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神经退行性疾病关键蛋白拷贝数变异与神经罕见病

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摘要 神经罕见病种类繁多、表型复杂且绝大多数无法被治愈. 目前对于神经罕见病发病机制的认识仍十分欠缺. 多项临床研究提示阿尔茨海默病、帕金森病等神经退行性疾病关键蛋白的拷贝数变异可能导致神经罕见病. 本文拟通过讨论神经退行性疾病关键病理蛋白如Aβ、tau、α-Syn等相关拷贝数变异诱发神经罕见病的基础与临床证据, 阐述阿尔茨海默病、帕金森病与神经罕见病的区别与联系, 为这些疾病的发病机制与治疗策略提供新的思路.

关键词 神经罕见病, 神经退行性疾病, 拷贝数变异, 阿尔茨海默病, tau蛋白

罕见病患者约占全世界总人口的10%, 开发和制定罕见病的诊断和治疗策略面临巨大挑战[1]. 各国监管机构对罕见病的定义并不统一: 在美国, 基于在该国受影响个体的数量将罕见病定义为患病人数少于20万的疾病; 欧盟国家基于患病率将罕见病定义为患病率小于1/2000的疾病[2]. 而《中国罕见病定义研究报告(2021)》将罕见病定义为"新生儿发病率小于1/万、患病率小于1/万、患病人数小于14万的疾病".

目前已知罕见病种类至少有7000种, 其中超过1200种涉及中枢神经系统的损伤, 如影响认知、运动、神经发育等, 因此统称此类疾病为神经罕见病[3]. 大多数神经罕见病由遗传因素导致, 病情严重, 病程以进行性、耗竭性地发展, 甚至造成残疾及威胁生命. 遗传因素导致的罕见病存在多种形式, 包括基因突变、基因组结构变异等. 单基因神经罕见病的遗传表现为典型的孟德尔遗传方式, 如常染色体显性遗传病——亨廷顿病(由位于4号染色体的*HTT*基因CAG三核苷酸重复序列扩增异常所致, 患者主要临床表现为不自主舞蹈样动作、精神症状、进行性痴呆)[4]; 常染色体隐性遗传病——Tay-Sachs病(由位于15号染色体的*HEXA*基因突变所致, 患者多于出生后6个月左右发病、5岁前死亡, 主要症状为精神运动衰退、智力下降、发育障碍、癫痫等)[5].

拷贝数变异(copy number variations, CNVs)指基因组片段(数百个到数百万个碱基对不等)拷贝数的增加或减少, 是基因组结构变异的主要形式之一, 由基因组重排导致[6,7]. 拷贝数重复或缺失具有多种可能的类型, 图1为其中几种较简单的变异形式. CNVs导致该片

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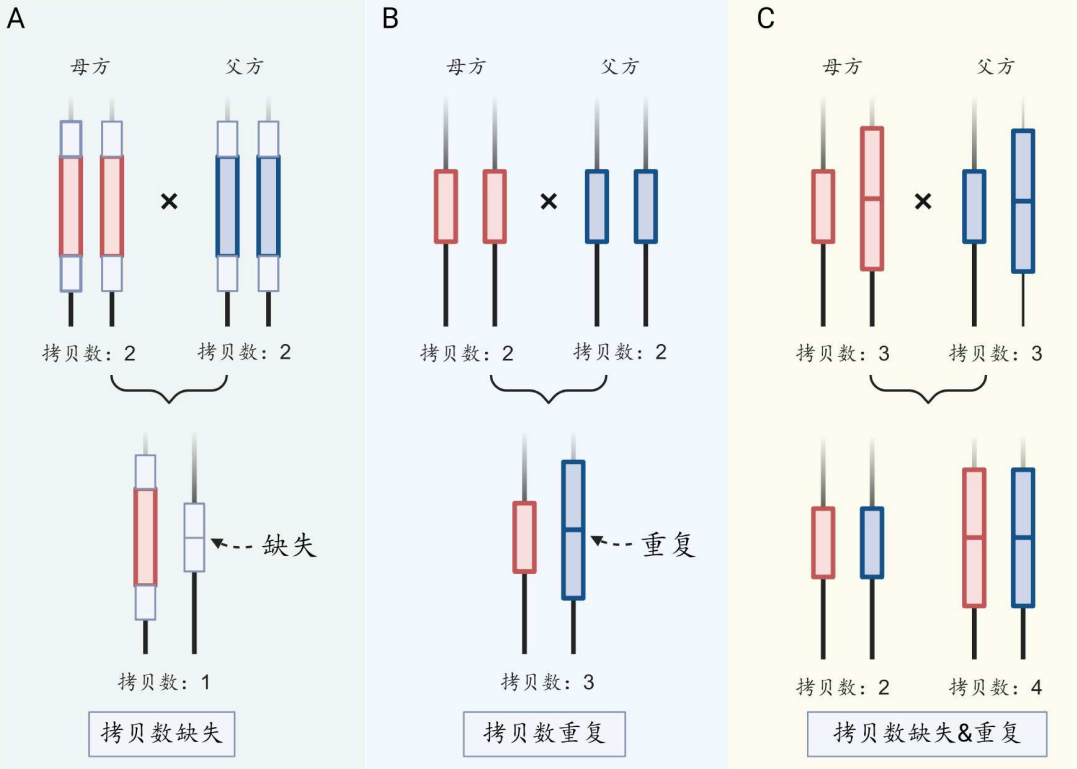

图 1 拷贝数变异的多种类型. A: 父母双方基因组均有2个拷贝数, 而后代先天缺失导致拷贝数减少, 如17q21.31微缺失综合征; B: 父母双方基因组均有2个拷贝数, 后代先天重复导致拷贝数增加, 如由*SNCA*拷贝数重复导致的早发型帕金森病; C: 父母双方各有3个拷贝, 不同的重组方式使得后代拷贝数相对增加或减少

Figure 1 Various types of copy number variations. A: Both parents have 2 copy numbers, and the *de novo* deletion in the offspring results in a decrease in copy number, such as 17q21.31 microdeletion syndrome; B: both parents have 2 copy numbers, and the *de novo* duplication in the offspring results in an increase in copy number, such as early-onset Parkinson's disease caused by *SNCA* copy number duplication; C: both parents have 3 copies, different recombination forms cause a relative increase or decrease in the copy number of the offspring

段内的一个/多个基因缺失或多倍表达, 可能致使多种神经罕见病的发生及增加部分疾病的患病风险. 20世纪90年代, Lupski[8]报道染色体17p12区域的*PMP22*基因的重复和缺失分别导致Charcot–Marie–Tooth病和遗传性压力敏感性周围神经病, 这是首个被报道与疾病相关的拷贝数变异. Helbig等人[9]通过比较分析3699例对照个体与1223名患有特发性全身性癫痫(idiopathic generalized epilepsy, IGE)患者染色体15q13.3的结构变异, 发现12名患者表现出包含*CHRNA7*基因在内的15q13.3微缺失, 表明染色体15q13.3微缺失会增加患有IGE的风险.

