Advances in camel genomics and their applications: A review

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1.Introduction

Taxonomy and history

The origin of the Old World camelids traces back to the end of Eocene (40–45 mya), where the first ancestors of the camelid family were found in North America. After splitting into New World (Lamini) and Old World (Camelini) camels, the latter migrated via the Bering land bridge to the eastern hemisphere (Janis et al. 1998; Ji et al. 2009; Wu et al. 2014, 2015). Camel domestication was believed to begun in the Arabian Peninsula around 3000 BC (Mikesell 1955). Since then it has dispersed to the whole Africa via Horn of Africa (Gifford-Gonzalez and Hanotte 2011). Camels facilitated the trading and cultural dialog between three continents by connecting and helping in the expansion of civilizations (e.g. Roman Empire, Arab).

Camel is belonging to Camelidae family, order Artiodactyla (even-toed ungulates), sub-order tylopoda (animals with padded feet)(Figure1). In spite the camel is a ruminating animal, it is not a ruminant. Differences such as foot anatomy, stomach system and the absence of horns confirm this fact (Schwartz and Dioli 1992; Fowler 1998). The family Camelidae comprised two main types (large and small camelids) distributed into three genera: Camelus, Lama and Vicugna. The small camelids originate from Andin Mountains of South America include two domestic species (lama and alpaca) and two wild species (guanaco in genus Lama, and vicuna in genus Vicugna). The large camelids are represented by two domesticated species, the one-humped camel (dromedary) and the two-humped camel (Bactrian), the first are living in the hot arid lands from North of Africa and eastern part of Asia, the second in the cold steppes and deserts in Central Asia. Also in the desert Gobi there is still a population of wild Bactrian camels classified as Camelus ferus (Rao et al. 1970; Fowler 1998). The dromedary camel has been extinct in the wild for several hundred years. There are no wild herds in existence in the native lands of the Middle East and Asia where they first came to be, but some escaped domestic animals roam Australia (Roth and Merz 1997). According to latest studies worldwide total camel population is 24.7 million head and the largest population has been found in Somalia (7 million). Eighty nine and fourteen different camel breeds of dromedary and Bactrian respectively are currently listed on FAO DAD-IS data-base (FAO 2016). An evolutionary history reconstructed for the family Camelidae based on cytb sequences suggested that the split of Bactrian and dromedary may have occurred in North America before the tribe Camelini migrated from North America to Asia (Cui et al. 2007). Mitochondrial cytb gene analyses from domestic and wild Bactrian camels revealed that the extant wild two-humped camel may not share a common ancestor with the domestic Bactrian camel

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and they are not the same subspecies at least in their maternal origins, and the extant wild camel is a separate lineage but not the direct progenitor of the domestic Bactrian camel (Ji et al. 2009; Silbermayr et al. 2010). In addition, mtDNA sequence analysis of ancient DNA proved to be crucial in resolving domestication processes in dromedaries (Almathen et al. 2016). Phylogenetic study based on complete mitochondrial genomes excluding the control region suggested that the *C. ferus* and *Lama pacos* may occurred much earlier than what was deduced from the fossil record (Cui et al. 2007).

A set of microsatellites were established in New World camelids successfully amplified in the Camelini (Mariasegaram et al. 2002) and was applied to study the genetic distance between Mongolian and Chinese domestic Bactrian camels (Jianlin et al. 2004). Sadder et al. (2015) developed thirty STR loci by sequencing dromedary genome at low coverage utilizing Roche and Illumina platforms. The number of alleles ranged from 1 to 3 while polymorphic information content averaged 0.38. Prasad et al. (2014) validated 374 SNPs based on a set of 672 dromedary and Bactrian camels using golden gate assay of Illumina.

**The camel, a multipurpose animal**

Camel is a multipurpose animal. It can be used for milk, meat and wool production, for transportation, racing contests, tourism, agricultural work, and for beauty contest. In Egypt for example, there are different dromedary camel breeds used for different purposes; Maghrabi used for milk and meat production, Sudani and Somali for racing and Falahi or Baladi for agricultural works as shown in Table 1 and Figure 2 (Wardeh et al. 1991). The camel racing is an

| Breed              | Main purposes for each breed                  |
|--------------------|------------------------------------------------|
| Maghrabi           | Dual-purpose, for meat and milk               |
| Somali             | Common for riding and racing                  |
| Sudani             | Common for riding and racing                  |
| Falahi or Baladi   | Transportation and agricultural operations     |
| Mowaled            | Hybrid between Maghrabi and Falahi            |

