

肌萎缩侧索硬化症遗传学机制研究进展

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【摘要】 肌萎缩侧索硬化症是一组选择性侵犯运动神经元的神经系统变性疾病。随着基因检测技术的迅速发展,肌萎缩侧索硬化症基因检测从单基因位点测序逐步发展至全外显子组测序或全基因组测序,越来越多影响疾病发生发展的致病基因相继被发现。目前肌萎缩侧索硬化症病理生理学机制主要包括蛋白稳态失衡、DNA 或 RNA 功能异常、细胞骨架和轴突动力学改变、自噬过程和溶酶体功能紊乱、线粒体功能障碍,探究肌萎缩侧索硬化症遗传学机制对阐明其病理生理学机制具有重要意义。本文综述肌萎缩侧索硬化症主要致病基因、遗传学研究方法及相关致病机制,为肌萎缩侧索硬化症治疗提供新的策略。

【关键词】 肌萎缩侧索硬化; 运动神经元病; 遗传学; 综述

Advances on the genetic mechanism of amyotrophic lateral sclerosis

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【Abstract】 Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive involvement of upper motor neuron (UMN) and lower motor neuron (LMN). With the rapid development of sequencing technique, genetic screening of ALS improved from a single locus site sequencing to whole exome sequencing (WES) or whole genome sequencing (WGS), more and more pathogenic genes affecting the occurrence and development of diseases have been discovered. At present, the pathophysiological mechanisms of ALS mainly include abnormal protein aggregation, abnormal DNA or RNA function, changes in cytoskeleton and axon dynamics, autophagy process, lysosome dysfunction, and mitochondrial dysfunction. Exploring the genetic mechanism of ALS has great significance to elucidate its pathophysiological mechanism. This paper reviews the main pathogenic genes, genetic research methods and related pathogenic mechanisms of ALS, reveals the pathogenesis and development of the disease and related pathophysiological mechanisms, and provides new strategies for the treatment of ALS.

【Key words】 Amyotrophic lateral sclerosis; Motor neuron disease; Genetics; Review

This study was supported by National Key Research and Development Program of China (No. 2021YFA0805202, 2018YFC1312003), the National Natural Science Foundation of China (No. 82171431, 81671120), Natural Science Fund for Distinguished Young Scholars of Hu'nan (No. 2020JJ2057), Clinical Research Project of National Clinical Research Center for Geriatric Diseases (No. 2020LNJJ13), and Graduate Education and Teaching Reform Project of Central South University (No. 2020JGB136).

Conflicts of interest: none declared

doi:10.3969/j.issn.1672-6731.2023.03.017

基金项目:国家重点研发计划项目(项目编号:2021YFA0805202);国家重点研发计划项目(项目编号:2018YFC1312003);国家自然科学基金资助项目(项目编号:82171431);国家自然科学基金资助项目(项目编号:81671120);湖南省自然科学基金-杰出青年基金资助项目(项目编号:2020JJ2057);国家老年疾病临床医学研究中心(湘雅医院)临床研究基金资助项目(项目编号:2020LNJJ13);中南大学研究生教育教学改革资助项目(项目编号:2020JGB136)

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肌萎缩侧索硬化症(ALS)是一种选择性侵犯运动皮质、锥体束等上运动神经元(UMN)以及脑干运动核团、脊髓前角等下运动神经元(LMN)的神经系统变性疾病,临床表现主要包括肌无力、肌萎缩、延髓麻痹和锥体束征等,最终死于呼吸肌无力导致的呼吸衰竭。其中 90%~95% 为散发性肌萎缩侧索硬化症(sALS),余 5%~10% 为家族性肌萎缩侧索硬化症(fALS),多呈常染色体显性遗传,常染色体隐性遗传和 X 连锁遗传仅见个案报道^[1]。肌萎缩侧索硬化症高峰发病年龄 55~75 岁,中位生存期约 27.5 个月^[2]。不同国家及地区发病率存在一定差异,欧洲为(2~3)/10 万,亚洲(0.7~0.8)/10 万^[3];中国约为 1.65/10 万^[4]且发病年龄更早,平均发病年龄约为 53.7 岁^[5]。根据已知致病基因分为 27 种亚型,包括仅表现为肌萎缩侧索硬化症的 23 种亚型以及额颞叶痴呆合并肌萎缩侧索硬化症(FTD-ALS)的 4 种亚型。病理生理学机制复杂,主要包括蛋白质异常聚集、DNA 或 RNA 功能异常、细胞骨架和轴突动力学改变、自噬过程及溶酶体功能紊乱、线粒体功能紊乱等(图 1),目前尚无证据支持单一机制可作为肌萎缩侧索硬化症主要病因^[6]。本文拟综述肌萎缩侧索硬化症主要致病基因、遗传学研究方法及相关致病机制,揭示疾病发生发展过程及相关病理生理学机制,以为肌萎缩侧索硬化症治疗提供新的策略。

