A Novel Mutation in the Mitochondrial 16S rRNA Gene Associated with MELAS Syndrome, Diabetes Mellitus, Hyperthyroidism and Cardiomyopathy.

謝榮鴻
Hsieh RH;Li JY;Pang CY;Wei YH.

Abstract

Using RNase protection analysis, we found a novel C to G mutation at nucleotide position 3093 of mitochondrial DNA (mtDNA) in a previously reported 35-year-old woman exhibiting clinical features of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome together with diabetes mellitus, hyperthyroidism and cardiomyopathy. The patient also had an A3243G mutation in the tRNA(Leu(UUR)) gene and a 260-base pair duplication in the D-loop of mtDNA. The fibroblasts of the patient were cultured and used for the construction of cybrids using cytoplasmic transfer of the patient's mtDNA to the mtDNA-less rho(0) cells. RNA isolated from the cybrids was subjected to RNase protection analysis, and a C3093G transversion at the 16S rRNA gene and a MELAS-associated A3243G mutation of mtDNA were detected. The novel C3093G mutation together with the A3243G transition were found in muscle biopsies, hair follicles and blood cells of this patient and also in her skin fibroblasts and cybrids. The proportion of the C3093G mutant mtDNA in muscle biopsies of the patient was 51%. In contrast, the mutation was not detected in three sons of the proband. To characterize the impact of the mtDNA mutation-associated defects on mitochondrial function, we determined the respiratory enzyme activities of the primary culture of fibroblasts established from the proband, her mother and her three sons. The proportions of mtDNA with the C3093G transversion and the A3243G transition in the fibroblasts of the proband were 45 and 58%, respectively. However, the fibroblasts of the proband's mother and children harbored lower levels of mtDNA with the A3243G mutation but did not contain the C3093G mutation. The complex I activity in the proband's fibroblasts was decreased to 47% of the control but those of the fibroblasts of the mother and three sons of the proband were not significantly changed. These findings suggest that the C3093G transversion together with the A3243G transition of mtDNA impaired the respiratory function of mitochondria and caused the atypical MELAS syndrome associated with diabetes mellitus, hyperthyroidism and cardiomyopathy in this patient.