**Table 1 Egyptian camel breeds and purposes of each breed**

**Figure 2** Photos show Egyptian dromedary camel breeds; A: Maghrabi, B: Hand milking of Maghrabi during calf sucking C: Sudani, and D: Somali
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important cultural event in the Arabian Peninsula and becomes popular also in Africa. The dromedary camel has in average 40 km/h speed but Bactrian camel racing speed has 27.2 km/h (Biichee 1998). The tourism attraction is on development, not only for riding on beach, dunes or around the pyramids in Egypt, but also for festival, fantasia and other spectacles like the dancing camel at Pushkar fair in India (Faye 2015). Camel milk is rich in insulin and insulin-like proteins. Camel insulin, unlike the insulin contained within other animal milks, is contained within micelles and is thus protected from digestion and proteolysis in the upper gastrointestinal tract (Agrawal et al. 2011; Malik et al. 2012). Camel milk is rich in lactoferrin and immunoglobulin with potent antimicrobial and anti-inflammatory properties, including bacterial inhibition, antiviral effects (HCV, HIV), antifungal, antioxidant, anti-inflammatory and anti-cancer actions (Konuspayeva et al. 2007; Alhaider et al. 2013; Habib et al. 2013; Ismael et al. 2013; Kanwar et al. 2015). This review will give an overview about the molecular genetic studies performed over the past years, and deals with molecular markers and their application in versatile aspects that will prove beneficial for researchers and scientists to undertake further research to improve camel health and production.

Application of molecular markers in camel genetic research

Genetic improvement of livestock has been mainly depending upon the selective breeding with superior phenotypes. The use of molecular genetic techniques in association with conventional animal breeding tools are important to balance the process of selection and thus to optimize the animal breeding program (Olesen et al. 1999; Beuzen et al. 2000). In this review we will summarize report of camel genome SNPs and their relation with different traits.

2. Genome sequence information to unravel the camel’s adaptation to harsh desert environment

First draft whole genomes of the Old World camelids have recently been published (Jirimutu et al. 2012; Burger and Palmieri 2014; Wu et al. 2014, 2015; Almathen et al. 2016; Fitak et al. 2016). The assembled genome sizes were 2.01, 2.01 and 2.05 GB while the annotated genes were 20.251, 20.714 and 20.864 for the Bactrian, dromedary camels and alpaca genomes respectively (Wu et al. 2014, 2015). Functional analyses of the gene sets indicated that >91% of the genes were functionally annotated in each genome. The estimated divergence time between Camelini and Lamini was 16.3 while between Bactrian and dromedary was 4.4 million years ago (Wu et al. 2014, 2015).

The high quality genome sequences of the Bactrian, dromedary camels and alpaca in addition to comparative genomic analyses provided new insights into the adaptations of camels to the harsh desert environment. Many genes related to metabolism are under accelerated evolution in the camel compared with other even-toed ungulates such as cattle. Genes involved in energy storage and production capacities, immune and stress responses of camel were evolved more rapidly in the camels than in cattle. High blood glucose levels and a diet loaded with high salt are considered adaptation mechanisms that may help camels to survive in driest and harshest condition. The camel rapidly evolving genes include some that regulate insulin signaling pathways, salt metabolism and also duplications of genes which play critical roles in sodium reabsorption and water balance in the kidney (Jirimuta et al. 2012; Burger and Palmieri 2014; Wu et al. 2014, 2015; Almathen et al. 2016; Fitak et al. 2016). The identification of key genes involved in the adaptation to the desert environment may have applications in breeding programs and may provide some perspective for disease-resistance research in different animal species. Future studies on camel genomes and transcriptomes may contribute to a detailed understanding of these important physiological mechanisms with relevance to human medical conditions (for example, the links between sodium metabolism and hypertension, hyperglycemia and diabetes, fat metabolism and obesity, and dust and respiratory diseases).

