TRAPPC家族在神经系统疾病中的作用研究进展

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摘要 转运蛋白颗粒复合体(transport protein particle complex, TRAPPC)是一种多亚基复合物, 参与构成TRAPP。TRAPPC家族在人体中参与囊泡转运、细胞自噬及糖基化等各种关键生理过程, 对神经系统稳态至关重要。随着分子生物学领域的进步以及微阵列分析和下一代测序等高通量方法的广泛应用, 遗传性中枢神经系统疾病的诊断变得更为准确, 且TRAPPC家族成员在神经系统疾病中的重要作用得以进一步明确。该文综述了TRAPPC家族对神经系统发育和功能的影响及各亚基相关的神经系统疾病的研究进展, 以期为相关神经系统疾病的临床治疗提供新思路。

关键词 转运蛋白颗粒复合体; 神经系统疾病; 囊泡转运; 自噬; 糖基化

Research Progress on the Role of TRAPPC Family in Neurological Diseases

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Abstract The TRAPPC (transport protein particle complex) is a multi-subunit complex that is involved in the formation of TRAPP. The TRAPPC family is involved in various key physiological processes such as vesicle transport, autophagy, and glycosylation in the human, and is essential for nervous system homeostasis. With the advancement of the field of molecular biology and the wide application of high-throughput methods such as microarray analysis and next-generation sequencing, the diagnosis of inherited central nervous system diseases has been more accurate, and the important role of TRAPPC family members in neurological diseases has been further clarified. This article reviews the effects of the TRAPPC family on the development and function of the nervous system and the research progress of each subunit-related neurological disease, to provide new ideas for the clinical treatment of related neurological diseases.

Keywords TRAPPC (transport protein particle complex); neurological disorders; vesicle transport; autophagy; glycosylation

转运蛋白颗粒复合体(transport protein particle complex, TRAPPC)是一种首先在酵母中被发现的多亚基蛋白复合物, 研究表明其存在三种组成形式, 分别为TRAPPI、TRAPPII和TRAPPIII。哺乳动物中目前只发现TRAPPII和TRAPPIII, 构成二者的共同核心亚基为TRAPPC1、TRAPPC2、TRAPPC2L、TRAPPC3、TRAPPC4、TRAPPC5、TRAPPC6, 除共同核心亚基外, TRAPPII还包括特异性亚基TRAPPC9和TRAPPC10, 而TRAPPIII还包括TRAPPC8、TRAPPC11、TRAPPC12和TRAPPC13。TRAPPC2

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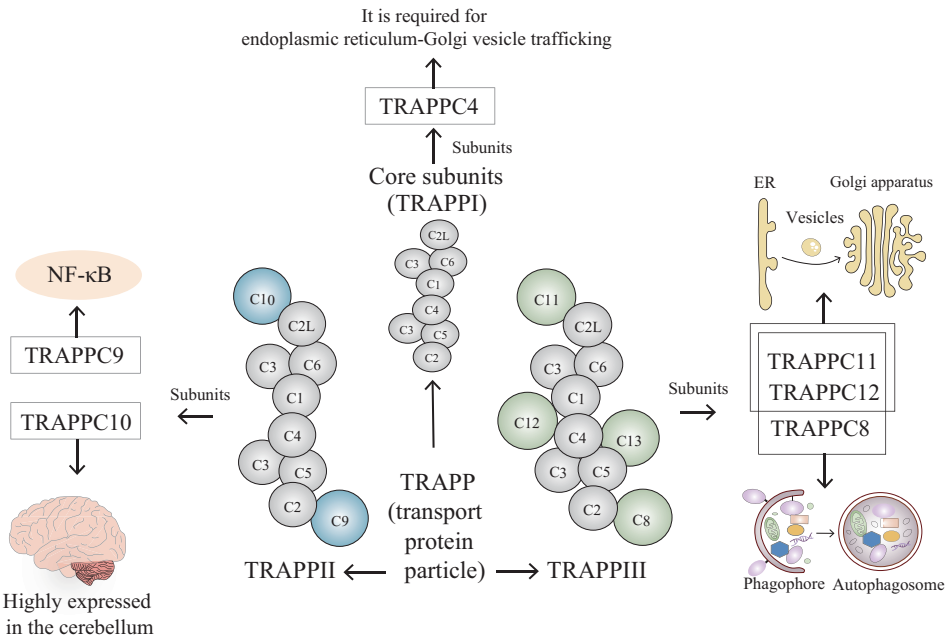

