Molecular Study of Energy Related Mitochondrial Genes in Arabian and Bactrian Camels

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ABSTRACT

The single-humped camel, *Camelus dromedaries* inhabiting Afro-Arabia and the double-humped camel, *Camelus bactrianus* inhabiting central Asia are the only species in their genus. The present study aimed to amplify and partially sequence the mitochondrial DNA genes encoding for NADH dehydrogenase subunit 1, cytochrome c oxidase subunit 1, ATP synthase subunit 6 (ATP6), cytochrome b and displacement region (d-loop) in the single-humped camel and compare it to their counterparts already sequenced for the double-humped camel. These energy-related genes showed amino acid substitutions gradually increased according to their locations among macromolecular energy transducers. Both ATP synthase 6 in the central core and cytochrome b in the inner mitochondrial membrane acquired the greatest substitutions of 5 and 7 amino acids, respectively. Cytochrome c oxidase is the terminal complex of the electron transport chain of the inner mitochondrial membrane and it showed no substitutions. These substitutions seemed to be correlated with the energy metabolism in both camel phenotypes. The d-loop showed tandem repeats of six nucleotides at its 3’ end with polymorphism between both species without any evidence relates such variation to energy production.

Keywords: Energy, Genes, Arabian, Bactrian, Camels

1. INTRODUCTION

The genus *Camelus* possesses two species, the single-humped *Camelus dromedaries* and the double-humped *Camelus bactrianus*. The first inhabits Afro-Arabia while the second inhabits Central Asia. Camel has been historically and economically an important species worldwide especially in the Arabian Peninsula where Saudi camels comprise 16% of the animal biomass (Al-Swailem et al., 2010). Both Bactrian and Arabian camels live in desert areas. The geographic range for Arabian camel is Northern Africa and the Middle East. The Arabian camel overlaps with the Bactrian one in the areas of Afghanistan, Pakistan and Southwest Asia (Burton, 1972; Cockrill, 1984).

Camel stores its energy reserves in the form of fat in different body fat depots of which the hump and abdomen depots comprise a considerable amount of the adult body weight and their fats contain mixtures of fatty acids (Emmanuel and Nahapetian, 1980; Kadim et al., 2002). Camel has unique characteristics enable it to adapt its desert environment such as fluctuation of its body temperature, tolerance of water loss and capability of drinking more water in little time (Schmidt-Nielsen, 1979). The physiology of camel is also unique and interesting (Holler et al., 1989; Shirazi-Beechy et al., 1994; Elmahdi et al., 1997; Zierath et al., 1998; Abdel-Fattah et al., 1999; Kaske et al., 2001; Duhlmeyer et al., 2007) so that it needs further biological investigation.
Despite its economical, cultural and biological importance, the molecular study targeting camel genome is limited and there is no much available information about the camel genome especially for Arabian camel. The present study focused on sequencing some mitochondrial genes related to energy metabolism such as NADH subunit 1 (ND1), cytochrome oxidase subunit 1 (CO1), ATP synthase 6 (ATP6), cytochrome b (cytb) and displacement region (d-loop).

Several proteins are involved in oxidative phosphorylation and encoded by mitochondrial DNA genes. Among these genes are ND1, CO1, ATP6 and cytb (Fonseca et al., 2008).

Respiratory complex I (NADH: quinone oxidoreductase) is an entry point to the electron transport chain in mitochondria. It couples NADH oxidation and quinone reduction to proton translocation across the inner mitochondrial (or plasma) membrane, so it is central to energy transduction (Bridges et al., 2010). Complex I dysfunctions are linked to an increasing number of neuromuscular and neurodegenerative diseases as well as to oxidative stress and aging (DiMauro and Schon, 2003).

CO1 is the terminal complex in the electron transport chain and is located in the inner mitochondrial membrane. The core subunits of CO1 (subunits I, II and III) are encoded by the mitochondrial genome. CO1 activity acts to prevent an excessive buildup of reactive oxygen species (Chen et al., 2009).