3. Molecular markers for camel milk quality and production

Camels used for milk production are mainly belonging to dromedaries (Zhang et al. 2005). In 2010 about 5.25 million camels were producing 2.12 million tons of milk. The greatest dairy camel population worldwide is found in the North East African countries including Somalia, Ethiopia and Sudan (El-Agamy 2006). The casein fraction of camel milk composes 52-89% of total milk protein (Al-Haj and Al-Kanhal 2010) and
distributes into four fractions: αS1, αS2, β-, and κ-CN and encoded by four genes, CSN1S1, CSN1S2, CSN2, and CSN3, respectively (Kappeler et al., 1998; El-Agamy 2006). The β-casein is the most abundant protein in camel milk and it is encoded by CSN2 gene. The nucleotide sequence of the whole β-casein-encoding gene (CSN2) plus 2141 bp at the 5′-flanking region in dromedary camels and the promoter region and the complete cDNA in Bactrian camel were determined by (Pauciullo et al. 2014). A total of 46 polymorphic sites had been detected. The transition g.2126A>G falls within the TATA-box of dromedary CSN2 promoter with a putative influence on the transcription factor binding activity. The frequency of the G allele was 0.35 in a population of 180 she-camels belonging to 4 different ecotypes. In the same population, a conservative SNP (g.4175C>A) was found at the codon 7 of the signal peptide. Four SNPs were found in the Bactrian camel. The SNP c.666G>A was responsible for the amino acid change Met → Ile and it represented the first missense allele at the β-casein in camels (Pauciullo et al. 2014).

In camel milk αS1-casein (22%) is considered the second main fraction after β-casein (65%) and before αS2-casein (9.5%) and k-casein (3.5%) (El-Agamy 2006). A non-synonymous amino acid exchange (Glu → Asp) in the CSN1S1*C exon 5 was detected due to g.942G>T SNP. This SNP can differentiate between the two protein patterns of s1-casein (22%) and κ-casein (65%) and before s2-casein (9.5%) and k-casein (3.5%) (El-Agamy 2006). A total of 46 polymorphic sites had been detected. The transition g.2126A>G falls within the TATA-box of dromedary CSN2 promoter with a putative influence on the transcription factor binding activity. The frequency of the G allele was 0.35 in a population of 180 she-camels belonging to 4 different ecotypes. In the same population, a conservative SNP (g.4175C>A) was found at the codon 7 of the signal peptide. Four SNPs were found in the Bactrian camel. The SNP c.666G>A was responsible for the amino acid change Met → Ile and it represented the first missense allele at the β-casein in camels (Pauciullo et al. 2014).

Pauciullo et al. (2013) characterized the nucleotide sequence of the whole κ-casein-encoding gene (CSN3) plus 1045 nucleotides at the 5′flanking region in dromedary camels. Highly conserved sequences located in the 5′flanking region, have been found. 17 polymorphic sites have been detected, one of these (g.1029T>C) is responsible for the creation of a new putative consensus sequence for the transcription factor HNF-1. Tahmoorespur et al. (2016) showed that κ-casein exon 4 sequence analyses of Iranian dromedary and Bactrian camels had high level homology in sequence and nucleotide content. The sequence analysis of dromedaries camels indicated one SNP (G/T) in intron 3 and a synonymous SNP (G/A) in exon 4. For Bactrian camels the nucleotide analysis showed one SNP (T/C) in exon 4.

Khabiri et al. (2014ab) sequenced 1,112 bp of promoter region of κ-casein gene plus the first 100 bp from exon 1 and found 4 and 3 haplotypes in Bactrian and dromedary camels respectively. They found 14 transcription factors binding sites, where four of them (C/EBP-α, OCT1, MGF/STAT5 and TPB) almost perfectly conserved. Othman et al. (2016) amplified 488 bp of κ-casein gene in 50 Maghrabi breed samples reared in Egypt and digested them with Alul endonuclease. They observed three genotypes; CC (12%), TT (48%) CT (40%). Tanegonbady et al. (2016) studied the k-casein gene polymorphism and its relationship with some milk traits (fat, protein, lactose and solids non-fat milk) in 3 populations of Iranian camels (Bandar Turkman, AqQala and Gonbad) and found a non-significant association between kappa-casein gene polymorphism and milk production and composition traits.

