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线粒体tRNAIle A4317G突变可能影响12S rRNA A1555G突变相关的耳聋表型表达

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摘要 线粒体12S rRNA基因A1555G突变与非综合征型耳聋和氨基糖甙类抗生素(Aminoglycoside antibiotics, AmAn)致聋相关。文章通过对一个携带线粒体12S rRNA A1555G突变的中国汉族母系遗传耳聋大家系成员进行听力学检查和遗传学分析, 发现该家系耳聋外显率很高, 包括AmAn使用史的耳聋外显率为81%, 不包括AmAn使用史的耳聋外显率66.7%, 明显高于其他携带A1555G突变的耳聋家系。对该家系进行线粒体基因组全序列分析发现存在同质性的tRNAIle A4317G突变和38个多态位点, 属于东亚线粒体B4c1b2单体型。进一步分析发现A4317G突变位于tRNAIle的tRNAIle TΨC环区的高保守性区域(第59通用位点), 该突变可能影响tRNAIle二级结构和功能, 从而导致线粒体功能缺陷, 且在961例正常对照中未发现该突变。同时, 其他线粒体DNA并未发现有功能意义的突变位点。因此, A4317G突变可能影响tRNAIle的代谢并加重A1555G突变导致的线粒体功能缺陷, 最终导致耳聋的外显率增高。从而推测线粒体tRNAIle A4317G突变可能是一个影响12S rRNA A1555G突变的耳聋表型表达的因素。

关键词: 耳聋 突变 线粒体 tRNA 表型表达

Abstract: Mitochondrial 12S rRNA A1555G mutation has been associated with both aminoglycoside-induced and nonsyndromic hearing loss. In this report, we performed a clinical and genetic evaluation, and mitochondrial genome analysis of one hearing-impaired Chinese family carrying the A1555G mutation. Strikingly, the penetrances of hearing loss in this family, which were 81% and 66.7%, respectively, when aminoglycoside-induced hearing loss was included or excluded. The penetrances of hearing loss in this family were significantly higher than those in other Chinese families carrying the A1555G mutation. Sequence analysis of their mitochondrial genomes revealed the presence of homoplasmic tRNAIle A4317G mutations and 38 mtDNA polymorphisms belonging to East-Asian haplogroup B4c1b2. Further analysis revealed that other mitochondrial DNA variants were not functional significantly, while the A4317G mutation is localized to a highly conserved nucleotide (conventional site 59) at tRNAIle TΨC loop of tRNAIle. The mutation may alter secondary structure and function of this tRNA, thereby leading to mitochondrial dysfunction. Allelic analysis showed that this mutation was absent in 961 hearing normal Chinese controls. Thus, the altered tRNAIle metabolism by the A4317G mutation may aggra-vate mitochondrial dysfunction associated with the A1555G mutation, and contribute to the higher penetrance of hearing loss. Therefore, the tRNAIle A4317G mutation may act as a mitochondrial modifier to influence the phenotypic manifesta-tion of the A1555G mutation.

Keywords: hearing loss, mutation, mitochondrial, tRNA, phenotypic expression

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