A Novel Gene Mutation Associated with Leigh Syndrome and Optic Atrophy

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Mitochondria are found in all nucleated cells and are principal generators of ATP, the primary energy source for the cell. Protein components of the complexes that synthesize ATP are encoded in both nuclear and mitochondrial genomes. Mutations in mitochondrial DNA (mtDNA) can affect many tissues and manifest as neurological (i.e., Leigh Syndrome), cardiac, respiratory, endocrinial and ophthalmological (i.e., optical atrophy) disorders.

We have identified a family with two affected children with potential mtDNA disease. A daughter died in infancy of a Leigh-like syndrome, and the son, now in his teens, has optic atrophy. Direct sequencing of mtDNA revealed a nucleotide change from an adenine to a guanine at the 3145 nucleotide position (A3145G), which lies within the 16S rRNA coding sequence. Semi-quantitative radiolabeled PCR followed by digestion with the endonuclease Stul reveals the presence of this change in the mtDNA of the son, daughter, and asymptomatic mother, but not in the father or 93 unrelated control specimens. This nucleotide change was reported in the Human Mitochondrial Genome Polymorphism Database, however its pathogenicity cannot be ruled out since it was identified only in 5 individuals, all of whom were either Parkinson or type II diabetes patients.

16S rRNA is a key structural and functional component of the ribosome, which carries out protein synthesis in the cell. A3145 is located in the close proximity of the binding site for elongation factors. Therefore, identity of this nucleotide might have impact on mitochondrial protein synthesis. This hypothesis is currently tested by pulse-labeling of mitochondrial proteins. Alternatively, since 16S rRNA is transcribed together with tRNA(Leu) and ND1 genes as one polycistrionic transcript, the A3145G change might affect the further processing of the primary transcript and/or result in abnormal levels of the tRNA(Leu) and ND1 mRNAs. To determine this, quantitative RT-PCR is being performed on samples from patients and normal controls to assess the relative levels of 16S rRNA, tRNA(Leu) and ND1.