

— REVIEW ARTICLE —

***Bos indicus* associated alleles in Anatolian cattle breeds support zebu introgression into Near East**

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Origin and expansion of cattle domestication has always been an important field of research. Two main species of cattle, *Bos taurus* and *Bos indicus* have been domesticated separately in the Fertile Crescent and Indus Valley, respectively. Anatolia is accepted as a primary centre of taurine cattle domestication and it is accepted that considerable levels of *Bos indicus* (zebu) introgression have occurred at this centre. Molecular genetic studies on Anatolian breeds are especially important for obtaining information about cattle domestication, due to the geographic and cultural position of Anatolia. The genetic database of Anatolian cattle breeds has been established only recently and the conclusions of the previous studies related to this topic need to be brought together. This review summarizes the autosomal data of these breeds acquired in recent years to show the gene flow from zebu cattle. The results of the studies on prolactin (*PRL*), insulin-like growth factor-1 (*IGF-1*), pituitary-specific transcription factor 1 (*PIT-1*), growth hormone (*GH*), growth hormone releasing hormone receptor (*GHRH-R*), diacylglycerol O-acyltransferase (*DGAT1*) and prion protein (*PRNP*) genes showed that *Bos indicus* associated alleles are present in South Anatolian Red (SAR) and East Anatolian Red (EAR) breeds with different levels. Characteristics like adaptation to climatic conditions, resistance to poor breeding, feeding conditions and parasitic diseases might be inherited from zebu to Anatolian cattle. A better understanding of genetic characteristics of Anatolian cattle breeds will not only contribute to the development of livestock breeding, but it will also contribute to the knowledge about the history of domestication.

Key words: Anatolian cattle breeds, autosomal genes, *Bos indicus* associated alleles, domestication, zebu introgression.

INTRODUCTION

In the last decades, molecular genetics have become very important to understand the location, timing and expansion of domestication events. A large number of datasets have become available with the use of microsatellite, mitochondrial DNA (mtDNA), Y-chromosome and Amplified Fragment Length Polymorphism (AFLP) analyses (Bruford *et al.*, 2003). Also in recent years, ancient DNA studies have begun to provide new insights into the history of livestock animals (Troy *et al.*, 2001; Edwards *et al.*, 2007a; Singh *et al.*, 2011).

Most livestock domestication events are considered to have occurred at around the same time, around 8000-11000 years Before Present (BP). The archaeological data suggest the principal areas of livestock domestication as Southwest Asia (the Fertile Crescent and its eastern margin, towards the Indus valley), East Asia, as well as Northern and Central Africa and the Andean chain of South America. These regions are thought to have more appropriate climatic conditions for the beginning of domestication in the early Holocene (Gupta, 2004). Cattle, sheep, goats, pigs and buffalo were domesticated in two Asian regions, while llamas and alpacas were domesticated in South America. The horse differs from other species with its origin, whose domestication is thought to be through

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various independent events in different and more northerly regions (Bruford *et al.*, 2003).

ORIGIN AND EXPANSION OF CATTLE DOMESTICATION

Cattle have always been economically very important and had a key role in the cultural history of humankind because of the changes in diet, behaviour and socio-economic structure (Bellwood, 2004). There are two principal taxonomic groups of cattle, *Bos taurus* and *Bos indicus* (zebu cattle). Archaeological and genetic studies suggest that the domestication process of both of these subspecies from *Bos primigenius* has begun around 11000 years ago (Edwards *et al.*, 2007b). The genetic evidence argues for a separate domestication of these two types of cattle from two strains of *Bos primigenius*. mtDNA analyses suggest that major clades diverged at least 200000 years ago (Loftus *et al.*, 1994). The taurine cattle breeds were domesticated in the region called Fertile Crescent in the Near East. Early evidences have been found in Dja'de el Mughara in the Middle Euphrates Valley, dating from around 10650-10250 BP (Simmons, 1989; Helmer *et al.*, 2005). The domestication of zebu cattle breeds occurred in Baluchistan, Indus Valley and Pakistan (Meadow, 1993). According to the Y-chromosomal analyses, it has been suggested that a putative domestication event in Africa probably included Y2-like wild sires and the West African zebu cattle Y-chromosome may have partially originated from an ancient zebu introgression into Africa (Pérez-Pardal *et al.*, 2010).

Archaeological evidence and results from microsatellite analyses indicate that after the neolithisation in the Near East, farming and settlement spread to Europe and there is no evidence for an independent domestication of European aurochs (Edwards *et al.*, 2007a). The expansion developed through two major paths. One way is called the Danubian route, from the Near East through Balkan rivers to Northern and Central Europe. Another group migrated from the Near East following the Mediterranean coasts and settled in Southern Europe (Bogucki, 1996; Götherström *et al.*, 2005).

