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ScienceDirect
Metabolism Clinical and Experimental 59 (2010) 62 – 63
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Preliminary report: mitochondrial DNA 5178 polymorphism in male elite Japanese endurance runners

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Received 17 March 2009; accepted 7 July 2009

Abstract

Elite athletic endurance ability involves multiple genetic and environmental factors, with little known about the specific genotypes involved. As a first step to finding genetic markers of endurance performance, we recruited 66 male endurance runners and 110 control athletes. We investigated the distribution of m.5178CA polymorphisms in male endurance runners. Although the m.5178A genotype has been reportedly associated with longevity, endurance runners in this study showed a significantly higher frequency (71.2%) of the m.5178C genotype than control subjects (52.7%). The-m.5178C genotype may be favorable for performance in elite endurance runners.

1. Introduction

Multiple genetic and environmental factors interact to deliver an elite athletic performance level. Although methods and mechanisms of training to enhance athletic activity have been extensively studied, genetic associations remain poorly understood.

Endurance performance requires high-level aerobic or cardiorespiratory fitness, often represented by maximal oxygen uptake (V_{O_2}max) [1]. It is well known that endurance runners have higher V_{O_2}max levels than normal subjects and other types of athletes [1,2], and genetic factors have been implicated in determining the potential V_{O_2}max of an individual [3]. Accordingly, endurance performance might be substantially determined by genetic factors.

Mitochondria generate adenosine triphosphate (ATP) by oxidative phosphorylation in the metabolic respiratory chain. Because the ability of aerobic ATP generation correlates with endurance performance, it is feasible that mitochondrial DNA (mtDNA) polymorphisms could influence an individual's natural ability for endurance performance. In fact, mtDNA haplogroup A has been associated with performance in endurance running [4], whereas a variant of mitochondrial NADH dehydrogenase complex (MTND) 5, one of the mitochondrial respiratory complex I subunits, is associated with V_{O_2}max [5].

The *MTND2* gene is another mitochondrial respiratory complex I subunit, and m.5178 nucleotide is in the *MTND2* gene. C-to-A transversion at the nucleotide position 5178 within the NADH dehydrogenase subunit 2 gene causes leucine-to-methionine replacement. Tanaka et al [6] reported a higher m.5178A allele frequency in Japanese centenarians than in the general population, suggesting that the m.5178CA polymorphism is closely associated with longevity. We and others also showed previously a link between m.5178A and an antiatherogenic phenotype [7-9]. Considered together, these findings suggest that m.5178CA polymorphism could affect mitochondrial function through an unknown mechanism. However, no studies have linked

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doi:10.1016/j.metabol.2009.07.005

Table 1
Characteristics of participating subjects

	Control	Endurance runners
n	110	66
Age (y)	22 ± 0.1	21 ± 0.1*
Height (cm)	173.2 ± 0.5	170.8 ± 0.5*
Weight (kg)	67.2 ± 0.8	57.4 ± 0.7*
BMI (kg/m^2)	22.4 ± 0.2	19.6 ± 0.1*
mt5178 genotype (A/C)	52/58	19/47*

Data are mean ± SEM. BMI indicates body mass index.
* $P < .05$ vs control.

the m.5178CA polymorphism and endurance performance. This study compared the frequency of m.5178CA polymorphisms in endurance runners and control subjects.

2. Results and discussion

We recruited 66 male endurance runners and 110 control male athletes (42 baseball players, 39 soccer players, and 29 basketball players) for this study. The mean time for running 5000 m was 14 minutes, 58 seconds ± 6 seconds for endurance runners. This implies that the recruited endurance runner can run more than 4000 m in 12 minutes. On the other hand, the mean distance run in 12 minutes by control athletes was 3018 ± 27 m. Blood samples were obtained from all subjects. Using mtDNA extracted from peripheral blood leukocytes, the mt5178 genotype was assayed by polymerase chain reaction–restriction fragment length polymorphism analysis as described previously [7].

Table 1 presents the characteristics of participating subjects. The mean age, height, body weight, and body mass index were significantly lower in endurance runners than control athletes. The m.5178C allele frequency was 52.7% in controls, which was consistent with a previous report of 55% for the same allele [6]. In contrast, the frequency of m.5178C was significantly higher (71.2%) in endurance runners compared with controls (odds ratio, 2.22; 95% confidence interval, 1.16-4.25; $P = .017$) (Table 1). We also performed logistic regression analysis to adjust for height and age. After adjusting those parameters, the association between m.5178C and endurance runner was still significant (odds ratio, 2.95; 95% confidence interval, 1.41-6.18; $P = .004$). Interestingly, this genotype is the opposite of the longevity- and antiatherosclerotic phenotype–associated genotype (m.5178A) [6,7]. Interestingly, previous studies have shown none of the endurance athletes belonged to haplogroup K or subhaplogroup J2, both of which have previously been associated with longevity among Europeans [11]. Taken together, it is supposed that complementary mitochondrial genotypes between longevity and endurance performance may induce opposite mitochondrial function, thus resulting in different phenotype.

The m.5178CA polymorphism results in the changes of the coding amino acids for *MTND2*, a subunit of mitochondrial respiratory complex I that may be mutated in Leber hereditary optic neuropathy [10]. Thus, *MTND2* is an important regulator of cell homeostasis, through ATP and reactive oxygen species production. Niemi and Majamaa [11] speculated that longevity-associated haplogroups are "uncoupling genomes" and, as such, should not be beneficial to endurance performance. Rather, this genotype would benefit longevity because uncoupling of oxidative phosphorylation reduces ATP production and the release of reactive oxygen species, and generates heat [11]. Accordingly, this uncoupling genomes hypothesis could explain the inverse relationship between longevity and endurance performance observed in this study.

On the other hand, mtDNAs are classified into several haplogroups. m.5178A defines haplogroup D, and all the m.5178C samples belong to other haplogroups. Accordingly, it is possible that variation of other genes could affect the endurance performance. It is also possible that only several haplogroups of the m.5178C might be favorable for endurance performance. Regarding the underlying mechanisms, further analysis is clearly needed.

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