一、主要致病基因

迄今已发现 50 余个肌萎缩侧索硬化症致病基因以及 100 余种可增加疾病易感性或影响临床表型的相关基因变异^[7]。由于遗传背景的差异,不同国家或地区肌萎缩侧索硬化症致病基因谱系不同,欧洲最常见的致病基因为 *C9orf72*,其次依次为 *SOD1*、*TARDBP*、*FUS*^[8],而 *C9orf72* 基因变异在亚洲患者中较少见,特别是国内患者^[9];亚洲最常见的致病基因为 *SOD1*,其次依次为 *FUS*、*C9orf72*、*TARDBP*^[8];国内基因变异率最高的亦为 *SOD1*,约占家族性肌萎缩侧索硬化症的 25.60%,散发性肌萎缩侧索硬化症的 1.60%^[9]。

二、遗传学研究方法

1. 全外显子组测序 全外显子组测序(WES)通过目标序列捕获技术捕获并富集全基因外显子组区域 DNA,进行高通量测序和生物信息学分析^[10]。不仅可以鉴定已知致病基因的新发变异,而且可以通过与传统连锁分析和全基因组单核苷酸多态性(SNP)芯片拷贝数变异(CNV)结合以克隆新型致病

基因,如 *NEKI*^[11]和 *ANXA11*^[12]等。与 Sanger 测序相比,WES 具有简便、高效的特点,但对基因组拷贝数变异、短串联重复扩增、内含子区域变异等复杂结构变异(SV)的检出率较低^[13]。

2. 全基因组测序 全基因组测序(WGS)包括第二代和第三代测序技术,后者在单分子水平读取核苷酸序列,称为单分子测序(SMS)^[14]。WGS 对检测基因组复杂结构变异具有较大优势,业已在肌萎缩侧索硬化症患者中发现染色体易位或倒位、基因组拷贝数变异^[15]、数目可变的串联重复序列(VNTR)^[16]等多种复杂变异。第三代测序技术具有快速、长读长、无需逆转录直接对 RNA 测序等优势。未来有望通过 WGS 发现更多肌萎缩侧索硬化症相关复杂结构变异。

3. 全基因组关联分析 全基因组关联分析(GWAS)通过 WGS 或 SNP 芯片技术在全基因组范围内检测变异序列,并筛选疾病相关风险位点^[17],可以筛选出低变异风险的等位基因。2013 年,Deng 等^[18]采用 GWAS 在中国汉族人群中检出与肌萎缩侧索硬化症相关的两个易感基因——*SUSD2* 和 *CAMK1G*。目前已经通过 GWAS 发现多个肌萎缩侧索硬化症相关潜在致病基因,如 *C21orf2*、*KIF5A*、*CCNF* 等^[19]。

4. 寡基因遗传 寡基因遗传系指较少几个基因变异共同致病的发生发展过程和临床表型改变。与多基因遗传不同,寡基因遗传涉及的基因相对较少,包括决定疾病发生的主效基因以及发挥修饰作用的微效基因,二者共同影响疾病进展、临床特征及预后。研究显示,多个基因变异的肌萎缩侧索硬化症患者较单基因变异患者的发病年龄更早、疾病进展更迅速^[20]。寡基因遗传模式不符合单基因遗传性疾病的遗传规律,提示肌萎缩侧索硬化症的发病可能由多个基因共同发挥作用,给疾病致病基因的克隆带来较大困难。

5. 表观遗传学研究 表观遗传学研究系指在不改变基因组 DNA 核苷酸序列的前提下,通过 DNA 甲基化、组蛋白重构、RNA 编辑等方式调节基因表达以影响基因功能^[21]。近年研究显示,表观遗传学机制通过调节基因表达,改变基因生物学功能,导致细胞内或细胞间信号转导通路破坏,使神经元变性或凋亡,最终导致肌萎缩侧索硬化症^[22]。DNA 甲基化是目前肌萎缩侧索硬化症表观遗传学研究热点^[23],*OPTN* 基因低甲基化^[24]、*C9orf72* 基因