随着近年来测序技术的发展及基因编辑技术的成熟, 多项临床报道及基础研究表明常见神经退行性疾病中关键病理蛋白的缺失或双倍/多倍表达可能参与神经罕见病的发生发展过程, 提示在常见神经退行性疾病中扮演重要角色的病理蛋白在神经罕见病中发挥独特作用(表1). 阿尔茨海默病(Alzheimer's disease, AD)作为最为常见的神经退行性疾病, 其组织病理学特征为β-淀粉样蛋白(amyloid-β, Aβ)形成的胞外淀粉样斑块及由tau蛋白聚集形成的神经纤维缠结(neurofibrillary tangles, NFTs). 与这两大病理蛋白直接相关的基因*APP*及*MAPT*被证明与多种神经罕见病相关: *APP*基因的拷贝数变异不仅可导致早发型阿尔茨海默病(early-onset Alzheimer's disease, EOAD), 且与唐氏综合征(Down syndrome, DS)患者的AD表型密切相关[10]; 17q21.31微缺失综合征患者缺失片段包含*MAPT*基因在内, 且涉及*MAPT*基因拷贝数变异的部分患者表现出神经发育障碍、精神分裂及神经退行性变等多种表现. 帕金森病(Parkinson's disease, PD)是第二大神经退行性疾病, 路易小体(Lewy bodies, LBs)是其主要的病

表 1　*APP*、*MAPT*、*SNCA*拷贝数变异与神经罕见病

Table 1　Copy number variations of *APP*, *MAPT*, *SNCA* and rare neurological diseases

基因	位点	相关神经罕见病	变异类型
APP	21q21	早发型阿尔茨海默病(EOAD)	拷贝数重复
		唐氏综合征(DS)	拷贝数重复
MAPT	17q21.31	17q21.31微缺失综合征	拷贝数缺失
		进行性核上性麻痹(PSP)	拷贝数重复
		额颞叶变性(FTLD)	拷贝数重复/部分缺失
SNCA	4q21	早发型帕金森病(EOPD)	拷贝数重复
		多系统萎缩(MSA)	拷贝数获得

理特征之一. 由*SNCA*基因编码的α-突触核蛋白(alpha-synuclein, α-Syn)被确定为LBs的关键成分, 且*SNCA*基因的拷贝数变异可导致早发型帕金森病(early-onset Parkinson's disease, EOPD)的发生, 也与多系统萎缩(multiple system atrophy, MSA)相关. 迟发型AD与迟发型PD为常见神经退行性疾病, 而EOAD及EOPD由于发病率低, 既属于神经退行性疾病, 又可归为神经罕见病范畴, 如《中国罕见病参考名录(修订版)》将EOPD纳入其中, 罕见病数据中心(Rare Disease Data Center, RDDC)将EOAD及EOPD均收录其中. 由此可见, 常见神经退行性疾病的关键病理蛋白的基因变异亦可诱导神经罕见病.

本文将以上述提及AD、PD核心病理蛋白Aβ、tau、α-Syn为主要探讨对象, 具体阐述神经退行性疾病关键蛋白相关的拷贝数变异在神经罕见病中的重要作用, 及不同疾病间的联系与区别.

1　淀粉样前体蛋白

1.1　淀粉样前体蛋白的生理及病理功能研究

淀粉样前体蛋白(amyloid Precursor Protein, APP)属于单次跨膜蛋白, 由位于第21号染色体的*APP*基因编码, 通过选择性剪接产生3种主要亚型APP_{695}、APP_{751}和APP_{770}[11]. 神经元主要表达APP_{695}, 而APP_{751}和APP_{770}存在于许多外周组织细胞中. APP经历经典分泌酶以及非经典分泌酶的复杂加工, 产生大量具有生物活性的片段. 与AD密切相关的Aβ生成具体过程为: APP经β-分泌酶裂解为N端sAPPβ及C端片段(C-terminal fragments, CTF); 进一步地, CTF经γ-分泌酶水解为无序的APP胞内结构域(APP intracellular domain, AICD)及Aβ[12]. 根据切割的具体位置, Aβ肽段的长度可在39~43个氨基酸之间. APP通过α-分泌酶切割并不会导致Aβ的产生.

APP在神经发育、神经元可塑性、记忆等方面具有重要的生理功能. APP缺失小鼠虽具有存活能力和生育能力, 但表现出体重/大脑重量减轻、反应性神经胶质增生、前肢握力及运动活动降低等[13]. 锥体细胞中APP与突触共定位, 而APP缺失的老年小鼠表现出长时程增强(long-term potentiation, LTP)受损以及空间记忆缺陷[14]. APP缺失的海马神经元通常表现出较低的棘突密度和树突复杂性, 这表明APP可能参与树突动态的维持[15,16].

除上述功能外, APP被证明调节神经元铁输出[17~19]. 作为大脑中最为丰富的过渡金属, 铁参与多种重要的大脑活动, 如神经递质的合成、髓鞘形成等[20]. 铁在大脑中受到严格调节, 铁缺乏和铁过载都可能导致神经细胞功能受损及大脑功能障碍[21~24]. 研究表明, APP通过稳定胞内铁泵蛋白(ferroportin, Fpn)以促进神经元铁输出, 而APP的敲除导致小鼠原代神经元内铁的滞留及小鼠脑内及周围组织铁的累积[17,25]. 鉴于APP在铁调控中的参与, APP功能异常导致铁稳态的紊乱可能作为一些神经系统疾病中神经元死亡及疾病表型的促成因素.