4. Molecular markers for growth and meat quality

It is necessary to select genotypes with high growth and meat quality for more contribution of camels to the agricultural economy. Growth hormone (GH) is an anabolic hormone which plays an important role in postnatal longitudinal growth, tissue growth, lactation, reproduction as well as protein, lipid and carbohydrate metabolism (Dybus 2002; Daverio et al. 2012). Six Sudanese camel breeds (Kenani, Lahwee, Rashaidi, Anafi, Bishari and Kabbashi) were genotyped for 419C>T SNP. The Bishari and Anafi breeds that are classified as riding camels had slightly higher T allele frequencies than those of the other four breeds which are classified as pack camels (Ishag et al. 2010). Ali et al. (2014) found a significant association of 450T>C SNP in GH gene and it was associated with the increased estimated body weight. Both male and female Saheli Saudi camels with the CC genotype had higher body weights than the CT and TT genotypes (P ≤ 0.05). Shawki et al. (2015) found a SNP (419C>T) in the GH intron1 by genotyping 23 Maghrabi camels reared in Egypt. Abdel-Aziem et al. (2015) amplified a 613-bp fragment of camel GH in five camel breeds reared in Egypt (Sudani, Somali, Mowaled, Maghrabi and Falahy). The result shows that the Maghrabi breed that is classified as a dual purpose breeds had higher frequency for allele C (0.75) than those in the other tested.
four breeds. Moreover, two SNPs (111G>C and 380G>A) were detected in 630 bp of 5’UTR region of the GH gene in 11 male dromedary camels and showed significance with many meat characters including dressing percentage with hump, dressing percentage with liver and number of fibers hump (El-Kholy et al. 2016). The myogenic factors 5 (MYF5) gene has been reported to contribute to muscle growth and development, therefore they are considered as candidate genes for growth and meat quality related traits (Sabourin and Rudnicki 2000; Maak et al. 2006). The MYF5 showed a non-synonymous SNP (377A>T) which resulted in Met → Lys amino acids change. This SNP was found to be correlated with both carcass width at brisket and fat thickness of longissimus dorsi muscle (El-Kholy et al. 2016). Hedayat-Evrigh et al., (2016) found two non-synonymous SNPs in MYF5 exon 1 which resulted in Ser → Asn and Trp → stop codon amino acid changes respectively.

Myostatin (MSTN), also called growth differentiation factor-8 (GDF-8) a negative regulator of skeletal muscle development in mammals, represents a key target for genetic investigations in meat-producing animals (Grobet et al. 1997; Gonzalez-Cadavid and Bhasin 2004). Myostatin gene is highly conserved in camels. Shah et al., (2008) amplified 256 bp of exon 1 among six Pakistani camel breeds (Marecha, Dhatti, Larri, Kohi, Sakrai and Cambelpuri) and found no polymorphism. Interestingly, only 3 variant sites in the first intron (486G/C, 798G/A, 799C/T) were detected in the 3.6 kb of nucleotide sequence of MSTN gene spanning the three exons and part of the three introns, 5’UTR and 3’UTR regions by Muzzachi et al. (2015) in 22 dromedary camels from three different African populations (Tunisia, Egypt, and Algeria). Leptin (LEP) and Calpain (CAPN1) have been considered as two candidate genes for carcass performance and meat quality traits in the farm animals (Goll et al. 2003; Nkrumah et al. 2006). Tahmoorespur and Shojaei (2013) amplified 471 bp and 787 bp from LEP and CAPN1 genes respectively. They found no polymorphism among the 25 studied Iranian native camels, and also between dromedary and Bactrian camels.

5. Molecular markers for immunity and disease resistance

The Camelidae species occupy a peculiar niche within the adaptive immune response and the camel lineage has been proposed as a fascinating model in the evolution of immune systems (Ciccarese et al. 2014). Transmissible spongiform encephalopathies (TSE), also known as prion diseases, are a group of fatal neurodegenerative disorders of animals and humans. The etiology of TSE has not been fully elucidated but prions are believed to be the infectious agents (Chiesa and Harris 2001). The sequence of prion protein gene (PRNP) in many animal species has been elucidated and they are found to be highly conserved in the course of evolution (Yang et al. 2005). Little is known about PRNP of domestic camels. The polymorphisms of PRNP in both species of camels were observed in codons 16 (Ala → Val), 17 (Met → Thr), 120 (Asn → Ser), 176 (Arg → Lys), 215 (Ile → Val), 234 (Ser → Tyr), 237 (Tyr → Ser), and 239 (Gln → Gly) by comparing with other ruminants (Xu et al., 2012). In comparison to other mammalians, all camels possessed an amino acid deletion at position 71 of amino acid sequence of PRNP gene; the amino acid G has been deleted from this position. The existence of such genetic variations must be taken into consideration, if they are found to be related to the host resistance against the prion disease (Tahmoorespur and Jelokhani-Niaraki 2014).