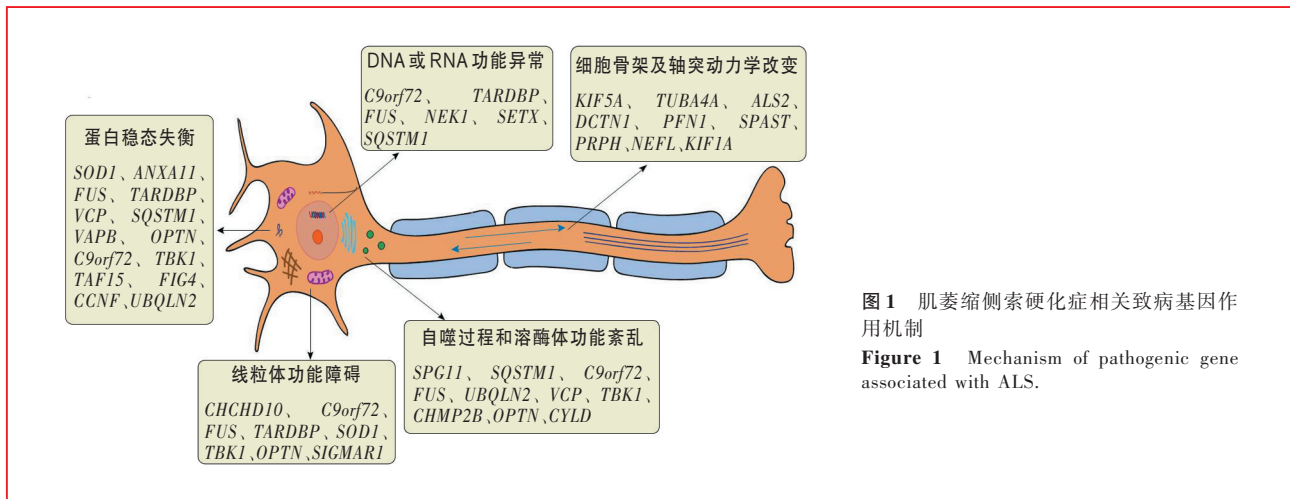


图 1 肌萎缩侧索硬化症相关致病基因作用机制

Figure 1 Mechanism of pathogenic gene associated with ALS.

GGGGCC 六核苷酸重复扩增、CpG 岛超甲基化^[25]等与肌萎缩侧索硬化症发生发展密切相关。

三、主要致病机制及相关基因表型

1. 蛋白稳态失衡 肌萎缩侧索硬化症相关致病基因变异可导致蛋白质错误折叠、异常聚集或降解受损,引起蛋白质异常聚集并产生神经毒性作用,最终导致运动神经元变性坏死。(1) *SOD1* 基因: *SOD1* 基因是首个被发现的肌萎缩侧索硬化症致病基因,定位于染色体 21q22.11,编码超氧化物歧化酶(SOD),该基因变异导致肌萎缩侧索硬化症 1 型(ASL1)^[3]。迄今已发现超过 180 种 *SOD1* 基因变异类型,主要为错义突变,多集中于外显子区域^[26]。*SOD1* 基因变异导致毒性羟自由基聚集,破坏蛋白质正常折叠,影响运动神经元轴突运输。*SOD1* 突变蛋白可激活内质网应激反应,将错误折叠的蛋白质自内质网转运至泛素-蛋白酶体系统(UPS)进行降解,长时间内质网应激反应可诱发细胞凋亡^[27]。*SOD1* 基因变异还可下调蛋白酶体亚基表达,使蛋白酶体活性降低,导致错误折叠的蛋白质无法被有效清除^[28]。(2) *ANXA11* 基因: *ANXA11* 基因定位于染色体 10q22,编码膜联蛋白 A11,该基因变异导致肌萎缩侧索硬化症 23 型(ASL23)^[12]。膜联蛋白 A11 是一组钙依赖性磷脂结合蛋白,参与囊泡运输。*ANXA11* 基因变异可能与膜联蛋白 A11 异常聚集、异常结合钙周期蛋白(calycyclin)、抑制囊泡运输有关。有研究显示, *ANXA11* 基因变异的肌萎缩侧索硬化症患者脊髓神经元存在大量膜联蛋白 A11 异常聚集^[12]。除外上述基因, *VCP*、*UBQLN2*、*OPTN*、*TBK1*、*FIG4*、*CCNF*、*TARDBP*、*FUS*、*UBQLN2*、*VAPB*、*SQSTM1*、*C9orf72*、*TAF15* 等基因通过参与蛋白质降

