·专题综述·

面-肩-肱型肌营养不良症分子学机制研究进展

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【摘要】 面-肩-肱型肌营养不良症(FSHD)呈常染色体显性遗传,以面肌、肩胛带肌和上臂肌群肌无力和肌萎缩发病,逐渐累及躯干肌群和下肢肌群,临床异质性较高,预后相对较好。临床分型包括FSHD1型和FSHD2型,前者与4q35区域*D4Z4*串联重复序列缺失有关,其上游简单序列长度多态性和下游特殊等位序列*4qA*/*4qB*具有选择致病性。4q35区域DNA低甲基化启动表观遗传效应,使*D4Z4*串联重复序列内*DUX4*基因去抑制致异常表达,导致多种肌细胞损害效应。后者由DNA甲基化调控基因——*SMCHD1*基因突变所致。支持面-肩-肱型肌营养不良症是毒性功能获得性疾病学说,为其治疗研究提供重要靶点。

【关键词】 营养不良,面肩肱型; 基因; 突变; 综述

Progress in research on molecular mechanism of facioscapulohumeral muscular dystrophy

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【**Abstract**】 Facioscapulohumeral muscular dystrophy (FSHD), characterized by symmetric or asymmetric muscular weakness of the initial onset of facial, shoulder-girdle and upper arm muscles, and descending to limb muscles, is a classical autosomal dominant myopathy with high clinical diversity and relatively good prognosis. FSHD is catigorized into two types, FSHD1 and FSDH2. Previous studies have demonstrated that 95% patients with FSHD1 were associated with a contraction of *D4Z4* microsatellite repeats on chromosome 4q35, which was pathogenic in the genetic backgrounds, including a special sequence of simple sequence length polymorphism (SSLP) proximal to the *D4Z4* repeats and the *4qA*/*4qB* polymorphism distal to the repeats. In recent years, several reports have confirmed that 4q35 locus leads to DNA hypomethylation and inner *DUX4* gene transcription by epigenetic effect. The abnormal expression of *DUX4* further activates several genes, which inhibit myogenesis, sensitize cells to oxidative stress and induce muscle atrophy. And not only that, FSHD2 is formed by another methylation regulation gene——*SMCHD1* mutations. More and more evidences supported that toxic gain of function mechanism plays an important role in the occurrence of FSHD. The *DUX4* gene becomes an important target for treatment study in the future.