APP蛋白的功能异常对于AD发病机制具有重要参与, 主要体现在: APP蛋白经β-分泌酶途径加工产生Aβ[26]; AD大脑中铁的积累与APP功能异常有关[17]; APP功能异常还会诱发突触缺陷等. *APP*在同一位点的突变——致病性突变A673V及保护性突变A673T, 被认为分别通过使APP加工更倾向于β-分泌酶途径或更不倾向于β-分泌酶途径, 导致两种截然不同的效果,

即促进或抑制Aβ的产生. 另外, 致病性突变A673V无法稳定神经元表面的Fpn, 从而诱导铁滞留; 而保护性突变A673T通过稳定神经元表面Fpn, 促进更多的铁输出[27]. 由此可推测, *APP*致病性或保护性突变可能通过影响神经元Aβ的水平、铁的水平等多方面作用参与疾病的进程. 近年来, 单克隆抗体Lecanemab、donanemab在清除Aβ和延缓早期AD进展方面显示出一定程度的疗效[28,29], 为Aβ在AD发病机制中的作用提供了临床支持, 也更加提示APP在此过程中的重要作用.

1.2 *APP*拷贝数变异与神经罕见病

1.2.1 唐氏综合征

唐氏综合征由21号染色体多出一整条或部分拷贝所致, 是遗传学最为复杂的疾病之一, 同时是最常见的可存活常染色体非整倍体疾病[30]. 伴随全球人口的增长, DS的患病率大幅增加. 以美国为例, DS的患病率从1950年的3.3人/万人增加至2013年6.7人/万人[31]. 我国在产前检查中建议开展DS筛查, 以减少发病率. DS具有多种表型, 涉及肌肉骨骼、神经和心血管系统等. DS患者发育延迟, 通常身材矮小、肌肉张力低下、小脑发育不良、智力障碍等, 其寿命较普通人群显著缩短. 患有DS的人也更易并发某些疾病, 如甲状腺功能减退、自身免疫性疾病、癫痫等. DS患者也表现出与AD患者相似的淀粉样斑块和NFTs特征[32].

21号染色体具有200多个蛋白质编码基因, 对细胞、组织、器官和系统的动态平衡产生直接和间接的影响. DS患者携带的第3条21号染色体导致位于该染色体的*APP*拷贝数及APP蛋白剪切产物增加[33], 这被认为是DS-AD患者的遗传基础. 在过去30年里, DS患者的预期寿命翻了一番, 伴随寿命增加而来的是DS患者并发AD的风险已超过90%[34]. *APP*的基因剂量对DS-AD具有重要作用, 据Doran等人[35]报道的一例21号染色体部分片段拷贝异常但*APP*拷贝正常的DS患者, 即使到老年也并未表现出认知障碍及AD的病理学特征. 包含*APP*拷贝异常的DS病例报告同样证实*APP*过度表达在AD发病机制中发挥的关键作用[35,36], 这些罕见和不寻常的病例表明*APP*是导致DS中AD的关键驱动因素. 另外, 尽管AD病理学在DS中几乎是不可避免的, 但临床痴呆的发病年龄差异较大. 症状通常出现在30~65岁, 平均年龄为52岁, 大约80%的人在65岁前出现认知障碍[37].

1.2.2 早发型阿尔茨海默病

据报道, *APP*基因的特定突变或拷贝数增加可导致早发型阿尔茨海默病(early-onset Alzheimer's disease, EOAD)[10]. EOAD患者通常在30~65岁首次出现症状, 约占所有AD患者的10%. 相较于晚发型AD, EOAD患者更易发生视觉功能障碍、计算障碍、执行功能障碍等非典型临床表现[38]. 已有多篇报道由*APP*基因重复而导致EOAD的研究, 如在一项法国的队列中发现5名携带*APP*重复的伴有脑淀粉样血管病(cerebral amyloid angiopathy, CAA)的EOAD个体, 重复片段为0.58~6.37 Mb[39]. APP的过度表达除直接影响Aβ的产生外, 对于细胞代谢及信号转导产生多方面影响, 如导致线粒体代谢受损、异常钙转运、氧化应激等, 这些细胞内的变化可能驱动认知障碍的发生及神经退行性病变[34,40]. 然而值得注意的是, 仍有一些携带*APP*重复的个体并未发展为EOAD[10,41], 这说明可能存在着遗传或非遗传因素能够降低*APP*重复带来的影响, 能够大大延迟或阻止AD的发生. 更好地了解*APP*重复的保护因素将有利于AD的早期预防和治疗.

1.2.3 唐氏综合征与早发型阿尔茨海默病的比较

DS-AD、*APP*拷贝数重复导致的EOAD临床表现在很大程度上与迟发型AD类似, 最明显区别体现在发病年龄的不同. 与迟发型AD患者神经病理学的表现一致, DS-AD患者内侧颞叶萎缩及海马等区域萎缩[42], 反映出神经退行性病变的发生. DS患者30岁时即表现出淀粉样沉积, 远早于迟发型AD患者, 这与临床上更早的痴呆发病年龄一致[43]. 40岁后DS患者大脑淀粉样蛋白的积累以指数级增长且扩散至整个皮质[44]. 另外, 与迟发型AD不同的是, DS患者21号染色体关键炎症基因剂量先天增加, 可能与DS患者大脑炎症状态相关[45]. 目前尚不清楚炎症基因剂量的改变对DS中AD神经病理学的影响程度.

*APP*拷贝数重复所导致的EOAD被认为与DS-AD的致病机制类似, 均是由于*APP*基因剂量增加. 两类患者均表现出较早的发病年龄、典型的AD神经病理学、高发的CAA概率[46]. 其中, DS患者CAA的表现虽不如*APP*重复患者常见, 但概率高于迟发型AD[47,48]. 无论是唐氏综合征还是由*APP*拷贝数重复导致的AD患者, 均由于*APP*基因剂量的增加导致Aβ过量产生, 并

随后形成淀粉样斑块及后续痴呆的表现, 而迟发型AD中Aβ斑块的形成原因则更为复杂, 受到多种因素影响(图2). DS与AD之间的联系表明通过揭示DS-AD的共患病机制, 有望为理解散发性AD的病理过程提供新的方向和线索. 另外, 阿尔茨海默病的治疗策略也可能在一定程度上适用于DS-AD患者.