解、转运和异常聚集等病理生理学过程,直接或间接导致肌萎缩侧索硬化症^[29]。

2. DNA 或 RNA 功能异常 (1) *C9orf72* 基因:

C9orf72 基因定位于染色体 9p21.2,内含子区域存在非编码 GGGGCC 六核苷酸重复扩增(可达数百次甚至数千次)^[30],导致不同临床表型。重复序列的活跃转录可触发 RNA-DNA 杂交链形成,激活 DNA 损伤反应。GGGGCC 重复扩增序列转录形成的 RNA 以及翻译形成的二肽重复蛋白可使 DNA 断裂,导致运动神经元损伤^[31]。(2) *TARDBP* 基因: *TARDBP* 基因定位于染色体 1p36.2,编码 TAR DNA 结合蛋白 43(TDP-43),在维持 mRNA 稳定、蛋白质翻译和细胞核质转运中发挥重要作用。TDP-43 蛋白功能丧失可导致细胞核畸形、细胞周期失调和细胞凋亡,而 TDP-43 蛋白过表达则可引起细胞核 mRNA 异常聚集,使细胞丧失正常功能,导致运动神经元功能异常^[7]。除外上述基因, *SETX*、*FUS*、*NEK1*、*SQSTM1* 等通过基因转录和翻译、基因沉默、微小 RNA(miRNA)生成、RNA 结合和转运等过程调节 DNA 或 RNA 功能,参与肌萎缩侧索硬化症发生过程^[31-32]。

3. 细胞骨架和轴突动力学改变 细胞骨架失稳

和轴突动力学改变可影响神经元轴突物质转运,轴突转运障碍在肌萎缩侧索硬化症发生发展中发挥重要作用。(1) *KIF5A* 基因: *KIF5A* 基因定位于染色体 12q13.3,编码驱动蛋白家族 5A(KIF5A),该基因变异可导致肌萎缩侧索硬化症 25 型(ASL25)。*KIF5A* 基因仅在神经系统呈特异性高表达,参与真核细胞内细胞器的运输^[33]。动物实验发现, *KIF5A* 基因敲除小鼠神经元出现明显的轴突转运障碍、轴突生长减少、神经元存活率降低、线粒体转运障碍

等,表明 *KIF5A* 基因变异可导致细胞骨架缺陷和轴突运输障碍,使运动神经元能量供应、物质代谢和内环境稳态受到损害,进而导致运动神经元变性坏死^[34]。(2)*TUBA4A* 基因:*TUBA4A* 基因定位于染色体 2q35,编码微管蛋白 α 4A。*TUBA4A* 基因变异临床罕见,通常呈现典型肌萎缩侧索硬化症表现,部分可伴随额颞叶痴呆症状^[35]。*TUBA4A* 基因错义突变主要集中于与微管蛋白其他亚基或轴突转运蛋白相互作用的结构域,可抑制微管蛋白合成,导致细胞骨架失稳,破坏运动神经元结构和功能^[36]。此外,*ALS2*、*DCTN1*、*PFN1*、*SPAST*、*PRPH*、*NEFL*,以及近期国内团队新发现的 *KIF1A* 基因^[37]等在纤毛形成、微管稳定、轴突转运等细胞骨架和轴突动力学相关机制中发挥重要作用,破坏神经元功能,诱发肌萎缩侧索硬化症的发生发展^[34]。