ATP synthase is one of the most important molecular motors of the living cell. It occupies a special location among macromolecular energy transducers. One type of ATP synthase protein complexes performs synthesis of the overwhelming majority of ATP molecules in the cell (Skulachev, 1988; Nicholls, 2002; Nelson and Cox, 2004). These molecules are the smallest macromolecular electric motors in nature (Romanovsky and Tikhonov, 2010).

Mitochondrial cytb is conserved hydrophobic protein containing eight or nine transmembrane domains and two heme groups. To date, about 27 different mutations have been identified in cytochrome b, mostly in patients with skeletal muscle weakness and exercise intolerance (Andreu et al., 1999; Fernandez-Vizarra et al., 2007).

The signature form of mammalian mtDNA is the d-loop molecule, which maintains a short piece of the Heavy (H) strand at the origin of replication. The d-loop is thus defined as a three-stranded structure with the nascent leading H strand defining the origin of leading-strand replication (OH) at its 5’ end. D-loop strands are variable in size in a species-specific manner and are turned over more rapidly than the rate of genomic replication would require (Clayton, 1996).

In our proposed study, we aimed to investigate the genetic differences between the Arabian and Bactrian camels in the respect to mitochondrial genes responsible for energy production (ND1, CO1, ATP6, Cytb and d-loop). The proposed study may also provide valuable information for Arabian camel genetics.

2. MATERIALS AND METHODS

Blood samples were withdrawn into heparinized tubes from the jugular vein of 10 different Arabian camel males from production breed at slaughter house (Taif, KSA). Similarly, for racing breed, blood samples were collected from 5 different individuals from a private local farm after taking the owner’s permission. Different blood samples were numbered and labeled with full information.

Mitochondrial DNA was extracted from 0.5 mL blood samples with QIAGEN spin-column kits according to the manufacturer’s instruction (QIAamp DNA Micro Kit). Extracted DNA concentration and quality were determined spectrophotometrically at 260/280 nm and was used for Polymerase Chain Reaction (PCR).

PCR was conducted in a final volume of 50 µL containing 2 µL DNA template and 2 µL of 10 picomolar forward primer, 2 µL of 10 picomolar reverse primer of the corresponding genes as listed in Table 1 and 25 µL PCR master mix (Promega Corporation, Madison, WI) and 19 µL autoclaved deionized distilled water. PCR was carried out using a PeX 0.5 thermal Cycler with the cycle sequence at 94°C for 4 min one cycle, followed by 40 cycles each of which consisted of denaturation at 94°C for one min, annealing at corresponding specific temperature (as shown in Table 1) for one min and extension at 72°C for one min with a final strand elongation for one cycle at 72°C was done for an additional 5 min. The PCR products were analyzed in 1% agarose gel electrophoresis in TAE buffer (40 mm Tris, 40 mM acetic acid and 1 mM ethylenediamine-tetra acetic acid) with ethidium bromide staining. 100bp DNA ladder (Biolabs) was used as a molecular marker. Then PCR products bands were visualized under UV light and photographed. The PCR products were then excised from agarose gels and purified using spin column (BioFlux, Tokyo, Japan) according to the manufacturer’s instructions and sequenced in an ABI PRISM 3730xl sequencer (Applied BioSystems) and BigDyeTM Terminator Sequencing Kits with AmpliTaq-DNA polymerase (FS enzyme) (Applied Biosystems) following the protocols supplied by the manufacturer.
Table 1. Primers designed and used for PCR amplification and sequencing. Annealing temperature refers to that of the conducted PCR to obtain the amplified fragments.

