The Roles of Mutation Rate and Selective Pressure on Observed Levels of the Human Mitochondrial DNA Deletion mtDNA^{4977}

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Abstract

The mitochondrial deletion mtDNA^{4977} has been found at high levels in individuals with certain neuromuscular and neurological diseases, and at lower levels in older normal individuals. We use experimental estimates of the mutation rate of mtDNA^{4977} and of the half-life of mitochondrial genomes to construct a model of mitochondrial replication and mutation that is consistent with observed levels of the deletion. We conclude that deleted genomes have a slight selective advantage, at least in some tissues. Our results suggest that for an individual to attain a clinically significant level of the deletion, between 0.2% to 0.5% of the mitochondrial genomes in the original oöcyte must have been deleted.

Keywords: branching process; Kearns-Sayre syndrome; mitochondria; selection

1 Introduction

The human mitochondrial mutation mtDNA^{4977} is a 4977 base pair deletion originating between two 13 bp direct repeats in normal mtDNA. This deletion is associated with the neuromuscular and neurological diseases progressive external ophthalmoplegia (PEO), Kearns-Sayre syndrome (KSS) and Pearson's marrow/pancreas syndrome. Symptoms of these sporadic diseases range from mild to severe, depending on the level to which the deleted molecules have accumulated. For a review of diseases associated with mutations in mitochondrial DNA, see DiMauro and Wallace [10], Wallace [26], DiMauro [9] and Bianchi *et al.* [3]. MITOMAP (`http://www.mitomap.org`) is a very useful resource for human mitochondrial data and references.

The mtDNA^{4977} deletion has also been found at low levels in normal adults and appears to accumulate with age, primarily in non-mitotic tissues (Cortopassi *et al.* [8], Arnheim and Cortopassi [1], Corral-Debrinski *et al.* [7], Hattori *et al.* [14], Yen *et al.* [27], Zhang *et al.* [28]). The level of accumulation is found to vary among different tissues and even within tissues. For example, studies on the brains of old normal individuals has shown that the substantia nigra, caudate and putamen can have hundreds of fold higher levels of mtDNA^{4977} than the cerebellum (Corral-Debrinski *et al.* [7], Soong *et al.* [25]).