4. 自噬过程和溶酶体功能紊乱 溶酶体在自噬过程中发挥重要作用,清除结构和功能异常的蛋白质,自噬功能异常使神经元内异常物质沉积,导致神经元变性坏死。(1)*SPG11* 基因:*SPG11* 基因定位于染色体 15q21.1,编码 Spatacsin 蛋白,该蛋白主要参与细胞自噬后溶酶体再循环。*SPG11* 基因变异导致肌萎缩侧索硬化症 5 型(ALS5),目前发现的变异类型多为无义突变。Spatacsin 蛋白缺失可使溶酶体内脂质异常聚集,导致溶酶体自噬功能紊乱,敲除 *SPG11* 基因的小鼠可出现运动神经元细胞过早凋亡,推测 *SPG11* 基因变异通过扰乱溶酶体功能诱发肌萎缩侧索硬化症^[38]。(2)*SQSTM1* 基因:*SQSTM1* 基因定位于染色体 5q35.3,编码 P62 蛋白。*SQSTM1* 基因致病性变异多为错义突变,主要与 FTD-ALS3 有关^[3]。P62 蛋白通过自噬受体与泛素化蛋白结合并组装成自噬体,通过蛋白之间相互作用影响自噬底物的选择和传递,促进自噬体进入溶酶体降解^[39]。*SQSTM1* 基因变异可导致自噬缺陷,使自噬体无法正常降解。肌萎缩侧索硬化症患者运动神经元存在自噬体异常聚集^[39];敲除 *SQSTM1* 同源基因的斑马鱼运动神经元轴突缩短并表现出运动障碍,注射人源性 *SQSTM1* 基因或自噬激活剂后运动功能恢复正常^[40]。此外,*C9orf72*、*UBQLN2*、*FUS*、*VCP*、*TBK1*、*CHMP2B*、*OPTN*、*CYLD*、*TARDBP*、*SOD1* 等基因也通过调节自噬过程和溶酶体功能参与肌萎缩侧索硬化症的发生^[39]。

5. 线粒体功能障碍 *CHCHD10* 基因定位于染色体 22q11.23,编码线粒体蛋白 CHCHD10,该基因

变异可导致 FTD-ALS3^[3]。*CHCHD10* 基因在维持线粒体基因组稳定性、线粒体嵴完整性和线粒体融合过程中发挥重要作用,突变的 CHCHD10 蛋白过表达可以导致线粒体网路破碎,使 ATP 生成减少,无法满足神经元能量代谢所需,从而加速神经元变性坏死^[41]。除 *CHCHD10* 基因外,还有 *SOD1*、*FUS*、*OPTN*、*SIGMAR1*、*VAPB*、*C9orf72*、*TARDBP*、*SOD1*、*TBK1* 等基因参与细胞能量代谢、线粒体钙稳态、线粒体呼吸功能等多种过程,参与肌萎缩侧索硬化症的发生发展^[42]。

6. 其他机制 (1)*GLT8D1* 基因:*GLT8D1* 基因定位于染色体 3p21.1,编码的糖基转移酶是合成神经节苷脂的关键酶。神经节苷脂可增强星形胶质细胞对神经元的保护作用,促进神经轴突生长,抑制神经炎症。*GLT8D1* 基因变异可导致糖基转移酶活性降低,使神经节苷脂合成减少,导致运动神经元变性或坏死^[43]。(2)*SPTLC1* 基因:*SPTLC1* 基因定位于染色体 9q22.31,编码丝氨酸棕榈酰转移酶长链亚基 1(SPTLC1)。*SPTLC1* 基因变异与青少年型肌萎缩侧索硬化症密切相关^[44]。丝氨酸棕榈酰转移酶(SPT)是鞘脂合成关键酶,*SPTLC1* 基因变异破坏丝氨酸棕榈酰转移酶的正常稳态调节,使其活性不受调节,引起鞘脂水平升高^[45],鞘脂在细胞内聚集产生的细胞毒性可导致神经元变性坏死。研究显示,肌萎缩侧索硬化症患者脑脊液脂质升高,抑制鞘脂合成可加快肌萎缩侧索硬化症模型小鼠病程进展^[46]。(3)*TP73* 基因:*TP73* 基因定位于染色体 1p36.32,编码 TA-p73 和 Δ N-p73 两种蛋白亚型,参与 DNA 损伤后细胞周期阻滞和凋亡反应,促进细胞正常分化。其中, Δ N-p73 蛋白主要存在于脑组织,具有抗凋亡作用,可促进神经元存活。*TP73* 基因变异可导致抗凋亡细胞 Δ N-p73 表达水平降低,使运动神经元凋亡增加^[47]。

综上所述,遗传学机制在肌萎缩侧索硬化症研究中占据十分重要的地位,遗传学研究进展与基因检测技术的发展密切相关。近年来,利用新的基因检测技术已经鉴定出多个肌萎缩侧索硬化症相关新型致病基因,如 *TP73*、*KIF5A*、*DNAJC7* 等^[48]。同时,越来越多的学者认为肌萎缩侧索硬化症是多个基因相互作用的结果,应对肌萎缩侧索硬化症的遗传学机制进行更多研究。随着对疾病遗传学机制认识的提高,将对肌萎缩侧索硬化症的致病机制有更深入的了解,为更有效的药物研发奠定基础。

利益冲突 无

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(收稿日期:2023-01-27)

(本文编辑:栢钰)