图1 转运蛋白颗粒复合体组成及TRAPPC亚基在神经系统中的作用

Fig.1 Composition of TRAPPC and the role of TRAPPC subunits in the nervous system

亚基作为核心亚基中的衔接蛋白分别与特异性亚基TRAPPC9和TRAPPC8相结合构成TRAPPII和TRAPPIII; 另一种结构蛋白为TRAPPC2L亚基, 它与TRAPPC10结合形成TRAPPII, 与TRAPPC11结合则形成TRAPPIII(图1)。TRAPPC家族成员在神经稳态的调节中发挥关键作用, 由TRAPPC亚基构成的TRAPP转运蛋白颗粒作为一种高度保守的多亚基复合物, 参与囊泡运输、细胞自噬、糖基化等过程。其中TRAPPC家族参与了突触形成和维持、细胞膜的动态稳定以及神经元发育过程中关键信号通路的调控。因此, TRAPPC家族基因突变通常会导致TRAPP转运蛋白功能紊乱导致神经系统发育异常、突触功能紊乱和神经变形等疾病的发生。

1 TRAPPC家族成员影响神经系统发育和功能的潜在机制

1.1 囊泡转运对神经系统稳态的重要性

囊泡运输是胚胎和成体神经发生过程中调节神经发生、脊髓发生和突触发生的关键因素, 其正常功能对维持神经系统稳态起到重要作用。

TRAPPC4(又称synbindin)在中枢神经系统中高丰度表达, 尤其在锥体神经元、浦肯野细胞及运动神经元中高度表达, 对于神经元中的树突棘形态发生至关重要[1]。Synbindin作为生理性syndecan 2(MIM*142460)配体, 通过将细胞内囊泡募集到突触后位点来诱导树突棘形成, 在这种蛋白质功能丧失的儿科患者中观察到的严重神经系统表现支持其在早期神经发育中的重要性[2]。内质网到高尔基体的运输作为真核细胞分泌系统的一个核心过程, 可确保蛋白质和脂质的正确时空分类, 研究发现TRAPPC11及TRAPPC12在内质网到高尔基体的早期运输中起重要作用[3]。

1.2 自噬功能正常对神经系统稳态的重要性

自噬属于细胞的一种保护机制, 指在自噬相关基因调控下利用溶酶体降解自身细胞质蛋白和受损细胞器的过程, 成年后神经元不再分裂更新, 自噬可以通过降解和循环利用胞内的受损细胞器和异常蛋白聚集体及时有效地清除积累的细胞废物, 来维持神经系统稳态[4]。研究发现, *Atg7*变异的患者出现不同方面和程度的神经发育障碍, 表现出共济失调、发育迟缓和小脑发育不全等症状[5], *Atg7*敲除可以影响自噬通路, 从而改善慢性约束应激导致的情绪和认知功能障碍[6]。同时, 启动细胞自噬的关键靶点UNC-51激酶1(unc-51 like kinase 1, ULK1)变异会导致轴突再生受损[7]。

虽然在酵母中TRAPPIII已被证明可对自噬起作用, 但TRAPPIII在人体内自噬过程中的作用尚不明确, 在蛋白质组学中的一项研究将TRAPPC8确定

为人类自噬相互作用网络的一个组成部分[8]。同时，STANGA等[9]的研究发现TRAPPIII中的特异性蛋白TRAPPC11、TRAPPC12和TRAPPC8影响自噬，其中TRAPPC8会影响隔离膜的形成，而TRAPPC11和TRAPPC12共同在自噬体形成的上游起作用，其中TRAPPC11募集自噬蛋白2和磷脂酰肌醇-3-磷酸，参与膜分离过程。因此，TRAPPC家族功能障碍会影响正常自噬功能进而导致神经系统紊乱的发生。

