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强直性肌营养不良症DMPK基因CTG重复序列与Alu±1kb单倍型研究

Studies of the Haplotypes of CTG Triplet Repeat and Alu±1kb in DMPK Gene of Myotonic Dystrophy

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摘要　强直性肌营养不良(myotonic dystrophy,DM)是由于DMPK基因3′非翻译区CTG重复序列异常扩展所致的、主要累及神经肌肉系统的常染色体显性遗传病。在该基因的第8内含子中还存在一个Alu重复序列的1kb插入/缺失多态性,即Alu±1kb多态性。为了帮助阐明汉族人群中DM突变的起源,并为解释DM在不同群体中发病率的差异提供更多依据，本文从300例已知CTG拷贝数的正常汉族群体中随机挑选60例,首先通过PCR扩增确定其Alu±1kb多态性，然后对Alu±1kb和CTG双杂合的标本,采用长PCR方法先行扩增含Alu±1kb和CTG重复序列的DNA片段,再分别对含Alu(+)和Alu(-)的DNA片段中的CTG拷贝数进行常规PCR分析,以确定二位点的单倍型。结果表明60例正常人中二位点间呈连锁不平衡。其单倍型为:(CTG) 5均与Alu(+)连锁；多数(CTG)11～14与Alu(-)连锁；在两个(CTG)≥19的等位基因中一个与Alu(+)连锁，另一个与Alu(-)连锁。各民族相关资料的比较提示，汉族人群中(CTG)11～14与非洲黑人的起源可能不同;(CTG)19～30/Alu-1kb在汉族人群中的频率远比欧洲人群的高；(CTG)19～30/Alu-1kb与(CTG)19～30/Alu+1kb在汉族人群中是以一定比例共存的；(CTG)19～30在不同民族间的起源不尽相同；如果从(CTG)5到(CTG)19～30的假设成立的话，则很可能是一个较为复杂的过程。

Abstract: Myotonic dystrophy(DM),an autosomal dominant disease of the neuromascular system,is caused by expansion of the CTG repeats in the 3′ untranslated region of the DMPK gene. In the eighth intron of this gene,there is another polymorphism—the insertion/deletion of 1kb Alu repeat(Alu±1kb). In order to help elucidate the origin of DM mutation in Chinese Han patients,and explain the difference of incidence of DM in different populations, 60 normal Han individuals were randomly chosen from 300 Chinese,whose CTG copy number had been previously ascertained. The polymorphism of Alu±1kb of the 60 cases were firstly analyzed by in vitro amplification; then the 22 cases in which both sites were heterozygous were analyzed as following:the fragments containing both Alu±1kb and CTG repeat sequence were first amplified by long PCR method; and then the CTG copy numbers were analyzed in the Alu(+)and Alu(-)alleles. In the 60 cases studied,a remarkable linkage disequilibrium between CTG triplet repeats and Alu±1kb were observed. All the(CTG)5 alleles were linked with Alu(+),and most of the(CTG) 11—14 alleles were linked with Alu(-); one of the two alleles of(CTG) ≥19 was linked with Alu(+),the other was linked with Alu(-). This suggests that the origin of(CTG)11—14 in Chinese Han may be different from that of African Blacks; the frequency of (CTG)19—30 /Alu—1kb in Chinese Han might be much higher than that in Europeans Caucasians. The (CTG)19—30/Alu—1kb and(CTG)19—30/Alu+1kb coexist in Chinese Han in some proportion; the origin of (CTG)19—30 in different population may be different; if the hypothesis of(CTG)5 to(CTG)19—30 is true,then the progress should have been a relatively complicated process.

关键词　强直性肌营养不良症　单倍型分析　长PCR　三核苷酸重复序列　Alu重复序列 Key words　myotonic dystrophy　haplotype analysis　long PCR　triplet repeats　alu repeats

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