【**Key words**】 Muscular dystrophy, facioscapulohumeral; Genes; Mutation; Review

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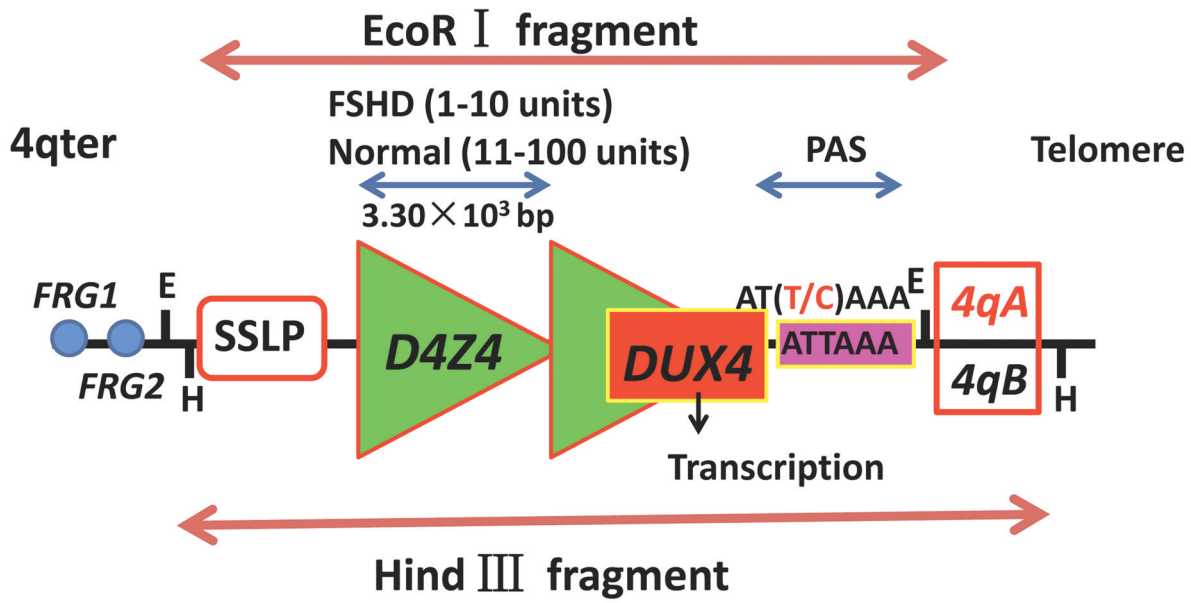
面-肩-肱型肌营养不良症[FSHD,在线人类孟德尔遗传数据库(OMIM)编号:158900]于1882年由法国神经病学家Louis Landouzy和Joseph Dejerine首次报告,亦称为Landouzy-Dejerine型肌营养不良症[1],是继Duchenne型肌营养不良症(DMD)和强直性肌营养不良症(DM)后临床最常见类型,呈常染色体显性遗传,发病率约为1/2万,20岁时外显率达95%,30%患者为新发突变[2]。通常于青少年期发病,主要表现为对称性或不对称性肌无力和肌萎缩,累及面肌、肩胛带肌和上臂肌群,呈现猫脸、鱼嘴、翼状肩胛、游离肩、衣架肩等典型外观,逐渐向下进展累及躯干肌群和下肢肌群。面-肩-肱型肌营养不良症患者存在高度家系间和家系内临床异质性,包括无症状携带者、仅面部轻微受累者和四肢瘫痪者,病程进展缓慢,预后相对较好,一般不直接影响寿命,约20%患者最终依靠轮椅[3]。除骨骼肌受累外,部分患者出现神经性耳聋和视网膜毛细血管扩张,少数严重患者还出现癫痫发作、智力障碍等症状[4-5]。面-肩-肱型肌营养不良症发病机制有别于其他单基因遗传病,不遵循传统致病性突变导致编码蛋白变异的经典模式,成为神经肌肉病领域的研究难点。本文拟对近年来面-肩-肱型肌营养不良症相关分子学机制研究进展进行概述。

一、分子病理学与分子诊断

面-肩-肱型肌营养不良症的致病基因定位于第4号染色体长臂亚端粒区(4q35),是首个发现的由大卫星重复序列缺失导致的神经系统遗传性疾病,与该区域多态性EcoR Ⅰ片段内长度为3.30×10^3 bp的*D4Z4*串联重复序列(DRs)缺失直接相关:正常人群*D4Z4*基因拷贝数为11~100个;面-肩-肱型肌营养不良症患者减少至1~10个,EcoR Ⅰ片段长度缩短至$<38\times10^3$ bp[6]。面-肩-肱型肌营养不良症不仅基因突变类型独特,而且存在2个少见的分子遗传学现象:(1)10q26区域存在与4q35区域高度同源的多态性EcoR Ⅰ片段,此片段长度亦$<38\times10^3$ bp,但无致病性,二者之间存在高频易位现象,应注意鉴别[7-8]。(2)4q35区域*D4Z4*串联重复序列与上游3×10^3 bp处特异性简单序列长度多态性(SSLP)和下游10×10^3 bp处特殊等位序列*4qA*/*4qB*存在密切连锁关系,*D4Z4*基因缺失与特异性SSLP-*4qA*基因型共存而致病[9-10](图1)。研究显示,我国面-肩-肱型肌营养不良症的主要基因型是*4A161PAS*[11]。因此,大片段致病基因的分离和鉴定是基因检测和分子学机制研究的基础。采用脉冲场凝胶电泳(PFGE)联合多重Southern blotting法,是目前国际指南推荐的分子诊断技术[12]。约5%面-肩-肱型肌营养不良症患者存在相应临床表型,未见4q35区域*D4Z4*串联重复序列缩短,称为面-肩-肱型肌营养不良症2型(FSHD2型)[13]。2012年,Lemmers等[14]采用全外显子测序(WES)证实FSHD2型致病基因为*SMCHD1*基因,该基因突变与导致*DUX4*基因表达的*4qA*等位基因共同作用而致病,称为双遗传模式。*SMCHD1*基因单倍体剂量不足机制表明,*SMCHD1*基因突变导致编码蛋白表达下调,使*D4Z4*串联重复序列甲基化降低,进而通过与面-肩-肱型肌营养不良症1型(FSHD1型)相同的表观遗传学机制而发挥作用,因此,不同亚型面-肩-肱型肌营养不良症具有相似的分子通路。

