主要临床表现为复发性横纹肌溶解、肌肉疼痛、肌无力等等^[14],与本例患者症状相符。因此推测,LPIN1基因c.357_358insCT纯合变异可能为该受检者的致病突变。其父亲、母亲、弟弟均在LPIN1基因上检出c.357_358insCT杂合变异(图2);因此推测,患者在LPIN1基因c.357_358insCT纯合变异分别遗传自其父母(图4)。人类LPIN1基因定位于2号染色体2p25.1处,基因长度为2672 bp,编码890个氨基酸^[15]。LPIN1基因最初是Langner在fld(fatty liver dystrophy)基因突变小鼠中发现的^[16],Zeharia等^[17]认为LPIN1的常染色体隐性突变是严重复发横纹肌溶解的原因。LPIN1主要在骨骼肌和脂肪组织中表达^[15,18,19]。LPIN1在肌肉中显著表达,是一种依赖于 Mg^{2+} 的磷脂酸磷酸水解酶,催化磷脂酸去磷酸化生成二酰甘油和无机磷酸盐^[20]。LPIN1突变会造成多种疾病,迄今为止已有

48 例患者共计 46 个 LPIN1 突变位点被报道, 见图 5^[21]。我们首次报告了 LPIN1 基因 c.357_358insCT 纯合变异见于先天性肌病。

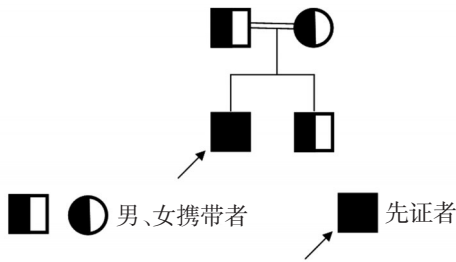


图4 本例患者家系图

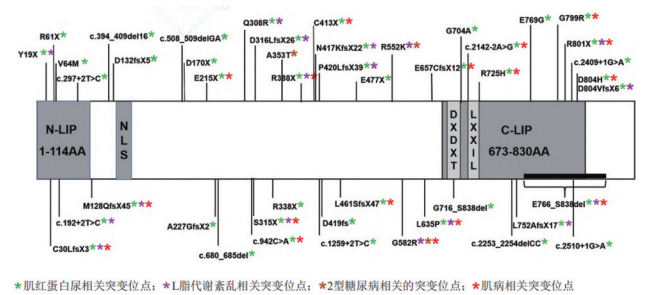


图5 LPIN1 蛋白结构及已报道的人类LPIN1突变位点^[21]

幼年起病、横纹肌溶解是该病例的主要特点。1例 LPIN1 基因纯合突变的患者,只有母亲为携带者,多次横纹肌溶解发作糖皮质激素(地塞米松)治疗有效^[22]。这与糖皮质激素具有抗炎作用而且影响碳水化合物、蛋白质、脂肪代谢有关。已报道的患者均有横纹肌溶解表现,LPIN1 病的预后差,有报道 1/3 的患者在横纹肌溶解危象中死亡^[23]。

目前还没有可以治愈先天性肌病的方法,只能给予对症治疗^[24,26]。如关节挛缩及脊柱侧弯者给予矫形治疗;吞咽障碍和喂养困难可予吞咽训练或鼻饲,甚至胃造瘘术以保证充足的营养支持;呼吸功能障碍者给予呼吸训练、肺部物理治疗,必要时可给予机械通气支持。因此,先天性肌病患者的治疗需要多学科共同参与,如神经科、康复医学科、儿科、整形外科、神经心理科等^[25,26]。基因诊断将为患者家庭的遗传咨询提供帮助,明确的基因诊断可以通过产前诊断,降低下一胎及下一代患相同疾病的风险。目前先天性肌病尚无根治方法,但已有动物实验显示基因替代治疗将是单基因遗传先天性肌病最具希望的治疗措施^[27]。

参考文献

- [1] Cassandrini D, Trovato R, Rubegni A, et al. Congenital myopathies: clinical phenotypes and new diagnostic tools[J]. Ital J Pediatr, 2017, 43: 101.
- [2] 徐春晓, 赵亚雯, 张巍, 等. 常见类型先天性肌病骨骼肌磁共振成像改变特点研究[J]. 中国神经免疫学和神经病学杂志, 2015, 22: 177-181.
- [3] Maggi L, Scoto M, Cirak S, et al. Congenital myopathies--clinical features and frequency of individual subtypes diagnosed over a 5-year

period in the United Kingdom[J]. Neuromuscul Disord, 2013, 23: 195-205.

