G164 Evaluating Length Heteroplasmy in the Human Mitochondrial DNA Control Region

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After attending this presentation, attendees will have a better understanding of length heteroplasmy in the human mitochondrial DNA control region. The importance of point heteroplasmy in forensic casework is already known; what is less understood, but more commonly encountered, is length heteroplasmy. The purpose of this research was to examine the mechanisms and mutation rates of human mitochondrial DNA length heteroplasmy, to assist forensic practitioners to identify length heteroplasmy, and to use our guidelines to analyze data where heteroplasmy is present.

This presentation will impact the forensic science community by showing forensic scientists how to analyze mitochondrial DNA results that are complicated by exhibiting length heteroplasmy. Previously, these types of mtDNA results may have been disregarded due to the unknown mutation rate and mechanisms of length heteroplasmy. In this presentation, pedigree data from families in Kerala, India, have been analyzed to elucidate the mutation mechanism and the mutation rates of length heteroplasmy. For the application of length heteroplasmy to forensic science, these results demonstrate the importance of understanding heteroplasmy to be able to confirm maternal relationships, and shows that new point mutations are heteroplasmic in the first generation. Worked examples to assist the forensic practitioner will also be presented.

Examination of the mitochondrial DNA control region found that in more than five percent of mother-child pairs a mutation has occurred in at least one mtDNA C-stretch, blurring the biological relationship between the woman and her alleged child. How then should the forensic practitioner handle fast-mutating C-stretches? This problem was explored experimentally and statistically in five steps: (1) first, DNA samples were collected from 248 families (1,172 individuals) living in the most highly radioactive area in the world (Kerala, India). The natural radiation levels in coastal Kerala are about 10mSv and are, therefore, around ten times higher than normal. This provides an environment which speeds up the mutation rate and allows mutations to be observed as they happen and are transmitted to the children. DNA samples were collected from members of the family covering up to four generations, so mutations occurring between generations could be examined; (2) second, the presence of three known C-stretches and identified a fourth new C-stretch in the mtDNA have been confirmed. The mtDNA control region in humans is approximately 1,122-bp long and is comprised of regions with repetitive tracts of consecutive cytosines. Such “C-tracts” are prone to length heteroplasmy; in other words, one individual can have various mtDNA lengths in his or her cells which differ by the number of C’s at these C-tracts; (3) third, a consistent classification of C-stretch status was developed based on the underlying biological process; (4) fourth, the mutation rate observed in the irradiated families was determined, the mutation rate being accelerated and therefore a highly conservative "worst-case" estimate for any situation likely to be encountered in a forensic mtDNA deficiency case context worldwide; and, (5) finally, based on the mutation rate that was calculated, a simple statistical treatment of C-stretch mutations, which will be demonstrated in a worked example is proposed.

Mitochondrial DNA, Heteroplasmy, Radioactivity

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