2　tau蛋白

2.1　tau蛋白的生理及病理功能研究

微管相关蛋白tau(microtubule-associated protein tau, MAPT)由*MAPT*基因编码, 主要表达于神经元轴突[49]. 通过*MAPT*基因外显子2、3和10的选择性剪接, 产生6种tau亚型. 依据N端插入片段的数量(0、1或2个)和微管结合重复结构域的不同(3R或4R), tau亚型分为0N3R、0N4R、1N3R、1N4R、2N3R、2N4R[50]. 0N3R是胎儿大脑中tau的主要亚型, 在成人大脑中3R和4R tau亚型的总体比例大致相等, 在特定大脑区域可能有所不同[51].

tau蛋白受到多种不同的翻译后修饰并参与多种功能. tau蛋白于1975年首次作为微管相关蛋白被发现, 后证实其为AD中NFTs的主要成分[52,53]. 普遍认为tau蛋白可以稳定微管, 最近的研究同样证明tau在调节微管动态中的作用[50,54,55]. tau蛋白在体外或培养细胞中被发现参与轴突运输, 但小鼠体内tau蛋白的缺失或过度表达并未显著改变轴突运输, 这意味着可能存在未知的体内机制来代偿tau蛋白对于轴突运输的作用[56]. 随着tau蛋白敲除小鼠作为实验模型的广泛使用, 已鉴定出tau蛋白的多种新生理功能以及其在神经退行性疾病中的病理功能. 体内外研究揭示tau蛋白对于Aβ诱导神经毒性的必要作用[57], 另外, tau蛋白对于APP的膜定位至关重要. tau蛋白介导APP向细胞膜的运输, APP的膜细胞膜正确定位保障Fpn功能的正常发挥[58,59]. tau蛋白敲除的小鼠原代神经元中APP被不当运输进而影响细胞铁稳态, tau蛋白敲除小鼠则表现出年龄依赖性的铁积累及运动功能障碍[58,60]. 虽然tau的

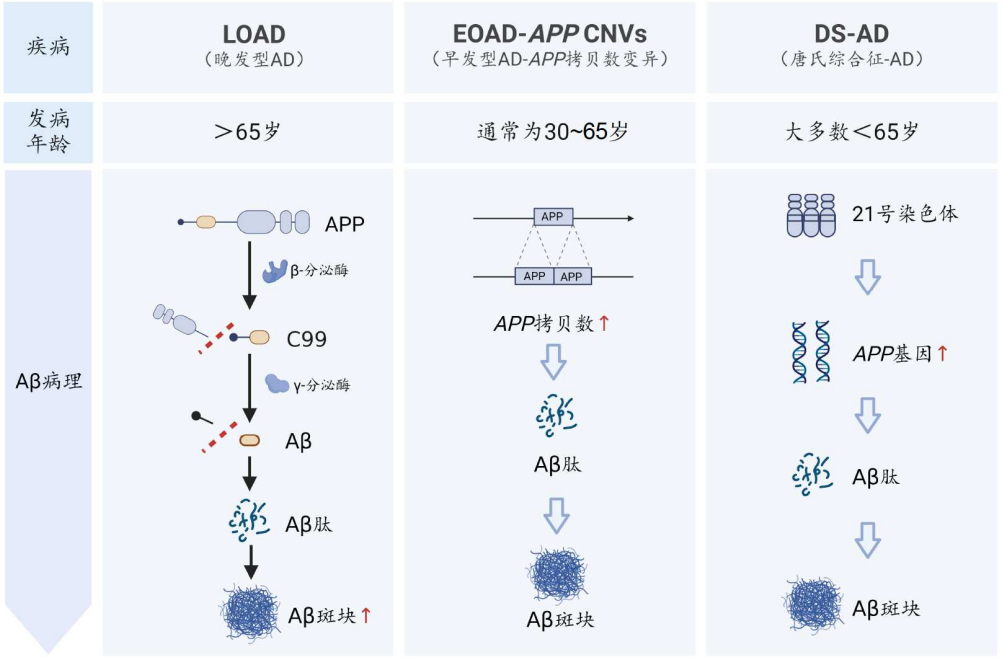

图 2　阿尔茨海默病与唐氏综合征Aβ病理的对比. 晚发型AD、*APP*拷贝数重复所导致的早发型AD及唐氏综合征导致的AD均具有Aβ沉积. 不同在于: 晚发型AD发病多为65岁后, 致病机制十分复杂, 可能涉及Aβ生成及降解异常等多个过程; *APP*拷贝数变异所导致的早发型AD及唐氏综合征导致的AD则是由于*APP*基因剂量增加所致, 并伴随脑淀粉样血管病风险的增加

Figure 2　Comparison of Aβ pathology in Alzheimer's disease and Down syndrome. LOAD, EOAD caused by *APP* copy number duplication or DS-AD all have Aβ plaques. The main differences include the age of onset and pathogenic mechanism. The pathogenic mechanism of LOAD is very complex and may involve multiple processes such as Aβ generation and degradation; EOAD caused by *APP* copy number variations and DS-AD are associated with increased *APP* gene dosage, accompanied by an elevated risk of cerebral amyloid angiopathy

功能可以被其他多余的微管相关蛋白部分补偿，但在老年tau蛋白敲除小鼠中观察到的行为损伤表明tau蛋白是正常神经元和大脑功能所必需的. tau蛋白的功能异常与AD、脑卒中、创伤性脑损伤等多种神经系统疾病相关[61~63]，其在铁调控中的作用提供了此类疾病中tau蛋白参与发病机制的一种可能解释.

目前已发现超过80种不同的*MAPT*基因致病性突变，不同突变对tau蛋白的功能和特性产生多种不同效应[49,64]. 这些影响在突变之间可能重叠或完全不同, 但都会导致聚集体的形成, 并导致神经元损失和萎缩[65]. *MAPT*突变可分为错义突变或剪接突变，且大多数错义突变不仅会改变序列，而且影响选择性剪接导致不同tau异构体的相对比例改变. *MAPT*基因突变可导致17号染色体相关额颞叶痴呆合并帕金森综合征(frontotemporal dementia with parkinsonism linked to chromosome 17, FTDP-17), 表现为认知能力的变化、行为和运动缺陷[66~68]，这提供直接证据表明tau蛋白功能异常对神经退行性病变的驱动作用. 通过分析2N4R野生型tau、P301L突变型tau及V337M突变型tau的相互作用蛋白组，发现突变导致tau与突触相关蛋白的相互作用被改变[69]. 其中, V337M tau已被证明改变tau与轴突起始段中EB3(一种与微管结合并稳定微管的蛋白质)的相互作用, 并损害轴突起始段的可塑性, 导致神经元过度兴奋和兴奋性稳态丧失[70]. 另外，P301L tau及V337M tau削弱了tau与部分核糖体蛋白及线粒体蛋白的相互作用，可能导致蛋白质合成减少及线粒体功能障碍[69].