二、分子遗传学及发病机制

面-肩-肱型肌营养不良症是典型人类孟德尔遗传性疾病,但4q35区域*D4Z4*串联重复序列致病性缩短的分子学机制极为复杂,一直是疾病研究的难点,研究者们致力于寻找*D4Z4*基因上下游和内部可能的效应基因。Gabellini等[15-16]发现,面-肩-肱型肌营养不良症患者4q35区域*D4Z4*串联重复序列上游120×10^3 bp处*FRG1*基因呈异常高表达,遂构建转基因小鼠模型,出现类似面-肩-肱型肌营养不良症临床表型和病理改变,故认为*FRG1*基因异常表达可以干扰mRNA前体剪切修饰,与骨骼肌生长发育有关。因此,*FRG1*基因成为重要候选基因[17-18]。此后多项研究显示,该转基因小鼠模型基因结构仅与面-肩-肱型肌营养不良症患者部分相似,未能验证转基因小鼠模型存在*FRG1*基因异常表达[19-20]。2010年,Snider等[21]发现,4q35区域*D4Z4*串联重复序列内*DUX4*基因表达上调,证实该基因在面-肩-肱型肌营养不良症发病机制中发挥重要作用。*DUX4*基因包含2个同源序列和2个富含鸟嘌呤-胞嘧啶(GC)的重复序列,形成读码框(ORF),其末端连接多聚腺苷酸信号(PAS)以稳定*DUX4*基因转录和翻译(图1)。研究显示,*D4Z4*基因富含CpG岛(CpG island),CpG岛主要位于转录调控区附近,是一种重要表观遗传学修饰方式[22]。2013年,Hartweck等[23]证实,面-肩-肱型肌营养不良症的4q35区域*D4Z4*串联重复序列内存在3个DNA低甲基化区域,即DR1、DR2和DR3区域,尤以DR1区域(位于*D4Z4*基因5'端)低甲基化程度最显著。2014年,Gaillard



FSHD, facioscapulohumeral muscular dystrophy, 面-肩-肱型肌营养不良症; E, EcoR Ⅰ 酶切位点; H, Hind Ⅲ 酶切位点; SSLP, simple sequence length polymorphism, 简单序列长度多态性; PAS, polyadenylation signal, 多聚腺苷酸信号

图1 面-肩-肱型肌营养不良症4q35区域相关基因结构模式图：4q35区域EcoR Ⅰ片段由数目不等的长度为3.30×10^3 bp的*D4Z4*串联重复序列组成，其上游简单序列长度多态性和下游特殊等位序列*4qA*/*4qB*具有选择致病性，*D4Z4*串联重复序列内存在*DUX4*基因，其末端连接多聚腺苷酸信号

Figure 1 The structure mode of FSHD related genes in 4q35 region: the fragment of 4q35-EcoR Ⅰ is consisted of a series of *D4Z4* repeats which is composed of numbers of 3.30×10^3 bp, its upstream SSLP and downstream specific allele sequence *4qA*/*4qB* have pathogenic selective effect. The *DUX4* gene exists inside *D4Z4* repeats and connects PAS on the terminal.

等[24]比较面-肩-肱型肌营养不良症患者与无症状携带者DNA甲基化水平，发现面-肩-肱型肌营养不良症患者DNA甲基化水平明显降低。DNA甲基化虽未改变基因结构，但可引起局部DNA构象稳定性改变，从而调控基因表达，进一步证实面-肩-肱型肌营养不良症是一种表观遗传效应的遗传性疾病学说，DNA甲基化检测成为参考诊断指标[24]。

