

Mitochondrial DNA and Maximum Oxygen Consumption

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Mitochondrial DNA contains genes for 13 mitochondrial proteins involved in oxygen consumption. Variation in the DNA sequence of these genes could therefore contribute to the differences in endurance performance between individuals. Recent studies have provided conflicting data on the relationship between mitochondrial DNA and an important factor influencing endurance performance, maximum oxygen consumption. The conflict may arise from poorly controlled maternal ethnicity or population differences between studies.

KEYWORDS: displacement loop, gene, mtDNA, polymorphism, VO₂max

Most of the energy for endurance exercise comes from oxidation of fuel. The maximal capacity of an individual to consume oxygen is therefore one of the important factors limiting endurance performance. The effect of training on maximum oxygen consumption (VO₂max) has been a major focus of researchers, but increased attention is now turning to the effect of genes. The early researchers addressing the contribution of inheritance to aerobic performance suggested that individual differences in VO₂max were determined primarily by genetic factors (Klissouras, 1971). Subsequent investigations have demonstrated a substantial but lesser effect of heritability on VO₂max of sedentary individuals (Bouchard et al., 1998) and on the response of VO₂max to training (Bouchard et al., 1999). Current estimates of heritability span the range of 20 to 50%. Additionally, a maternal influence for VO₂max has been observed (Lesage et al., 1985). This field of research forms the foundation for molecular investigations that aim to identify genetic markers associated with the heritability of aerobic performance--in essence, relating genotype to phenotype. Such investigations are in their infancy, and no clear relationships have been established between specific genetic markers and elite performance, as noted by Hagberg et al. (2001) in a recent review.

It is well known that different individuals have different DNA sequences. Collectively, DNA sequence differences occurring in more than 1% of the population are termed polymorphisms, or morphs. Morphs may account for some of the differences in performance capacity between individuals (phenotypic variance), including VO₂max. Research in this area has focused on mitochondrial DNA sequences, genes for creatine kinase, and genes for angiotensin converting enzyme (see Hagberg et al., 2001, for review). Mitochondrial DNA is of particular interest, because it contains the genes for several enzymes involved in oxygen consumption, and it is inherited only from the mother. Investigations of the relationship between mitochondrial DNA and VO₂max are the focus of this article.

Aerobic energy production involves the metabolic pathway for oxidative phosphorylation, particularly the electron transport chain in mitochondria. Mitochondrial DNA contains genes for 13 proteins of the electron transport chain as well as 22 transfer RNAs and two ribosomal RNAs required for their intra-mitochondrial synthesis (Shadel

and Clayton, 1997). Theoretically, variations within these genes and/or their associated regulatory regions could affect the passage of electrons and hydrogen ions through the electron transport chain to oxygen, thereby altering the capacity for energy production.

The first report to address the association between mitochondrial DNA sequences and aerobic performance was by Dionne et al. (1991). Through a 20-week endurance-training program, the authors assessed the relationship of baseline VO_2max and its response to training with mitochondrial DNA morphs detected by 22 restriction enzymes. The subjects were 46 North Americans who were sedentary at the time of the study. Of the variants identified, those subjects harboring a morph in the gene encoding Subunit 5 of NADH dehydrogenase demonstrated a significantly lower training response for VO_2max . Additional morphs located in the gene for Subunit 5 of NADH dehydrogenase, a transfer RNA gene for threonine, and one morph in the regulatory region of mitochondrial DNA known as the displacement loop (D-loop), demonstrated significant relationships to the training responses of VO_2max . Subsequently, Rivera and colleagues (1997) measured the frequency of each of the three morphs identified within the NADH dehydrogenase gene and of one morph of the D-loop in 125 elite endurance athletes and in 65 sedentary controls. They found no significant difference in the frequency of these morphs between the two groups. However, the interpretation of such results may be limited by the ancestral origin of the subjects. The elite group included Caucasian endurance athletes from three continents, whereas the control group consisted of Caucasian Americans and Canadians. The ancestral data from Dionne et al. (1991) were less complete, as their subject population comprised French Canadian and other subjects of unstated ethnicity. Furthermore, it is unclear whether the ancestral origin reflects the maternal origin of subjects from these investigations.

Recent Chinese studies (Chen et al., 2000; Ma et al., 2000) have involved subjects with well-defined maternal ethnicity. The researchers focused on the D-loop, which contains factors that modulate mitochondrial DNA replication and transcription (Shadel and Clayton, 1997). In the study of Chen et al. (2000), the morphs within the D-loop generated by four restriction enzymes (which fragment the DNA reproducibly) were examined in a sample of 120 Chinese subjects consisting of 67 elite endurance athletes, 33 general endurance athletes, and 20 sedentary controls. There were nine morphs, and their frequencies were significantly different between the three groups. Ma and colleagues (2000) used the same enzymes and investigated the occurrence frequencies of eight morphs in 27 junior female athletes. Carriers of three morphs showed higher values of VO_2max . These authors suggested that this apparent association between mitochondrial DNA D-loop polymorphism and endurance capacity needs confirmation. Chen et al. (2000) suggested that a better relationship might exist between the mitochondrial DNA morphs and endurance performance rather than VO_2max .

In light of the findings from the Chinese cohort and the paucity of genetic data available for Australian athletes, our laboratory has investigated the relationship between mitochondrial DNA D-loop morphs (generated by the four restriction enzymes) and VO_2max of 40 well-trained Australian male endurance cyclists (for methodology see Brearley et al., 2001). These cyclists were selected by a questionnaire screening for European maternal ethnicity, because European populations have very similar mitochondrial DNA sequences. (Melton et al., 1994). There was no significant association between VO_2max and the D-loop morphs in this population of athletes. We also used three more restriction enzymes to analyze genetic sequences within the D-loop, but we found no new sequence variations.

Our findings are in agreement with the reports of Dionne et al. (1991) and Rivera et al. (1998), who found no significant relationship between D-loop morphs and either

sedentary VO_2max or elite endurance athlete status. The discrepancy between these findings and those of Chen et al. (2000) and Ma et al. (2000) may be related to the ethnic differences between the subjects, because the D-loop region is known to vary between populations (Horai and Hayasaka, 1990). Also, in our study and that of Ma et al. (2000) the small sample sizes do not allow firm conclusions about the presence or absence of small effects. To date, only 7% of the D-loop region and 4% of the mitochondrial DNA genome have been analysed in athletic populations. These investigations (Brearley et al. 2001; Chen et al. 2000; Ma et al. 2000) have added new evidence, although conflicting, to the hypothetical relationship between mitochondrial DNA sequence, endurance performance, and VO_2max .

If the relationship between mitochondrial DNA polymorphisms and aerobic performance and/or responsiveness to training turns out to be substantial, the next challenge will be to explain how this relationship ties in with factors limiting VO_2max . There is some evidence that VO_2max in athletes is limited by the ability to deliver oxygen to the muscles, rather than the ability of muscles (and therefore mitochondria) to utilize oxygen (Bassett and Howley, 2000; Richardson et al., 1999). However, mitochondrial function could still be closely related to the trainability of VO_2max in previously sedentary populations and/or sub- VO_2max endurance performance in athletes.

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