tau蛋白复杂多样的翻译后修饰同样影响着疾病, 在病理性tau形成NFTs之前，tau蛋白经历一系列翻译后修饰, 包括过度磷酸化、糖基化、乙酰化等[71]. AD中，tau蛋白早期磷酸化破坏了其与微管之间的关联, 促使tau从轴突错误定位到树突区室，进而导致突触功能障碍[72]. 最新研究发现tau 217位的磷酸化与AD的神经退行性变相关，并且通过靶向该位点的免疫治疗可减少tau蛋白的病理聚集，进而改善疾病小鼠模型认知及运动表型[73]. tau蛋白的多个赖氨酸残基位点可被乙酰化并且具有不同的效应，如163、280、281、369位点赖氨酸乙酰化可以抑制tau的降解；而259、290、321、353位点赖氨酸促进tau的降解并抑制其磷酸化和聚集[74,75]. 在AD中已检测到tau蛋白在赖氨酸280的乙酰化[76]. 乙酰化作为新近发现的tau蛋白翻译后修饰形式, 提供一种治疗tau蛋白相关疾病的新型靶点.

tau蛋白虽主要表达于中枢神经系统，但在外周如胰腺、心脏中也有表达[77~79]. 最近研究表明tau蛋白在胰岛β细胞中发挥着独特的生理功能, 其通过促进微管组装限制胰岛素分泌[80]. 在葡萄糖刺激下，敲除tau蛋白或抑制微管组装导致小鼠胰岛素分泌增强，恢复血糖水平[80]. tau蛋白对血糖的调控作用暗示tau蛋白功能异常可能增加AD患者糖尿病的并发风险及严重程度.

2.2 tau蛋白相关动物模型的比较

不同的tau蛋白相关动物模型不仅提供研究tau蛋白正常生理功能的手段，也有助于模拟与tau蛋白表达或功能异常疾病的临床表型，进而更全面地认识疾病本质. 目前tau蛋白相关小鼠模型主要分为tau敲除、tau不同位点突变(P301L/P301S等)、引入人源tau蛋白(human tau, hTau)等.

不同tau蛋白相关小鼠模型的部分表型呈现出一定相似性，但在表型出现时间、具体表型及病理的表现等方面有所差异. tau敲除小鼠在年轻时并未表现出明显的表型或畸形，而在12月龄时出现行为变化和运动缺陷[58]. tau敲除后12月龄小鼠的损伤具体有脑萎缩、黑质神经元的丢失及帕金森样症状，在特定遗传背景下的小鼠可能出现认知缺陷[58,81]. 在tau敲除小鼠中引入hTau使其表达人类tau蛋白的6种亚型，该小鼠模型在6月龄表现出空间记忆异常[82]，并伴有与年龄相关的tau病理学，tau蛋白过度磷酸化并聚集，在9月龄出现神经纤维缠结[83]. TauΔK280小鼠携带与额颞痴呆相关的突变，即K280del，导致tau蛋白缺少第280位的赖氨酸. 虽然该突变小鼠在16月龄未见明显的神经元丢失，但其在海马区发生突触的丢失[84]. 就行为表现而言, TauΔK280小鼠在16月龄测试空间记忆以及情境学习中明显差于对照小鼠[85]. TauC3小鼠是在小鼠体内过表达C端缺乏20个氨基酸的人源tau蛋白截短体从而构建的疾病小鼠模型，该截短体模拟由半胱天冬酶裂解产生的tau片段，通过对TauC3小鼠tau病理及认知水平的评估，发现该小鼠模型早在1.3月龄时表现出过度磷酸化的tau及认知受损[86]. 过表达具有A152T突变的hTau 1N4R亚型的小鼠相较于过表达野生型hTau的小鼠在17月龄或以上时显示出记忆缺陷，并在20月龄时海马部分区域观察到神经元丢失[87]. 作为广泛使

用的tau病理模型小鼠之一，P301S小鼠在八个月内出现神经元丢失和脑萎缩，且具有明显的tau病理[88]. 在行为上，P301S小鼠表现出与年龄相关的认知障碍及运动缺陷，在7~10个月时发展为瘫痪，在12月内的死亡率达80%[88,89]. 另一种tau突变小鼠模型，P301L的突变小鼠表现出相对更早的tau病理及认知功能障碍[90].

tau蛋白过表达、突变及敲除小鼠均表现出不同程度的神经损伤(图3)，这提示在涉及*MAPT*基因拷贝数异常的罕见病中，神经系统的表型在一定程度上源于tau蛋白的功能异常.

2.3　*MAPT*拷贝数变异与神经罕见病

2.3.1　17q21.31微缺失综合征

17q21.31微缺失综合征又称Koolen-de Vries综合征(Koolen-de Vries syndrome, KDVS)，是指由染色体17q21.31区域500~650 kb的缺失导致的一类常染色体显性遗传罕见病[91,92]. 据估计，17q21.31微缺失综合征的患病率约为1/55000，该病主要临床表现包括肌张力低下、发育迟缓、智力障碍、语言发育受损、特征性面部畸形、多器官先天畸形等[93].

17q21.31微缺失综合征患者的缺失片段主要涉及*KANSL1*、*MAPT*、*STH*、*CRHR1*、*IMP5*基因，这些基因中的一个或多个基因剂量不足可能是导致疾病表型的原因. 通过对具有17q21.31微缺失综合征核心临床特征患者的DNA片段分析，证实*KANSL1*的单倍性不足可导致17q21.31微缺失综合征的表型[94,95]. *Kansl1*杂合小鼠表现出认知缺陷、大脑畸形及心脏功能受损，在一定程度上类似于17q21.31微缺失综合征患者的临床表现[96,97]. KANSL1的功能是对组蛋白H4第16位的赖氨酸进行乙酰化，以促进包括自噬相关基因在内一系列基因的转录激活[98,99]. 最近研究发现，*Kansl1*单倍体不足导致小鼠自噬功能障碍及线粒体清除缺陷[97]. 通过对*KANSL1*功能的分析也有望对17q21.31微缺失综合征的致病机制获得更清晰的认识. 然而，单独的*KANSL1*缺失难以解释该疾病全部表型的发生，可能由于位于17q21.31区域其他基因缺失所致.