| Gene  | Primer name | Sequence (5´-3´)          | Annealing temperature (°C) |
|-------|-------------|---------------------------|---------------------------|
| ND1   | Camel ND1-F | AGTGAAGCGAAAAAGTCCCTAG    | 49                        |
|       | Camel ND2-R | TTAATTCTGGATGATTATTC       |                           |
| CO1   | Camel CO1-F | CTATGGTCATTACTCGCTGA       | 54                        |
|       | Camel CO1-R | GATGTTGCTCCATCGAGTG        |                           |
| ATP6  | Camel ATP6-F| CCCTACGTAATAGGACTTC        | 52                        |
|       | Camel ATP6-R| GTGATGAAATACGGCT           |                           |
| Cytb  | Camel cytB-F| GACAAACATCCGAAAATCACAC     | 54                        |
|       | Camel cytB-R| CTTCAATTGAGATAACGTT        |                           |
| d-loop| Camel d-loop-F| AAAACGGCAATAGCCCTTGAG      | 50                        |
|       | Camel d-loop-R| GCCCCGTAAAAATTGCGTT       |                           |

After reading the targeted genes, the nucleotide sequences have been treated with different software programs (DNASIS, MacClade, PAUP) that enabled us to detect genetic relatedness between different samples. The same genes for the single-humped camel from Morocco and Dubai and the double-humped Bactrian camel were obtained from the Genbank database with their accession numbers JN632608 (Hassanin et al., 2012), NC_009849 (Huang et al., 2007), NC_009628 (Ji et al., 2009) to be compared to the Saudi breed samples.

3. RESULTS

In this study, unambiguous nucleotides of 783, 789, 550, 966 and 570 bp from ND1, CO1, ATP6, cytB genes and d-loop, respectively, were sequenced for 10 individuals of the Arabian production camel and 5 individuals of the Arabian racing camel. These data were deposited in DDBJ/EMBL GenBank database with their accession numbers (AB753101-AB753161). In order to estimate the base composition and frequencies for the obtained sequences, the data were concatenated and the gat-containing sites were deleted so that 3658 bp were left for analysis. The data showed base frequencies of A = 27.75%, C = 27.89, T = 27.97 and G = 16.38.

The sequenced fragments of the studied genes and the intra and inter-specific nucleotide and amino acid substitutions were summarized in Table 2. Seven hundred eighty three nucleotides from ND1 gene showed 54 base substitutions between Arabian and Bactrian camel species of which 38 were transitions and only 2 were transversions. Within these substitutions, 5 were non-synonymous with different amino acids for both camel species. The non-synonymous changes involved substitutions of valine with isoleucine at G158 ➔ A158, histidine with tyrosine at C145 ➔ T145, glutamine with arginine at A138 ➔ G138, alanine with threonine at G340 ➔ A340 which was characteristic to Saudi camel individuals and methionine with threonine at T363 ➔ C363 (Fig. 3). The inbred changes involved 6 synonymous substitutions without discrimination between racing and production. However, only one non-synonymous change was found in which alanine in Saudi breed was replaced with threonine in Dubai and Moroccan breeds (G340 ➔ A340).

For the barcoding gene encoding for CO1, the sequenced nucleotides of 789 bp contained 51 base substitutions between Arabian and Bactrian camel species (data not shown) without non-synonymous changes (Fig. 2). Of these substitutions, 47 were transitions (A-G and C-T) while only 4 were transversions (purines to pyrimidines and vice versa). Among the Arabian samples (either racing or production) there were 6 synonymous transitions.

The polymorphism of the 550 base pair representing the partial sequence of the ATP6 gene in 15 Arabian camel individuals and the Bactrian camel was analyzed. Forty substitutions were recorded between the two species of which 38 were transitions and only 2 were transversions. Within these substitutions, 5 were non-synonymous with different amino acids for both camel species. The non-synonymous changes involved substitutions of valine with isoleucine at G158 ➔ A158, histidine with tyrosine at C145 ➔ T145, glutamine with arginine at A138 ➔ G138, alanine with threonine at G340 ➔ A340 which was characteristic to Saudi camel individuals and methionine with threonine at T363 ➔ C363 (Fig. 3). The inbred changes involved 6 synonymous substitutions without discrimination between racing and production. However, only one non-synonymous change was found in which alanine in Saudi breed was replaced with threonine in Dubai and Moroccan breeds (G340 ➔ A340).