The major histocompatibility complex (MHC) is a genomic region containing immune response genes, which play a crucial role in host and pathogen interactions. Studies of MHCs in different model species contribute to our understanding of mechanisms of immunity, diseases and their evolution (Meyer and Thomson 2001). Physical mapping located the MHC region to the chromosome 20 in dromedary camels. DRA, DRB, DQA and DQB exon 2 sequences encoding the antigen binding site of the corresponding class II antigen presenting molecules showed high degree of sequence similarity and extensive allele sharing across the three camels species. The DRA locus was found to be polymorphic, with three alleles shared by all three species. The extent of molecular diversity of MHC class II genes seems to be substantially lower in Old World camels than in other mammalian species (Plasil et al. 2016). BoLA-DRB3 gene is responsible for the differences in the susceptibility to infectious disease in mammals and is considered more-appropriate for comparative evolutionary studies. Hussain et al., 2016 had detected 10 polymorphic sites of BoLA-DRB3 exon 2 gene in 20 individuals of Pakistani camel breeds. Ten identified haplotypes showed haplotype diversity 0.879 and nucleotide diversity 0.0145.
The detected polymorphic sites might be related to the variability in the immune responsiveness of different individuals to particular pathogens (Hussain et al. 2016).

For the first time in a mammalian organism, it was shown that T cell receptor evolution has been favored in the dromedary by mutation in the productively rearranged gamma (\(TRG\)) and delta (\(TRD\)) genes, thus contributing to the repertoire diversity of heterodimer. The T cell receptor have evolved in the dromedary by mutation in the gamma (\(TRG\)) and delta (\(TRD\)) genes and the diversity was generated by mutations, both clonal expansion and selection seem to be strictly related to an enhanced structural stability of the \(\gamma\delta\) subunits (Ciccarese et al. 2014; Antonacci et al. 2015).

6. Molecular markers for camel racing

Traditionally, the sport of camel racing was regarded as entertainment associated with the Bedouin festivals in the Middle East region. Today, camel racing is a multi-million dollar industry with regular race events being linked to extensive training and scientific breeding programs. Camel racing is a popular sport in the Middle East region, where the demand is high for racing camels with higher stamina and endurance. Devising a technique to measure oxidative capacity and endurance in camels should be useful (Wilson 1999; Soman and Tinson 2016).

Al-Harbi and Amer (2012) found low intensity band patterns of the mitochondrial malate dehydrogenase (\(Mdh\)) and malic (\(ME\)) iso-enzymes in dromedary camels for production than in dromedary camels for racing. They concluded that mitochondrial \(Mdh\) and \(ME\) iso-enzymes were useful as bioenergetic enzyme necessary for racing ability. The different expressions are indications of the difference in the physiological adaptations of both camel breeds and are not for a systematic value (Al-Harbi and Amer 2012). The ratio of mitochondrial DNA (mtDNA) to nuclear DNA (nDNA) is often used as an estimate for the metabolic status of the tissue. A greater quantity of mitochondria per unit of tissue translates into greater oxidative capacity and endurance. Soman and Tinson (2016) found that the racing camels demonstrated a higher mtDNA/nDNA ratio compared with dairy camels.

7. Molecular markers for reproductive traits

The two gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are complex heterodimer glycoproteins. The effects of the two gonadotropins on ovarian development are mediated by their receptors (FSHR and LHR). These receptors belong to the members of the GTP-binding protein super-family (McFarland et al. 1989). Jelokhani-Niaraki et al. (2015) found one SNP (319 C/T) in \(FSHR\) gene but no polymorphic site was found in \(LHR\) gene among 25 Iranian dromedary camels. By comparing \(FSHR\) and \(LHR\) sequences of dromedary with Bactrian there was one SNP in \(FSHR\) (319 C/T) and in \(LHR\) (205 C/T) genes.

8. Conclusion

The new era of omics technology provides us with genomic charts as well as genetic variations among individuals and groups that may prove beneficial processing as well as analysis and integration of a large amount of data. Thereby omics technology will provide valuable information regarding the precision of selection of molecular markers in the near future. Identification and use of molecular markers for camel milk quality and production traits, disease resistance, and thermo-tolerance will ensure better productivity of camels and subsequently human health. Also, markers for fertility and carcass quality traits ensure faster and preferred growth in camels. Moreover, molecular marker for improvement of temperament and personality will ensure better management, production and welfare of camels. Apart from these, the use of different markers such as microsatellites for assessment of biodiversity will help the conservation of camel populations. Integration of information from all sources along with a search for direct markers and finding their causative sites for the QTL is required. Finally, in light of ongoing global warming and the increasing incidence of droughts, these camelid genomes are valuable resources for studying biological adaptations to environmental changes.

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