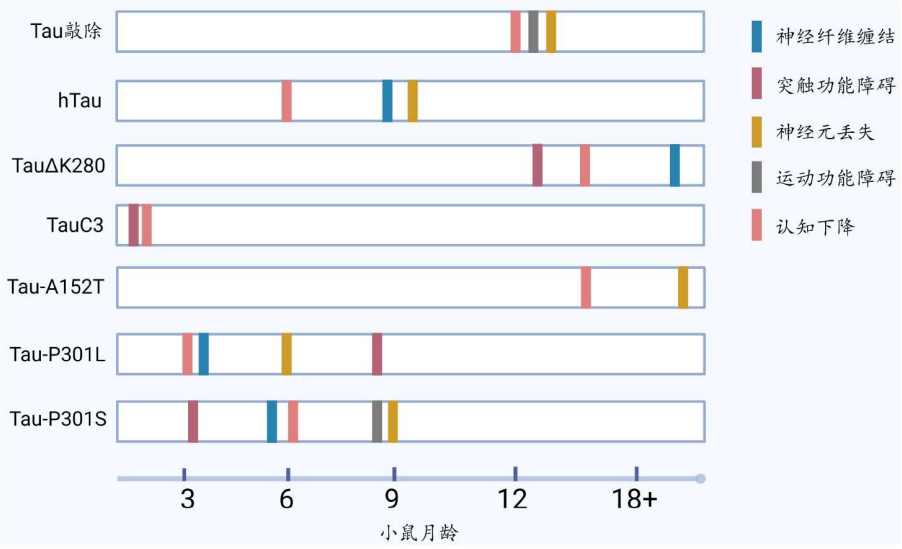

图 3　tau蛋白相关动物模型的对比. tau蛋白敲除、过表达、突变小鼠模型均表现出不同程度的神经损伤，不同模型在表型出现时间有所差异. 认知表型在不同小鼠模型中的具体情况为: 12月龄tau敲除小鼠Y迷宫的表现受损; hTau小鼠在6月龄的视觉空间学习测试中表现明显差于对照小鼠; 16月龄TauΔK280小鼠在Morris水迷宫及被动回避测试中表现受损; TauC3小鼠早在1.3月龄时Y迷宫表现受损及新事物识别缺陷; Tau-A152T、Tau-P301S及Tau-P301L小鼠分别在17月龄、6月龄、2.5~4月龄Morris水迷宫测试中表现出空间记忆能力受损

Figure 3　Comparison of tau protein-related animal models. The various mouse models, including tau knockout, overexpression, and mutations, all exhibited neurological damage, with differences in the timing of phenotypic onset. The cognitive impairments in the different mouse models were as follows: 12-month-old tau knockout mice showed impaired short-term memory in the Y-maze test; 6-month-old hTau mice showed poor performance in visuospatial learning test; 16-month-old TauΔK280 mice showed impaired performance in the Morris water maze and passive-avoidance paradigms; and TauC3 mice showed deficits in the Y-maze and Novel Object Recognition as early as 1.3 months of age; Tau-A152T, Tau-P301S and Tau-P301L mice showed impaired spatial memory in the Morris water maze at 17 months of age, 6 months of age and 2.5–4 months of age, respectively

位于17q21.31区域的*MAPT*基因缺失对于17q21.31微缺失综合征表型的贡献体现在许多方面, 包括脑部结构的异常、心脏的问题等[58,79]. 12月龄tau蛋白敲除小鼠表现出脑部结构的改变及运动功能严重下降, 并且在可溶性tau水平降低的大脑区域观察到铁的积累[58]. 一项基于17q21.31微缺失综合征患者的分子特征研究发现, 不同患者缺失片段的最小重叠区域为仅包含*MAPT*基因在内的160.8 kb[100], 为*MAPT*基因在该疾病中的参与提供直接证据. 因此, 鉴于17q21.31微缺失综合征患者缺失片段涉及多个具有重要生理功能的蛋白编码基因, 其病理及临床表型可能依赖于多基因功能缺失而导致的结果.

2.3.2 *MAPT*拷贝数变异其他临床表型

*MAPT*基因拷贝数缺失或重复均会导致神经系统的损伤: *MAPT*拷贝数缺失相关主要表型是智力低下和畸形; *MAPT*拷贝数重复相关的表型涵盖神经发育、精神分裂及神经退行性变等多种特征, 且患者之间表现出较强的异质性.

2007年报道第一例17q21.31微重复患者表现出明显的颅面特征性畸形及精神运动发育迟缓[101], Kitsiou-Tzeli等人[102]描述的另一名患者具有类似表型. 2009年, Grisart等人[103]描述的4名患者存在行为问题和社交互动不良, 但并未出现畸形. Rovelet-Lecrux等人[104]曾描述一个家族中3名患者表现出额颞叶痴呆的表型, 患者在17q21.31位点存在439 kb的微重复, 包括*MAPT*、*IMP5*、*CRHR1*和*STH*基因. 后续一项研究发现仅*MAPT*基因重复即可导致额颞叶痴呆表型[105]. 除17q21.31微重复导致额颞叶变性表型之外, 研究发现一例*MAPT*基因片段内部分缺失的患者具有额颞叶变性表型[106]. 该患者缺失片段涉及*MAPT*基因的外显子6~9及*STH*基因. 该缺失预计会产生两种截短的tau亚型, 均缺乏首个微管结合结构域, 截短的tau亚型结合微管能力急剧下降[106].

进行性核上性麻痹(progressive supranuclear palsy, PSP)是一种罕见的中枢神经系统疾病, 患病率约为每10万人5~7例, 其临床表型涉及行为、语言、运动等多方面的异常, 神经病理学特征以4R tau病理为主[107]. 2019年一项针对PSP的全基因组CNVs调查首次报道携带*MAPT*拷贝数重复的两例PSP患者[108]. 两名患者均具有典型的PSP神经病理学特征, 拷贝数变异片段涉及*MAPT*整个基因以及17q21.31区域其他基因部分外显子的重复[108], 为tau蛋白在PSP中的致病性提供了更多证据.

3 α-突触核蛋白

3.1 α-突触核蛋白的生理及病理功能研究

α-Syn由染色体4q21的*SNCA*基因编码, 主要定位于突触前末端, 在正常生理条件下处于未折叠的、膜结合的单体形式[109~111]. α-Syn由140个氨基酸组成三个结构域, N端结构域(残基1~60)包含大多数已知的α-Syn突变位点, 如A53T[112]; 中心非淀粉样成分结构域(残基61~95)由疏水侧链组成, 使其易于聚集和毒性[113]; C端结构域(残基96~140)存在多个磷酸化位点, 例如S129、Y125、Y133和Y136, 这些位点的磷酸化异常被认为有助于聚集并产生毒性[114].