The substitutions of the 966 base pair that have been sequenced for cytB gene in this study were analyzed. Ninety seven substitutions were recorded between the two species of which 90 were transitions and 7 were transversions. Within these variations, 7 were non-synonymous which involved substitutions of serine with leucine at G135 ➔ A135, valine with isoleucine at G352 ➔ A352, alanine with isoleucine at G712 ➔ A712, valine with isoleucine at G825 ➔ A825, phenylalanine with leucine at T907 ➔ C907, alanine with methionine at G916 ➔ A916 and threonine with methionine at G945 ➔ A945 (Fig. 4). The changes within the Arabian breed involved 13 synonymous substitutions of which only one was transversion discriminating one racing individual.
Table 2. The sequenced fragments of the studied genes and the intra and inter-specific nucleotide and amino acid substitutions

| Gene     | Size of sequenced fragment (bp) | Nucleotide substitutions (bp) | Amino acid substitutions |
|----------|---------------------------------|------------------------------|--------------------------|
|          |                                  | Interbreeds                  | Inter-specific           |
|          |                                  | Inter-breeds                 | Inter-specific           |
|          |                                  | Synonymous                   | Non-synonymous            |
| ND1      | 783                              | 0                            | 53                       | 1                        |
| ATP6     | 550                              | 6                            | 35                       | 5                        |
| Cytb     | 966                              | 13                           | 90                       | 7                        |
| d-loop   | 750 – 1050                       | 4                            | -                        | -                        |

Fig. 1. The aligned translated amino acids of the sequenced ND1 gene for Bactrian camel and the different haplotypes of the Arabian camel. The letters inside the box are polymorphic among taxa. Note that the data for taxa other than Saudi one were obtained from the GenBank database. The data of all taxa other than Saudi one are for the complete gene sequence.
Fig. 2. The aligned translated amino acids of the sequenced CO1 gene for Bactrian camel and the different haplotypes of the Arabian camel. Note that the data for taxa other than Saudi one were obtained from the GenBank database for the complete gene sequence.
Fig. 3. The aligned translated amino acids of the sequenced ATP6 gene for Bactrian camel and the different haplotypes of the Arabian camel. The letters inside the boxes are polymorphic among taxa. Note that the data for taxa other than Saudi one were obtained from the GenBank database for the complete gene sequence. The underlined column was a SNP discriminating the Saudi haplotype from other Arabian ones.
Fig. 4. The aligned translated amino acids of the sequenced cytb gene for Bactrian camel and the different haplotypes of the Arabian camel. The letters inside the box are polymorphic among taxa. Note that the data for taxa other than Saudi one were obtained from the GenBank database.

Variable lengths (750~1050) of the d-loop were recorded for different individuals. These sequences were obtained from amplified fragments with similar sizes and the variation was due to fuzzy electropherogram profiles. We were able to align the first 570 bp among individuals from the same breed and from the Bactrian camel (data not shown). This alignment showed complete identity within the Arabian camel with only 4 substitutions one of which was transversion. The inter-specific substitutions between Arabian and Bactrian camels were 13 transitions and one transversion. At the 3’ end of this conserved fragment, the d-loop showed 6 nucleotides tandem repeat of 5’-CACGTA-3’. This repeat showed gradual increase in its repetition to reach up to 18 times and seemed to be more in production breed. At the end of this repeat, the sequence tends to change to 5’-CACGCA-3’. This repeat was shown to be separated by short 4 bases repeat of 5’-CGTA-3’ (data not shown).

4. DISCUSSION

The mitochondrial DNA contributes 13 protein-coding, 22 tRNA and 2 rRNA molecules which are inherited only from the mother and are essential to mitochondrial function in mammalian cells. All of the 13 protein-coding genes encode enzymes of the oxidative phosphorylation apparatus (Shadel and Clayton, 1997; Devin and Rigoulet, 2007) and most of the energy for endurance and exercise comes from such oxidation. Differences in DNA sequence occurring in more than 1% of the population are termed polymorphism. Polymorphism may account for some of the differences in performance capacity between individuals including oxygen consumption. The effect of training on maximum oxygen consumption has been a major focus of researchers, but increased attention is now turning to the effect of genes. 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 of energy production.

