A combination of three common inherited mitochondrial DNA polymorphisms promotes longevity in Finnish and Japanese subjects

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Mitochondrial DNA (mtDNA) coding region polymorphisms, as well as the 150T polymorphism in the noncoding region, have been associated with longevity. We have studied here the association of 150T with longevity further and assessed differences in this association between various mtDNA haplogroups. We analysed a sample of 321 very old subjects and 489 middle-aged controls from Finland and Japan. 150T was more frequent among the very old than among the controls in both the Finnish and Japanese subjects. Interestingly, the association was not similar in all haplogroups, and a stratified analysis revealed that two additional common polymorphisms, 489C and 10398G, modified the association between 150T and longevity. These findings suggest that longevity is partly determined by epistatic interactions involving these three mtDNA loci.
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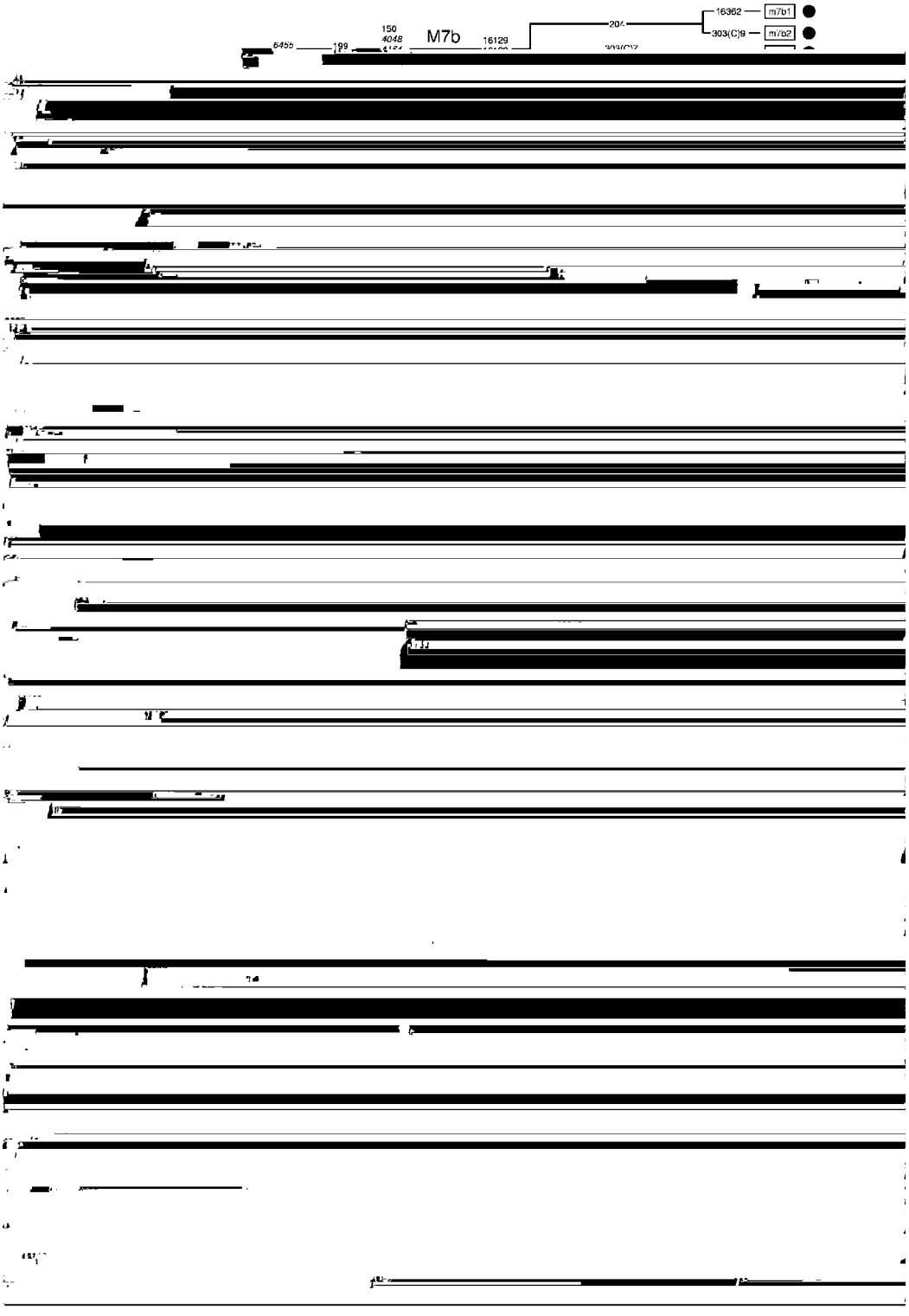
Introduction

Mitochondrial DNA (mtDNA) is a maternally inherited genome that encodes 22 tRNAs, two rRNAs and 13 subunits of the respiratory chain complexes and ATP synthase. These complexes catalyse the reactions of oxidative phosphorylation that produce ATP and also contribute to oxygen free radicals, which are thought to play a role in the aging process.[1] Interestingly, longevity shows maternal inheritance.[2] Uniparental inheritance and high mutation rate have led to mtDNA lineages (haplogroups), which are defined by ancient polymorphisms and characterised by considerable variation. The European population is almost exclusively distributed among the nine haplogroups designated as H, I, J, K, T, U, V, W and X, whereas haplogroups A, B, C, D, F, G and certain subclusters of macrohaplogroups M and N are characteristic to Asian populations, hap-

ch a 5178A (charac eri ing haplogro p D) in he Japane e[7] and 9055A (charac eri ing haplogro p K) in he French[8] and Iri h,[9] and m DNA haplogro p J in he I alian [10] and he Finn .[11] F r hermore, he 150T poly-morphi m hin a 1.1 kb noncoding con rol region of m DNA ha been repor ed o be more pre alen in cen enarian han in con rol .[12] In ere ingly, 150T i pre en in e eral haplogro p among he global pop la-ion incl ding haplogro p D and J.[13] In hi dy e

T2, or U5. Therefore, polymorphism near the origin of the head region of the replication could explain the association between lineage J and haplogroup J2, but not the association between lineage J and D5 and M7b.

150C>T polymorphism emerged separately in the early evolution of the European haplogroup J2, T2 and U5, and of the Asian haplogroup D5, M7b and N9a, but has only occasionally been noted elsewhere in the mtDNA phylogeny. Subhaplogroup D5 and M7b of the Japanese belong to mtDNA macrohaplogroup M, which has diverged from African haplogroup L3 and from macrohaplogroup N some 60 000 year ago.[18] On the other hand, N9a of the Japanese and J2, T2 and U5 of the Finn belong to macrohaplogroup N. Most of the haplogroup in macrohaplogroup N harbour an ancient 10398G>A mutation, which alters the amino acid 114 in the MTND3 gene, but haplogroup J has experienced a back-mutation at this site thereby losing the 10398G allele in common with macrohaplogroup M and, therefore, common with D5 and M7b. In addition, haplogroup J harbour the control region mutation 489T>C, which also occurred early in the evolution of macrohaplogroup M. Our data has now revealed that 150T is associated with lineage J in subhaplogroup J2, D5 and M7b that harbour 10398G and 489C, but not in subhaplogroup T2, U5 and N9a that lack the latter two polymorphisms. The association between a combination


16362
m7b1
303(C)9
m7b2
150
M7b
16129