1.3 糖基化正常对神经系统稳态的重要性

糖基化是一种发生在内质网和高尔基体中的酶调节过程，糖基化功能的异常会影响多种疾病的发生发展。自闭症谱系障碍是一种神经发育障碍疾病，表现为社交互动障碍、语言迟缓、重复行为等，最近的一项研究显示，与自闭症谱系障碍相关的神经配蛋白(neuroligin, NLGN)基因家族中R101Q残基的突变会损害N102残基的正常N-糖基化功能，从而影响NLGN4表面运输并导致神经干细胞衍生神经元的突触功能障碍[10]。此外，通过对阿尔茨海默病患者进行分析发现，BACE1的N-糖基化破坏会影响蛋白质的折叠和成熟，阻断其下游通路导致阿尔茨海默病的发生[11]。

研究发现，TRAPPC11是斑马鱼和人类糖基化过程所必需的[12]。而通过对54例*TRAPPC11*错义突变患者进行检测，发现其糖基化相关蛋白溶酶体相关膜蛋白2(lysosome-associated membrane glycoprotein 2, LAMP2)和细胞间黏附分子-1(intercellular cell adhesion molecule-1, ICAM-1)表达水平降低，TRAPPC11病变实际上是一种先天性糖基化障碍同时伴有肌肉萎缩症状的出现[13]。由此提示，TRAPPC家族功能障碍会影响正常糖基化功能进而导致神经系统紊乱的发生。

2 TRAPPC家族成员在神经系统疾病中的作用

2.1 TRAPPC2L

TRAPPC2L作为构成TRAPPII和TRAPPIII的核心亚基组分，在内质网到高尔基体的囊泡运输和分泌途径的后期阶段中发挥重要作用。MILEV等[14]研究发现，在两个无血缘关系的神经发育迟缓、伴有癫痫的患者中存在编码TRAPPC2L蛋白的*TRAPPC2L*基因纯合错义突变。此外，TRAPPII可激活三磷酸鸟苷酶RAB11，且*TRAPPC2L*突变会影响成纤维细胞中RAB11的表达。而*RAB11*突变与发育性和癫痫性脑病的发生密切相关[15]。同时，通过对患有发育迟缓和智力障碍的三名兄弟姐妹进行全基因组测序，发现其中*TRAPPC2L*出现纯合错义突变，突变导致TRAPPC2L和TRAPPC6a之间的相互作用减少，破坏TRAPP复合物的组装及稳定性，影响囊泡运输过程[16]。

2.2 TRAPPC4

TRAPPC4是将内质网产生的囊泡转运到高尔基体上所必需的[17]。多巴胺能神经元的单细胞测序结果显示*TRAPPC4*是帕金森病的差异基因，在患者中发现TRAPPC4蛋白表达量出现显著减少[18]。帕金森病动物模型中同样发现了突触囊泡内吞作用受损以及内质网到高尔基体的转运发生中断[19]。GHOSH等[20]对23名出现*TRAPPC4* c.454+3A>G变异的患者进行监测发现其出现进行性脑病、认知功能下降、小头畸形及癫痫症状。VAN BERGEN等[2]分离了*TRAPPC4* c.454+3A>G变异患者的成纤维细胞并进行了体外培养，发现了细胞出现高尔基体运输障碍、自噬功能障碍。这可能是由于*TRAPPC4*变异影响TRAPP复合物正常功能，而TRAPPC复合物可作为鸟嘌呤交换因子(GMP exchange factor, GEF)激活Ypt/Rab GEF酶来协调细胞内运输途径[21-22]，介导囊泡运输的不同阶段，而运输的失调又影响自噬过程[23]。除了上述纯合*TRAPPC4* c.454+3A>G剪接位点变体外，还发现一种新的表达框内纯合子缺失突变可导致终止密码子被破坏，此类*TRAPPC4*框内纯合缺失突变患者表现出发育迟缓和更明显的小脑萎缩[24]，进一步验证了*TRAPPC4*突变的相关神经系统疾病表型。此外，*TRAPPC4* c.454+3A>G变异患者出现肌张力障碍、四肢痉挛等肌肉受累的现象尚无明确解释[25]。

