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# 7例携带线粒体tRNA C5601T突变的Leber遗传性视神经病变家系的相关研究

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摘要 文章收集了7例携带线粒体tRNA$^{Ala}$ C5601T突变的中国Leber遗传性视神经病变(Leber’s he-reditary optic neuropathy, LHON)的家系, 通过眼科检查和遗传学分析, 发现7个家系的外显率很低, 分别为9.5%、14.3%、4.5%、8.3%、10.0%、22.2%和25.0%。用24对有部分重叠的引物对7个先证者线粒体DNA(Mitochondrial DNA, mtDNA)全序列进行扩增, 并进行相关的分子生物学分析, 结果发现这些家系均未携带G11778A、G3460A和T14484C这3个常见的原发突变位点, 而在tRNA$^{Ala}$上发现了C5601T同质性突变, 多态性位点分析分别属于东亚线粒体单体型G2、G2a1、G2a1、G2、G2b、G2a1、G2。C5601T突变位于线粒体tRNA$^{Ala}$的高度保守区(通用位点为59位), 可能引起tRNA空间结构和稳定性发生改变, 继而影响tRNA的代谢, 导致线粒体蛋白和ATP合成障碍, 最终导致视力损害。因此, tRNA$^{Ala}$ C5601T突变可能是与LHON相关的线粒体突变位点。同时低外显率提示其他因素(包括核修饰基因、环境因素)可能影响这7个中国C5601T突变家系的表型表达。

关键词： Leber遗传性视神经病变 线粒体 突变 视力损害 tRNA

Abstract： We reported here the clinical, genetic, and molecular characterization of Leber's hereditary optic neuropathy (LHON) with C5601T mutation in seven Chinese families. The ophthalmologic examinations of seven Chinese families who were clinically diagnosed LHON were conducted. Strikingly, these families exhibited very low penetrance of visual impairment, and the penetrance was 9.5%, 14.3%, 4.5%, 8.3%, 10.0%, 22.2% and 25.0%. Meanwhile, entire mitochondrial genome of seven probands was amplified by PCR using 24 pairs of oligonucleotide primers with overlapping fragments. Molecular analysis of mitochondrial DNA (mtDNA) in these pedigrees revealed the absence of three common LHON associated G11778A, G3460A and T14484C mutations but the presence of homoplastic LHON associated tRNA$^{Ala}$ C5601T mutation in probands and other matrilineal relatives. These mtDNA polymorphism sites belongs to the Asian haplogroups G2, G2a1, G2a1, G2, G2b, G2a1 and G2. By analyzing mitochondrial genome, seven LHON families all carry the C5601T mutation. The C5601T mutation occurs at the highly conserved nucleotide (conventional position 59) of tRNA$^{Ala}$, thereby contributing to the structural formation and stabilization of functional tRNAs and leading to mitochondrial dysfunction involved in vis-ual impairment. The incomplete penetrance of visual loss in these seven Chinese pedigrees strongly indicates that the tRNA$^{Ala}$ C5601T mutation was itself insufficient to produce a clinical phenotype. The lack of func-tional mtDNA variants in these pedigrees ruled out the role of mitochondrial background in the phenotypic expression of visual loss. Therefore, nuclear backgrounds and environmental factors seem to be modifying factors for the phe-notypic manifestation of the tRNA$^{Ala}$ C5601T mutation in the seven Chinese families.

Keywords： Leber’s hereditary optic neuropathy, mitochondrial, mutation, visual impairment, tRNA

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