Spinocerebellar ataxia and the A3243G and A8344G mtDNA mutations

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RESULTS

A3243G
The mtDNA tRNALeu(UUR) gene was amplified using the following primers: L8155 (5'-ggtatactacggtcaatgtc-3'), H8366 (5'-tctctagtgaaggaggtgg-3'), standard cycling conditions, and an annealing temperature of 52°C. After last cycle labelling with 0.3 µl FdNTP (PE Biosystems), the products were digested with BanII.

For both mutation analyses, the RFLP products were separated on a 6% acrylamide gel by electrophoresis using the ABI 373 automated sequencer (Perkin Elmer). The presence or absence of mutant peaks was determined using Genescan and Genotyper software (PE Biosystems), and the area of each peak was used to calculate the proportion of mutant mtDNA.

DISCUSSION

We have shown that the A3243G and A8344G mutations are rare causes of spinocerebellar ataxia in our region. Only 8% A3243G mutation was detected in the blood sample from case A3243G.

Abbreviations: ADCA, autosomal dominant cerebellar ataxia; SCA, spinocerebellar ataxia; FA, Friedreich’s ataxia; mtDNA, mitochondrial DNA.
The A3243G and A8344G mutations are at least twice as prevalent as the total number of other mtDNA point mutations known to cause disorders involving the central nervous system. It is therefore likely that other mtDNA point mutations account for a significant number of undiagnosed cases of ataxia in our series. It would be difficult to investigate this possibility without carrying out muscle biopsies on affected subjects from each family. The percentage level of mutant mtDNA in blood may fall below the detection threshold for mtDNA sequencing. Based upon dilution experiments performed in our laboratory, we would not have detected the A3243G mutation in case 1 by using automated mtDNA sequencing of blood mtDNA. Thus, even if we had sequenced the entire mitochondrial genome using blood mtDNA from the remaining 81 families studied here, there would be no guarantee that we would detect other pathogenic mtDNA mutations. Much higher percentage levels of mutant mtDNA are usually present in skeletal muscle, comfortably exceeding the threshold for detection by automated mtDNA sequencing. It is for this reason that muscle mtDNA is conventionally used when searching for novel mtDNA mutations.

It is important to consider the possibility that the presence of mtDNA mutations in patients with ataxia might be a coincidental association. Hereditary ataxia is a syndrome caused by abnormalities of central neurones, such as external ophthalmoplegia, proximal myopathy, diabetes mellitus, epilepsy, or myoclonus. Similarly, in the family reported by Santorelli et al., the proband and a maternal relative had neuropathological features of Leigh syndrome. Presumably this would have been apparent on MRI imaging had this investigation been available at the time of presentation. Similarly, in the family studied by Howell et al., one subject had cutaneous lipomata and myoclonic jerks, one had hypertrophic cardiomyopathy, and two children died with a cardiomyopathy and Leigh syndrome. These findings stress the importance of thorough clinical assessment of patients with spinocerebellar ataxia before genetic testing. Although there are many clinical similarities between autosomal spinocerebellar ataxia syndromes and mtDNA disorders, there are often key clinical clues that point to a mitochondrial aetiology. MtDNA analysis should be considered in patients with unexplained sporadic and maternally inherited ataxia.

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REFERENCES