2.3 TRAPPC6

TRAPPC6A也是TRAPPII和TRAPPIII所需的核心亚基组分，该亚基分为TRAPPC6A1和TRAPPC6A2两种亚型(统称为TRAPPC6AΔ)。MPP^+是一种常见的诱导帕金森病的药物，研究发现TRAPPC6A对MPP^+引起的聚合反应最敏感，因此TRAPPC6A聚合是帕金森病的常见原因[26]。研究表明，含WW结构域氧化还原酶(WW domain-containing oxidoreductase, WWOX)在阿尔茨海默病等神经退行性疾病发生发展中起到重要作用，它可以抑制tau蛋白

缠结从而抑制阿尔茨海默病的进展[27]。在正常生理条件下, WWOX可以通过与TRAPPC6AΔ的C-端结合防止TRAPPC6AΔ的自我聚集[28-29]。但随着年龄增长, 大脑中WWOX的下调会导致TRAPPC6AΔ、T1AF1和SH3GLB2蛋白质级联反应发生, 进而导致β淀粉样蛋白生成和神经变性发生, 最终引起阿尔茨海默病和帕金森病的发生[30]。研究发现, Zfra可以阻断TRAPPC6AΔ和β淀粉样蛋白的聚集, 并抑制NF-κB激活介导的炎症反应, 从而对阿尔茨海默病小鼠的症状起到改善作用[26,30]。此外, MOHAMOUD等[31]通过应用比较基因组和外显子组测序相结合的方法在儿童期智力障碍、多指畸形的患者中检测出*TRAPPC6A*的纯合突变。

此外, 在神经系统中精确的蛋白质运输对正常发育至关重要[32]。临床上对29名患有非进行性小头畸形、发育迟缓、智力障碍、癫痫等神经疾病的患者进行检测发现其存在*TRAPPC6B*双等位基因变异[33]。*TRAPPC6B*双等位基因变异患者的成纤维细胞具有内质网–高尔基体运输缺陷和高尔基形态改变, 这在癫痫[34]患者中表现出一致性。由于TRAPPC6B在TRAPPII中富集, 因此*TRAPPC6B*的双等位基因变异会影响TRAPPII的稳定性使得高尔基体–内质网的顺向运输受到影响, 这与患者成纤维细胞的检测结果具有一致性。

2.4 TRAPPC9

*TRAPPC9*突变可导致常表现为智力障碍的常染色体隐性遗传病, 目前已经报道了50多例携带*TRAPPC9*致病变异的个体, 其临床症状包括智力障碍、小头畸形、胼胝体发育不良和肥胖[35-36], 这些症状在*Trappc9*敲除小鼠模型中得到了验证[37]。研究表明, *TRAPPC9*的缺乏会破坏大脑中神经干细胞的可塑性[38], 这可能是*TRAPPC9*突变患者脑结构发育不良的基础。此外, TRAPPC9与经典和非经典的NF-κB通路相关[39], 因此TRAPPC9表达水平降低会显著抑制神经元内的NF-κB信号通路激活, 而NF-κB信号转导作为神经元细胞分化和髓鞘形成的关键途径[40], 其功能异常影响神经突触生长和髓鞘形成可能是*Trappc9*敲除小鼠小脑发育缺陷、大脑及胼胝体体积减小的基础[37,41]。另外, KE等[42]通过对*Trappc9*敲除小鼠进行研究发现其通过导致多巴胺D1和D2神经元失衡损害小鼠的学习和记忆行为。除上述智力障碍–肥胖–脑畸形–面部畸形综合征外, KUSHIMA等[43]发现*TRAPPC9*的突变和拷贝数变异还与自闭症谱系障碍和精神分裂相关。