面-肩-肱型肌营养不良症具有高度临床异质性，可能与以下因素有关：(1)4q35区域*D4Z4*串联重复序列拷贝数与临床表型呈负相关，EcoR Ⅰ片段长度缩短越明显、临床表型越严重、外显年龄越早、累及肌群越多[3]。(2)表观遗传效应，DNA甲基化水平与临床表型呈负相关，存在相同*D4Z4*串联重复序列拷贝数的患者，DNA甲基化水平越低、临床表型越严重[24]。(3)临床表型的调控基因，研究显示，*SMCHD1*和*DNMT3B*基因是FSHD1型的调控基因，*SMCHD1*或*DNMT3B*基因突变的FSHD1型患者表现出更严重的临床表型，即*SMCHD1*和*DNMT3B*基因可能与面-肩-肱型肌营养不良症的致病性存在协同作用[25-26]。目前公认的面-肩-肱型肌营养不良症发病机制是，4q35区域*D4Z4*串联重复序列缺失致DNA甲基化水平降低，在表观遗传效应调控下染色质构象改变失去稳定性，引起*DUX4*基因在骨骼肌细胞中表达，产生的DUX4蛋白对肌细胞产生多种毒性作用。

三、DUX4蛋白功能研究

*DUX4*基因表达失调和DUX4蛋白功能异常是面-肩-肱型肌营养不良症发病的关键环节。*DUX4*基因是反转录基因，编码2条全长(DUX4-fl)和截短(DUX4-s)的DUX4蛋白，在人类生殖细胞和早期胚胎干细胞(ESCs)中正常表达，晚近研究显示，*DUX4*基因在胚胎早期对诱导合子基因组激活(ZGA)起关键调节作用，此后则处于沉默状态[27]，但在面-肩-肱型肌营养不良症患者骨骼肌中呈异常表达。低水平DUX4-fl蛋白可以引起下游多种改变，激活一系列去抑制级联反应，导致肌细胞凋亡和萎缩、炎症反应、分化缺陷和氧化应激，但其具体生物学功能尚未完全阐明[28]。目前较为公认的DUX4蛋白在骨骼肌中表达的病理生理学机制包括：(1)细胞凋亡学说，DUX4蛋白可以诱导抑癌基因*p53*表达，导致细胞凋亡，引起肌肉损害[29]。(2)T淋巴细胞介导的细胞炎症反应学说，DUX4蛋白异常表达可以激活

免疫反应，类似吞噬细胞介导的抗肿瘤反应。免疫反应激活CD4$^+$T细胞和CD8$^+$T细胞，发生以T淋巴细胞介导为主的血管周围炎性细胞浸润，引起肌细胞肥大和细胞核聚集，导致肌肉损害[30]。(3)DUX4蛋白表达与长末端重复序列(*LTR*)的反转录转座子和内源性重复序列的转录激活相关，同时抑制自身免疫对逆转录病毒感染的应答，通过转录激活防御素DEFB103抑制肌细胞分化、再生[31]。Jones等[32]和Mitsuhashi等[33]予肌细胞、斑马鱼和蟾蜍注射微量*DUX4* mRNA以建立面-肩-肱型肌营养不良症细胞和动物模型，触发多种级联反应，导致肌细胞凋亡、卫星细胞发育抑制、炎症反应和氧化应激反应障碍等一系列病理生理改变。Ansseau等[34]通过显微注射腺相关病毒载体包装的*D4Z4*基因，向野生型小鼠C57BL/6导入不同长度的D4Z4串联重复序列，可以观察到与人类高度同源的*DUX4*基因高表达，但未出现相应临床表型。因此，目前普遍认为*DUX4*基因异常表达是面-肩-肱型肌营养不良症的分子学机制，但某些关键途径尚不明确，如面-肩-肱型肌营养不良症是受*DUX4*基因异常表达的单因素调控还是多因素联合调控。

四、小结和展望

面-肩-肱型肌营养不良症目前尚无有效治疗方法，适当的康复训练可以延缓疾病进展。发病机制已趋于明朗，是表观遗传效应导致的毒性功能获得性(toxic gain of function)疾病，其中*DUX4*基因去抑制致异常表达是关键致病机制，成为今后治疗研究的重要靶点。基因治疗方面，主要通过反义寡核苷酸(ASO)或干扰RNA(RNAi)技术抑制*DUX4*基因过表达，从而达到改善肌肉损害之目的[35-36]。近年来，采用新型基因编辑技术实现多靶点精准基因调控、体外调控*DUX4*基因表达、寻找抑制*DUX4*基因的小分子化合物为面-肩-肱型肌营养不良症的治疗带来新的曙光。

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