虽未完全阐明α-Syn的生理功能, 但其被认为参与记忆形成[115]、神经元存活[116]和神经递质的释放[117,118]等多种过程. 缺乏半胱氨酸串蛋白α(cysteine string protein α, CSPα)的小鼠会出现进行性神经退行性变和突触功能损伤, 而α-Syn的表达可挽救因CSPα缺乏而导致的神经变性和运动障碍, 表明α-Syn在突触处的生理神经保护功能. α-Syn在神经递质释放中的作用主要基于其对突触小泡回收的调节[119]. α-Syn负责促进由短间隔(秒)动作电位触发的多巴胺释放, 以及抑制长间隔(分钟)动作电位触发的多巴胺释放[120]. 这些形式的突触前可塑性与α-Syn在促进突触小泡融合和更新的作用一致, 进一步支持α-Syn的突触前效应取决于神经元活动的特定模式及与神经元活动之间的双向作用. 此外, α-Syn还可以与tau蛋白结合影响微管的稳定性和功能[121,122], 由此可见不同病理蛋白之间的相互作用可能引起协同有害效应.

与tau蛋白类似, α-Syn经历多种翻译后修饰, 如磷酸化、泛素化、乙酰化、O-GlcNac糖基化等, 导致大小、结构和电荷的变化, 影响PD的病理学[123]. 在所有磷酸化位点中, pSer129的研究相对较为充分. Ser129的磷酸化被认为是α-Syn的主要病理修饰形式, PD患者脑内不溶性pSer129 α-Syn水平显著升高[124]. 在体外, Ser129处的α-Syn磷酸化导致更容易形成原纤维[125]. 相反, 大鼠黑质中各种α-Syn形式的表达表明, 非磷酸化Ser129形式使α-Syn病理恶化, 而Ser129磷酸

化可防止神经变性[126], 可能是由于选择的模型不同导致结果之间的差异, pSer129 α-Syn对病理学的影响仍存在争议.

病理性α-Syn从一个神经元传播到另一个神经元, 并诱导正常的α-Syn聚集[127]. 按照病理性α-Syn扩散的模式, 可将α-Syn病理可分为6个阶段, 称为Braak分期[128]. 在第一阶段, 病理改变发生在周围自主神经系统、嗅觉系统及延髓; 在第二阶段, α-Syn病理扩展至脑桥; 在第三、四阶段, 中脑、基底前脑、边缘系统、丘脑、颞叶皮层出现病变. 在第五、六阶段, 多皮层区域出现α-Syn聚集体. 随着Braak分期级数越高, 病情愈发严重, 认知下降也更为显著. 最近一项研究通过在普通棉耳绒猴嗅球单侧注射α-Syn预制纤维分析非人灵长类动物脑内α-Syn病理传播的区域, 注射后在嗅觉系统及边缘系统中观察到严重的α-Syn病理, 病理分布及形态特征与PD患者嗅球表现类似[129]. 另外, 该模型导致嗅球体积的减小、广泛脑区(包括黑质致密部、蓝斑及迷走神经背侧运动核)轻度的α-Syn病理及葡萄糖代谢减慢[129], 该模型通过嗅球注射诱导大范围的α-Syn病理, 这为理解α-Syn病理在非人灵长类动物的驱动与传播提供线索.

3.2 *SNCA*相关拷贝数变异与神经罕见病

3.2.1 早发型帕金森病

*SNCA*的突变与拷贝数变异均可导致早发型帕金森病(EOPD)的发生[130~132]. EOPD属于神经罕见病, 患者发病早(50岁前)、病程长、进展慢, 约占所有PD患者的5%~10%. 目前在EOAD患者中已鉴定出*SNCA*的双倍重复、三倍重复、四倍重复[133,134]. *SNCA*拷贝数重复不仅存在于家族性PD中, 而且也存在于散发性PD中[135]. *SNCA*拷贝数重复的PD患者在临床上常表现出认知障碍及精神病性症状, 如抑郁症、痴呆、自杀倾向、幻觉等[136].

*SNCA*三倍重复的神经细胞表现出多种病理生理缺陷, 包括内质网应激增加[137]、溶酶体及线粒体功能障碍[138]、氧化应激水平升高[139]等. 一项基于*SNCA*不同基因剂量对多巴胺能神经元功能影响的研究[140]表明, α-Syn表达水平随着*SNCA*等位基因的数量增加而增加, 相较于携带2个*SNCA*等位基因的神经细胞而言, 携带4个*SNCA*等位基因的神经细胞线粒体明显受损、氧化应激加剧且表现出钙稳态的失调. 此外, 在外源性α-Syn的刺激下, 携带4个*SNCA*等位基因的神经细胞内α-Syn聚集严重并损害细胞活力. 临床案例同样显示, *SNCA*三倍复制的患者相较双倍复制的患者表现出更早的发病时间(三倍重复为40±14岁、双倍重复为50±11岁)及更迅速的疾病进展[141], 提示α-Syn表达水平与疾病进程密切相关.

3.2.2 多系统萎缩

多系统萎缩(MSA)是一种成人发病的罕见神经退行性疾病, 其临床表现主要有自主神经衰竭、PD样症状、共济失调等[142]. 大约80%的MSA患者具有PD特征(MSA-P亚型), 20%的患者表现出小脑性共济失调(MSA-C亚型). 虽有少部分MSA患者出现执行功能障碍, 但痴呆并非MSA的典型特征[143]. 少突胶质细胞胞质内错误折叠和聚集的α-Syn是MSA的组织病理学标志, 且与脑内神经元丢失相关[144]. 经过年龄校正后MSA患病率约为每10万人4.4例[145]. MSA病程进展快速, 患者通常在发病5~6年内严重残疾、10年内死亡[146]. 然而, 现有治疗策略均无法显著减缓MSA的进展. MSA患者对左旋多巴治疗的响应不佳, 左旋多巴治疗仅能短暂缓解部分MSA患者的帕金森样症状, 疗效随时间推移大幅减弱[147].

Mokretar等人[148]首次报道MSA患者脑细胞中存在体细胞*SNCA*的拷贝数增加, 并且不同分型的MSA患者在主要受累脑区具有不同的表现模式[149]. 另外, 神经元和少突胶质细胞中*SNCA*的体细胞拷贝数增加可能有助于MSA中α-Syn的大脑积累和聚集[150]. 目前对于MSA发病机制的了解仍知之甚少, 缺乏有效的治疗方法且预后不良. 基于对*SNCA*拷贝数重复的MSA患者的综合分析将有助于了解MSA潜在的分子致病机制, 以寻找疾病干预的新靶点.