2.5 TRAPPC10

SANTOS-CORTEZ等[44]通过对22个患有常染色体隐性遗传智力障碍的患者的DNA样本进行外显子组测序, 发现了其中存在*TRAPPC10*纯合变异。研究发现, 在严重小头神经发育障碍患者中存在*TRAPPC10*双等位基因变异[45]。通过对*Trappc10*敲除小鼠进行研究发现, *TRAPPC10*的C-端缺失导致TRAPPC10蛋白降解, 从而导致TRAPPC9蛋白缺失, 进而导致TRAPPII缺失[45]。而TRAPPII复合物失稳会导致Rab1、Rab2、Rab18的鸟苷酸交换因子活性丧失, 其活性丧失会导致髓鞘生成障碍和白质结构缺陷, 这是小头症发生的原因之一。

2.6 TRAPPC11

TRAPPC11是一个由11 333个氨基酸构成的亚基, 通过与TRAPPC2L和TRAPPC3结合形成TRAPPIII。TRAPPC11中一个区域被称为鹅肝结构域, 在蛋白质相互作用、复合物完整性和从内质网到高尔基体中间室的顺行膜转运中发挥重要作用[46]。*TRAPPC11*基因突变主要表现出一种遗传性神经肌肉疾病, 多项临床研究发现, *TRAPPC11*突变患者表现出肢带型肌营养不良症状[46-50]。其中MUNOT等[51]的研究发现, 一例*TRAPPC11*隐性突变患者的神经病理学检查显示出结构性小脑受累, 症状类似于N连锁先天性糖基化疾病, 提示TRAPPC11相关疾病中存在多种糖基化通路缺陷。随后, 在斑马鱼模型中验证了*TRAPPC11*是蛋白质糖基化过程所必需的基因[12]。而研究表明糖基化作为配体结合活性的关键其障碍会导致α-肌营养不良蛋白聚糖功能障碍进而导致肌营养不良的发生[52]。此外, 通过对120 033名重度抑郁症患者进行外显子组全基因组关联研究, 确定*TRAPPC11*是重度抑郁症的候选致病基因[53]。POPP等[54]通过对神经发育障碍患者进行筛查发现*TRAPPC11*突变会导致疾病的发生。

2.7 TRAPPC12

*TRAPPC12*在哺乳动物中是表达水平最一致的基因之一, 在不同物种中表达差异不大。研究发现*TRAPPC12*突变会导致进行性儿童脑病的发生, 通过对三名不相关患者进行检测发现其中*TRAPPC12*存在不同的纯合变异或杂合变异但其临床表型相似[55]。患者中存在高尔基体形态变化、膜泡运输

功能障碍和成纤维细胞有丝分裂延迟，这是由于TRAPPC12在膜泡运输、有丝分裂和着丝粒蛋白的正确定位中起重要作用[56]。另外，ASLANGER等[57]的研究表明*TRAPPC12*的不同位点变异会使患者表现出不同的症状，c.1880C>T(p.Ala627Val)突变的纯合子，表型包括重度进行性皮质萎缩、中度小脑萎缩、癫痫和小头畸形；新型纯合子c.679T>G(p.Phe-227Val)变异型，表现为轻度皮质萎缩、重度小脑萎缩，临床表现无癫痫和小头畸形，但患者都存在智力障碍和小头畸形症状。有临床研究显示，一对父母鉴定出携带*TRAPPC12*杂合子变异，其胎儿患有脑积水，表现为脑脊液在大脑中的异常积聚，这可能是由于*TRAPPC12*变异影响有丝分裂破坏胚胎期正常的脑发育，导致脑积水从而引起复发性流产的发生[58]。

通过对TRAPPC复合体亚基进行分析发现，其中基因的变异与重叠的临床表型有关，表明每个复合体亚基具有共同或独特的功能，如TRAPPC8和中心体蛋白之间的相互作用会抑制中心体蛋白和TRAPPC12之间的相互作用[59]。因此，通过对TRAPPC各亚基相关疾病进行分析进一步总结各个蛋白的作用，可发现各亚基对疾病表型的特异或共同影响(表1)。