The low G percentage in mitochondrial genes coding for ND1, CO1, ATP6 and cytb goes in accordance with the previous study reported that the scarcity of G for the light strand is a common feature found in metazoan mtDNAs (Asakawa et al., 1991). Nucleotide substitutions are generally considered in terms of
changes within the two structural classes of nucleotides (purines and pyrimidines), that is, in terms of transitions and transversions.

As ND1 is the start point for energy transduction (Bridges et al., 2010) and shows high mutations during abnormal cases such as oxidative stress and aging (DiMauro and Schon, 2003), we may consider that the little difference between Arabian and Bactrian camels was due to similar biochemical roles of this protein in both camel species.

The variations occurred in CO1 gene among all samples either inter-specific or intra-specific were in the second position with no amino acid changes. CO1 data therefore supported the stability of this gene in both camel species. Moreover, cytochrome C oxidase is the terminal complex of the electron transport chain and is activated to prevent an excessive buildup of reactive oxygen species (Chen et al., 2009). It is also not affected by the variation in the respiratory capacity (Devin and Rigoulet, 2007). These two reasons may explain the similarity in the amino acid contents of the gene coding for this protein in both camel species.

ATP6 gene showed great variation between the two camel species and therefore, it could be considered as an important marker to study the possible physiological differences between Arabian and Bactrian camels. In the cell, ATP metabolism is catalyzed by enzymes known as ATP synthases and ATPases, respectively. ATPase ensures the work of muscular proteins, biosynthetic reactions, ion transfer across biological membranes and other energy-consuming processes due to the energy results from ATP hydrolysis. The synthesis of ATP is catalyzed by ATP synthases using the energy from external sources. One type of ATP synthase complexes catalyzes both reactions, ATP synthesis and ATP hydrolysis (Romanovsky and Tikhonov, 2010). As one of ATP synthase complexes performs synthesis of the majority of ATP molecules in the cell (Skulachev, 1988; Feldkamp et al., 2005; Nelson and Cox, 2004) and the phenotype of both camel species are clearly different, the great amino acid substitutions of ATP6 gene may be correlated to its major role in energy synthesis.

Cytb gene showed the greatest variation between the two camel species and therefore, it could be considered as the most important marker to study the possible energy related adaptations for both Arabian and Bactrian camels. The hydrophilic protein of cytochrome b acquires higher mutations in abnormal cases of skeletal muscle weakness and exercise intolerance (Andreu et al., 1999; Fernandez-Vizarra et al., 2007). It is one of the cytochromes which showed variations when the respiratory capacity changes (Devin and Rigoulet, 2007). We therefore may correlate the highest amino acid substitutions of this gene to the great variation in the respiratory capacity of both camels.

There was an obvious repeat at the 3’ of the d-loop region. We did not find an interpretation to this repeat, in spite of, such repeat has been described for other vertebrates in this region (Moritz and Brown, 1987; Lunt et al., 1998). Brearley and Zhou (2001) agreed with Dionne et al. (1991) and Rivera et al. (1998) in that there was no significant relationship between d-loop polymorphism and either oxygen consumption or endurance. The discrepancy between these findings and those of Chen et al. (2000) may be explained by the fact that the d-loop region is known to vary between populations (Horai and Hayasaka, 1990).

Based on these arguments, we could not be able to relate the polymorphism in the d-loop repeat of both production and racing camels to the difference in the maximum oxygen consumptions which is usually high in those reared for racing.

5. CONCLUSION

The energy-related mitochondrial genes showed amino acid substitutions increased according to their roles in energy metabolism in both Arabian and Bactrian camels. These substitutions seemed to be correlated with the energy metabolism in both camel phenotypes. ATP6 acquired the greatest changes because it controls the majority of energy production. Cytb in the inner mitochondrial membrane came the second in such substitutions. Because CO1 is responsible for free radicals scavenging and considered as the terminal complex of the electron transport chain of the inner mitochondrial membrane, it showed no substitutions. The d-loop showed polymorphism between both species without any evidence relates such variation to energy production.

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