3.2.3 多系统萎缩与帕金森病的比较

基于对40例PD患者、5例MSA患者及25例对照者冷冻黑质切片的研究, 发现PD、MSA患者在多巴胺能神经元中出现*SNCA*拷贝数增加的可能性显著高于对照者[148]. 另外, PD患者的多巴胺能神经元拷贝数增加与发病年龄呈负相关, 与病程或死亡年龄无关, 在10名早发型PD患者(发病年龄<50岁)中, 9名患者表现出多巴胺能神经元*SNCA*拷贝数的增加[148]. 由此可见, 体细胞*SNCA*的拷贝数增加可能是EOPD及MSA的风险因

素, 或疾病发展的结果. 如上所述, *SNCA*的拷贝数变异可能与EOPD及MSA的发病相关, 而*SNCA*编码的蛋白——α-Syn的病理性聚集是EOPD与MSA的共同特征. PD与MSA均属于突触核蛋白病(Synucleinopathies), 此类疾病的特征为神经元或/和神经胶质细胞存在由α-Syn聚集形成的包涵体. 虽然PD与MSA患者均存在α-Syn病理, PD中形成路易小体的α-Syn纤维与MSA的α-Syn纤维却具有明显不同的构象[151,152]. MSA患者α-Syn纤维相较于PD患者表现出更多的β-折叠片层及较短的扭曲结构, 基于此可开发区分PD与MSA患者的生化检测方法[152].

4 总结与展望

对于Aβ、tau、α-Syn等在神经退行性疾病中扮演重要角色的蛋白, 研究仍聚焦于其异常组装形成的聚集体所造成的神经毒性[153,154]. 而如前所述, 近年来诸多证据表明编码这些蛋白的基因相关拷贝数变异可使得基因剂量改变进而导致神经罕见病的发生, 在常见的神经退行性疾病和罕见神经系统疾病之间建立了潜在的联系. *APP*、*MAPT*、*SNCA*基因的拷贝数变异与相关神经罕见病的不同临床表型相对应, 这有助于理解这些蛋白的多种生理功能, 并为神经退行性疾病中病理蛋白驱动的致病机制提供新的可能解释. 然而, 多数情况下神经罕见病的临床表型可能并不完全依赖于单一的基因而是多种拷贝数变异和其他遗传变异共同导致的结果, 因此还需基于更大样本的系统分析以明确疾病的发病机制.

目前大多数神经罕见病仍缺乏有效的治疗方法, 如何将神经罕见病的基础研究进展转化为潜在的药物治疗策略同样面临较大的挑战. 过往治疗神经罕见病专注于小分子药物, 随着分子生物学的进步, 生物治疗已成为新兴趋势(表2). 在已明确的单一蛋白功能缺陷致病的罕见病中, 酶替代疗法(enzyme replacement therapy, ERT)被作为治疗的一种可行方案, 如重组葡萄糖脑苷脂酶经美国食品药品监督管理局(Food and Drug Administration, FDA)批准治疗戈谢病(由*GBA*基因突变导致的溶酶体贮积病, 患者多有语言障碍、惊厥发作等神经系统症状)[155]. 然而, 以静脉注射的蛋白质难以穿过血脑屏障, 使得该疗法对于神经系统受累的罕见病治疗受限. 反义寡核苷酸(antisense oligonucleotides, ASOs)通过促进特定mRNA的降解减少病理蛋白的产生, 已成为一种高度特异性的疾病干预措施, 如2018年经FDA批准的inotersen用于治疗转甲状腺素蛋白淀粉样变性多发性神经病(transthyretin amyloid polyneuropathy, ATTR-PN)以改善周围神经中淀粉样沉积物的积累[156]. 然而, 寡核苷酸同样面临不易穿过血脑屏障的问题, 因此此类疗法用于神经系统疾病需要侵入性递送方法, 如鞘内或脑室注射. 以重组腺相关病毒(recombinant adeno-associated virus, rAAV)为载体的基因递送疗法已成为一种有效治疗手段, 显示出对神经系统疾病的有效性. 2022年, AAV基因治疗药物Upstaza经欧盟委员会获批上市, 用于治疗18个月以上芳香族L-氨基酸脱羧酶(aromatic L-amino acid decarboxylase, AADC)缺乏症[157]. Upstaza以AAV2为载体, 通过脑定位注射恢复AADC酶的表达, 实现患者运动及认知功能的改善. 相较于传统小分子治疗及蛋白质替代疗法等, 基因疗法仍处于早期发展阶段. 然而, 此类疗法有望一次性治疗甚至治愈疾病, 将对罕见病疗法的发展产生深远影响.

伴随对患者基因组拷贝数变异更大规模的识别以及多种治疗策略的开发应用, 未来有望更好地定义神经罕见病的分子特征, 为患者提供更精准有效的诊疗服务.

表 2 神经罕见病的治疗策略

Table 2 Treatment strategies for rare neurological diseases

	治疗策略	应用
酶替代疗法(ERT)	由缺失或有缺陷的酶引起的疾病可以通过从人类或动物组织中纯化或重组技术等外源提供的方式补充酶进行治疗.	重组葡萄糖脑苷脂酶治疗戈谢病[158]
反义寡核苷酸(ASOs)	通过促进mRNA的降解来减少特定疾病相关蛋白的产生, 原则上可以靶向任何基因产物.	Inotersen治疗ATTR-PN[156]
重组腺相关病毒(rAAV)	对于特定蛋白质功能丧失的疾病, 利用病毒载体用于构建所需蛋白质的编码基因, 在适当启动子控制下实现基因表达.	Upstaza治疗AADC缺乏症[157]

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Copy number variations of proteins associated with neurodegenerative diseases and rare neurological disorders

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Rare neurological disorder is a group of diseases that are phenotypically complicated and largely incurable, and its pathogenesis remains poorly understood. Multiple clinical studies have indicated that copy number variations in key proteins associated with common neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, may lead to rare neurological disorders. This review focuses on the copy number variations related to Aβ, tau, and α-Syn and provides evidence of their links to rare neurological diseases. Further, this review highlights the similarities and discrepancies between rare neurological disorders and common neurodegenerative diseases, with the aim of providing new insights into the therapeutic strategies for these diseases.

rare neurological diseases, neurodegenerative diseases, copy number variations, Alzheimer's disease, tau

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