3 总结与展望

TRAPPC家族作为一个重要蛋白质转运复合物，在调节神经系统稳态和神经系统疾病发生中发挥着重要作用，本文综述了TRAPPC家族对中枢神经系统稳态的影响及相关疾病，但其具体机制尚不明确。因此在未来的研究中应继续探索TRAPPC家族在神经系统发育和功能维持中的具体作用机制，深入探究TRAPPC家族成员之间的相互作用，进一步研究TRAPPC家族在不同神经系统疾病中的作用，以期寻找到潜在的治疗靶点。

基因编辑技术可以实现对特定位点的基因进

表1 TRAPPC相关亚基突变位点及相关神经系统疾病

Table1 Mutation sites of TRAPPC-related subunits and related neurological diseases

TRAPPC亚基 TRAPPC subunit	亚基作用 Subunit action	变体 Variant	相关神经系统疾病 Associated neurological disorders
TRAPPC2L	The core ingredient of TRAPP plays an important role in the later stages of the vesicle transport and secretory pathway from the endoplasmic reticulum to the Golgi apparatus	c.109G>T; (p.Asp37Tyr) homozygous mutations [14]	Neurodevelopmental delay, rhabdomyolysis, developmental arrest, epilepsy, tetraplegia [14]
		c.5C>G; (p.Ala2Gly) homozygous mutations [16]	Neurodevelopmental delay, intellectual disability [16]
TRAPPC4	The core ingredient of TRAPP	c.454+3A>G homozygous mutations [2,20,60]	Motor retardation, developmental deterioration, early-onset epilepsy, microcephaly, progressive spastic quadriplegia [2,20,60]
		Chr11:g.118894087_118894113del(hg19); c.638_*4del; (p.Gly213_Ser219delinsGluProValMetAspProGlnIleLeuArgValProAlaThrArgIleLeuLeuLeuThrLeuGlnTrpLysSerGlnGlnProCys) homozygous mutations [24]	Neurodevelopmental delay, unsteady gait, hypotonia, dysarthria, lateral nystagmus, thinning of the corpus callosum, mild cerebellar atrophy [24]
TRAPPC6A	The core ingredient of TRAPP. TRAPPC6A dysfunction can lead to inappropriate protein accumulation	c.T319A homozygous mutations [31]	Intellectual disability, speech delays, facial deformities, polydactyly [31]
TRAPPC6B	The core ingredient of TRAPP	hg19:14:g.39628756T>C homozygous mutations [61]	Neurodevelopmental delay, intellectual disability, autism spectrum disorder, language impairment, generalized tonic-clonic seizures, microcephaly in two patients, thin corpus callosum [61]
		c.454C>T, p.Q152* homozygous mutations [33]	Microcephaly, neurodevelopmental delay, intellectual disability, epilepsy, spasticity, dystonia [33]