[4] Romero NB, Clarke NF. Congenital myopathies[J]. Handb Clin Neurol, 2013, 113: 1321-1336.

[5] Ravenscroft G, Bryson-Richardson RJ, Nowak KJ, et al. Recent advances in understanding congenital myopathies[J]. F1000Res, 2018, 7: F1000 Faculty Rev-1921.

[6] Tubridy N, Fontaine B, Eymard B. Congenital myopathies and congenital muscular dystrophies[J]. Neurol Clin, 2001, 14: 575-582.

[7] North KN, Wang CH, Clarke N, et al. Approach to the diagnosis of congenital myopathies[J]. Neuromuscul Disord, 2014, 24: 97-116.

[8] Giannoglou GD, Chatzizisis YS, Misirli G. The syndrome of rhabdomyolysis: Pathophysiology and diagnosis[J]. Eur J Intern Med, 2007, 18: 90-100.

[9] Chavez LO, Leon M, Einav S, et al. Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice[J]. Crit Care, 2016, 20: 135.

[10] Zutt R, van der Kooij AJ, Linthorst GE, et al. Rhabdomyolysis: review of the literature[J]. Neuromuscul Disord, 2014, 24: 651-659.

[11] Nance JR, Mammen AL. Diagnostic evaluation of rhabdomyolysis[J]. Muscle Nerve, 2015, 51: 793-810.

[12] Fernandes PM, Davenport RJ. How to do it: investigate exertional rhabdomyolysis (or not)[J]. Pract Neurol, 2019, 19: 43-48.

[13] Chan EK, Kornberg AJ, Ryan MM. A diagnostic approach to recurrent myalgia and rhabdomyolysis in children[J]. Arch Dis Child, 2015, 100: 793-797.

[14] Pizzamiglio C, Lahiri N, Nirmalanathan N, et al. First presentation of LPIN1 acute rhabdomyolysis in adolescence and adulthood[J]. Neuromuscul Disord, 2020, 30: 566-571.

[15] Péterfy M, Phan J, Xu P, et al. Lipodystrophy in the fld mouse results from mutation of a new gene encoding a nuclear protein, lipin[J]. Nat Genet, 2001, 27: 121-124.

[16] Langner CA, Birkenmeier EH, Ben-Zeev O, et al. The fatty liver dystrophy (fld) mutation. A new mutant mouse with a developmental

abnormality in triglyceride metabolism and associated tissue-specific defects in lipoprotein lipase and hepatic lipase activities[J]. J Biol Chem, 1989, 264: 7994-8003.

[17] Zeharia A, Shaag A, Houtkooper RH, et al. Mutations in LPIN1 cause recurrent acute myoglobinuria in childhood[J]. Am J Hum Genet, 2008, 83: 489-494.

[18] Donkor J, Sariahmetoglu M, Dewald J, et al. Three mammalian lipins act as phosphatidate phosphatases with distinct tissue expression patterns[J]. J Biol Chem, 2007, 282: 3450-3457.

[19] Donkor J, Zhang P, Wong S, et al. A conserved serine residue is required for the phosphatidate phosphatase activity but not the transcriptional coactivator functions of lipin-1 and lipin-2[J]. J Biol Chem, 2009, 284: 29968-29978.

[20] Han GS, Wu WI, Carman GM. The *Saccharomyces cerevisiae* Lipin homolog is a Mg²⁺-dependent phosphatidate phosphatase enzyme[J]. J Biol Chem, 2006, 281: 9210-9218.

[21] 卢淑娟, 吕赵劫, 王志浩, 等. LPIN1 与人类疾病研究进展[J]. 生命科学, 2020, 32: 1-8.

[22] Meijer IA, Sasarman F, Maftei C, et al. LPIN1 deficiency with severe recurrent rhabdomyolysis and persistent elevation of creatine kinase levels due to chromosome 2 maternal isodisomy[J]. Mol Genet Metab Rep, 2015, 5: 85-88.