续表1

TRAPPC亚基 TRAPPC subunit	亚基作用 Subunit action	变体 Variant	相关神经系统疾病 Associated neurological disorders
TRAPPC9	Specific subunit of TRAPPII. It is an important binding site for Ypt32 (Rab11 yeast homolog) and plays an important role in the function of TRAPPII	c.1639A>C (p.Asn547His) homozygous mutations [35]	Intellectual disability, scoliosis, coordination disorders [35]
		c.64G>A (p.Glu22Lys) homozygous mutations [35]	Neurodevelopmental delay, thin corpus callosum, diffuse myelin dysplasia [35]
		c.1205G>T (p.Arg402Leu) homozygous mutations [35]	Thin corpus callosum, cerebellar hypoplasia, decreased white matter, scoliosis [35]
		c.3435delG (p.Thr1146Profs*8) heterozygous mutations [36]	Intellectual disability, microcephaly, autism [36,62]
		c.623A>C (p.His208Pro) homozygous mutations [36]	
		c.1678C>T (p.Arg560Cys) & c.3370C>T (p.Pro1124Ser) compound heterozygous mutations [62]	
		c.696C>G (p.Phe232Leu) homozygous mutations [63]	Severe developmental delay, intellectual disability [63]
		c.2415_2416insC (p.His806Profs*9) & c.3349+1G>A compound heterozygous mutations [64]	Intellectual disability, autism spectrum disorder, neurodevelopmental delay, microcephaly, abnormal brain development [64]
		c.2288dup, (p.Val764Glyfs*7) homozygous mutations [65]	Neurodevelopmental delay, cognitive impairment, learning disabilities, microcephaly, hypotonia [65]
TRAPPC10	Specific subunit of TRAPPII	(p.G1131Vfs*19) homozygous mutations [45]	Intellectual disability, neurodevelopmental delay, speech impairment, decreased muscle tone [45]
TRAPPC11	Specific subunit of TRAPPIII. Involved in autophagy and anterograde membrane transport before the endoplasmic reticulum and Golgi apparatus	c.2938G>T (p.Gly980Arg) & c.661-1G>T compound heterozygous mutations [66]	Congenital muscular dystrophy, fatty liver, congenital cataracts [66]
		c.2938G>A (p.Gly980Arg) homozygous mutations [46,67]	Developmental delay, muscle weakness, muscle spasms, hip dysplasia, scoliosis, and one patient presents with bilateral cataracts [46-67]
		c.1287+5G>A homozygous mutations [46,50,67]	EEG (electroencephalogram) abnormalities, mild brain atrophy, intellectual disability, early-onset muscle weakness, dyskinesia [46,50,67]
		TRAPPC11 c.3092C>G (p.Pro1031Arg) and *TTN* c.19481T>G (p.Leu6494Arg) two-gene variants [68]	Patients with *TRAPPC11* and *TTN* mutations develop proximal muscle weakness after the age of 35 years, consistent with symptoms of limb muscular dystrophy [68]
		c.1287+5G>A & c.3379_3380insT compound heterozygous mutations [67]	Neurodevelopmental delay, epilepsy, hypotonia, spasticity, cerebral atrophy, decreased white matter volume [67]
		c.1893+3A>G homozygous mutations [69]	Brain atrophy, neurodevelopmental delay, scoliosis, achalasia [69]
		c.751T>C & c.1058C>G compound heterozygous mutations [13]	Proximal muscle weakness, neurodevelopmental delay, EEG abnormalities, cerebral atrophy, decreased white matter volume [69]
TRAPPC12	Specific subunit of TRAPPIII. Play an important role in anterograde membrane transport from the endoplasmic reticulum to the Golgi apparatus and transport within the Golgi body	c.1880C>T (p.Ala627Val) homozygous mutations [55,57]	Cortical atrophy, cerebellar atrophy, epilepsy, microcephalia [55,57]
		c.679T>G (p.Phe227Val) homozygous mutations [57]	Severe disability, hearing loss, spasticity [55]
		c.145delG (p.Glu49Argfs*14) homozygous mutations [55]	
		c.360dupC (p.Glu121Argfs*7) compound heterozygous [55]	
		c.1880C>T (p. Ala627Val) compound heterozygous [55]	

前缀“g.”表示基因组参考序列; 前缀“c.”表示cDNA参考序列; 前缀“p.”表示蛋白质参考序列; >: 置换; del: 删除; dup: 复制; ins: 插入。
The prefix “g.” represents genomic reference sequences; the prefix “c.” represents the cDNA reference sequence; the prefix “p.” represents the protein reference sequence; >: replacement; del: deletion; dup: daplication; ins: insertion.

行“编辑”, 使得基因突变疾病的治疗成为可能。其中, CRISPR/Cas9系统因其具有克隆简单、靶序列设计简便、成本相对较低等优点, 在诸多基因疾病中发挥重要作用。研究显示, 在镰状细胞贫血的治疗中应用CRISPR/Cas9基因编辑技术对造血干细胞/祖细胞中B细胞淋巴瘤/白血病11A的红系特异性增强子区进行靶向编辑, 可以重新激活患者体内的胎儿血红蛋白起到摆脱输血依赖, 消除血管闭塞的治疗作用[70]。因此, 未来研究中可以应用CRISPR/Cas9系统等基因编辑技术, 通过对突变位点或突变基因的上下游基因进行编辑从而对TRAPPC家族突变导致的相关疾病起到治疗作用。

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