[23] Bergounioux J, Brassier A, Rambaud C, et al. Fatal rhabdomyolysis in 2 children with LPIN1 mutations[J]. J Pediatr, 2012, 160: 1052-1054.

[24] Claeys KG. Congenital myopathies: an update[J]. Dev Med Child Neurol, 2020, 62: 297-302.

[25] Wang CH, Bonnemant CG, Rutkowski A, et al. Consensus statement on standard of care for congenital muscular dystrophies[J]. J Child Neurol, 2010, 25: 1559-1581.

[26] 先天性肌病. 神经内科疾病诊疗指南[M]. 第3版. 北京: 科学出版社, 2013: 696-698.

[27] Guan X, Goddard MA, Mack DL, et al. Gene therapy in monogenic congenital myopathies[J]. Methods, 2016, 99: 91-98.

(本文编辑:唐颖馨)

(上接第571页)

区人群种族、遗传结构等不同, SREBF1 基因多态性存在差异。②PD 的发病同时受到基因环境交互作用影响, 不同地域环境因素差异也可能是重要原因之一。③不同研究中样本量大小及统计分析方式亦存在差异。

综上所述, 本研究结合病例及 Meta 分析, 发现 SREBF1 基因 rs11868035 位点与华中地区汉族人群 PD 的易感性无明显相关性。但由于本研究纳入的样本量有限, 统计效能有所下降。为进一步确定 SREBF1 基因 rs11868035 位点是否与中国人群 PD 发病相关, 研究者需要纳入更大样本进一步分析其与 PD 发病相关性。

参考文献

[1] Becker G, Seufert J, Bogdahn U, et al. Degeneration of substantia nigra in chronic Parkinson's disease visualized by transcranial color-coded real-time sonography[J]. Neurology, 1995, 45: 182-184.

[2] Lesage S, Brice A. Role of mendelian genes in "sporadic" Parkinson's disease[J]. Parkinsonism Relat Disord, 2012, 18 Suppl 1: S66-70.

[3] Wider C, Ross OA, Wszolek ZK. Genetics of Parkinson disease and essential tremor[J]. Curr Opin Neurol, 2010, 23: 388-393.

[4] Do CB, Tung JY, Dorfman E, et al. Web-based genome-wide

association study identifies two novel loci and a substantial genetic component for Parkinson's disease[J]. PLoS genetics, 2011, 7: e1002141.

[5] Jankovic J. Parkinson's disease: clinical features and diagnosis[J]. J Neurol Neurosurg Psychiatry, 2008, 79: 368-376.

[6] Shao W, Espenshade PJ. Expanding roles for SREBP in metabolism[J]. Cell Metab, 2012, 16: 414-419.

[7] Kim JB, Spiegelman BM. ADD1/SREBP1 promotes adipocyte differentiation and gene expression linked to fatty acid metabolism[J]. Genes Dev, 1996, 10: 1096-1107.

[8] Toledo EM, Yang S, Gyllborg D, et al. Srebf1 Controls Midbrain Dopaminergic Neurogenesis[J]. Cell Rep, 2020, 31: 107601.

[9] Ivatt RM, Whitworth AJ. SREBF1 links lipogenesis to mitophagy and sporadic Parkinson disease[J]. Autophagy, 2014, 10: 1476-1477.

[10] Lou F, Li M, Liu N, et al. The polymorphism of SREBF1 gene rs11868035 G/A is associated with susceptibility to Parkinson's disease in a Chinese population[J]. Int J Neurosci, 2019, 129: 660-665.

[11] Shulman JM, Yu L, Buchman AS, et al. Association of Parkinson disease risk loci with mild parkinsonian signs in older persons[J]. JAMA neurology, 2014, 71: 429-435.

[12] Li K, Tang BS, Yu RL, et al. Association study between two novel single nucleotide polymorphisms and sporadic Parkinson's disease in Chinese Han population[J]. Neurosci Lett, 2012, 517: 56-59.

[13] Yuan X, Cao B, Wu Y, et al. Association analysis of SNP rs11868035 in SREBF1 with sporadic Parkinson's disease, sporadic amyotrophic lateral sclerosis and multiple system atrophy in a Chinese population[J]. Neurosci Lett, 2018, 664: 128-132.

(本文编辑:唐颖馨)