ZEBU INTROGRESSION INTO ANATOLIA

Anatolia is accepted as a primary domestication centre of cattle and it is also accepted that considerable levels of *Bos indicus* introgression have occurred at this centre (Loftus *et al.*, 1999). Analysis of data from

biparental autosomal markers has showed that the Middle Eastern region represents a complex hybrid zone between taurine and indicine cattle. Use of a panel consisting of six microsatellites (ETH10, ETH152, ETH225, HEL13, ILSTS005 and INRA005) with zebu-diagnostic alleles revealed results describing that Anatolian breeds were found to have an autosomal zebu admixture between 14 and 35%. The highest frequency within this range belongs to the Anatolian Black cattle. Geographical distribution of the uniparental mitochondrial and Y-chromosomal zebu haplotypes showed a gradual decrease with increased proximity to Europe and Africa (Edwards *et al.*, 2007b). A comparison of European, Southwest-Asian and Indian cattle reveals a gradual autosomal indicine-aurine cline from India to Anatolia and a sharper cline of uniparental markers (Edwards *et al.*, 2007b; Groeneveld *et al.*, 2010). Near Eastern cattle breeds display an asymmetrical genome composition with very few zebu mtDNA haplotypes, sparse zebu Y-chromosomal markers and significant autosomal zebu levels. It has been suggested that original gene pool were taurine and were then subjected to introgression from zebu populations over time (Edwards *et al.*, 2007b). Microsatellite analyses on bovine X-chromosome showed that the indicine-aurine admixture in the Near East is relatively ancient (Freeman *et al.*, 2006). Large number of zebu herds might have migrated relatively easily because of the geographical conditions and these migrations might have led to an admixture in Anatolian cattle breeds.

Decline in genetic diversity from the Near East to European cattle populations also provides evidence about the centre of domestication (Cymbron *et al.*, 2005). Troy *et al.* (2001) suggested that Near Eastern cattle populations have a higher genetic diversity than the Europeans because they have retained more ancestral variation from their wild progenitors. Furthermore, *Bos indicus* introgression into the Near Eastern breeds is also a factor which increases diversity values; however, it is not explanatory only by itself (Loftus *et al.*, 1999). Cattle-accompanied human migrations led to a contact between zebu and taurine cattle and the emergence of mixed breeds of Southwest Asia, Africa, China and later America. It has been suggested that climatic changes or contacts along the Silk Road might have paved the way for zebu migration from India to Southwest Asia (Ajmone-Marsan *et al.*, 2010).

INDIGENOUS ANATOLIAN CATTLE BREEDS

Because of the geographic and cultural position of Anatolia, molecular genetic studies on Anatolian breeds are especially important for obtaining information about cattle domestication. The main indigenous breeds of Anatolia are South Anatolian Red (SAR), East Anatolian Red (EAR), Turkish Grey (TG) and Anatolian Black (AB) cattle (Fig. 1). All of these breeds are resistant to parasites in their habitat and are highly adaptable to the climatic conditions of the regions they live in. They are also suited to unqualified and poor pasture and unhygienic barn conditions (Mason, 1996; Kaymakci & Kocak, 2004).

SAR cattle are being bred in the southern part of Turkey. There are also varieties of this breed in Syria, Israel and Egypt. It is a dual-purpose cattle breed and its milk yield is higher than that of the other Anatolian breeds. Its milk production is around 1000-1500 kg in a lactation period. Depending on the feeding and breeding conditions, it can reach up to 5000 kg. Birth weight in SAR cattle is 18-22 kg and adult animals weigh approximately 280-320 kg. Weight gain per day in young male SAR cattle is 0.6-0.9 kg. It is the tallest cattle breed in Anatolia. The SAR breed is

well adapted to the hot climate and is resistant to parasitic diseases. Some individuals of SAR cattle breed display a small hump, which is characteristic of zebu cattle (Soysal *et al.*, 2003; Kaymakci & Kocak, 2004).

EAR cattle are being bred in the East Anatolian region of Turkey. They are well suited to the cold climate, poor pastures and severe conditions of East Anatolia. The East Anatolia region is 1300-2000 m above sea level with an average winter temperature of -15°C and has an annual rainfall of 350-400 mm. The EAR breed is used as a dual purpose breed, for meat and milk. This breed has the best meat quality among the indigenous breeds of Anatolia (Soysal *et al.*, 2003). Average lactation period in EAR cattle is 230-250 days. In this breed, milk production is 1000-1200 kg. Weight at birth is 20-22 kg and daily weight gain is 0.7-0.8 kg. Adult females weigh 280-300 kg (Kaymakci & Kocak, 2004).

TG breed, also called Grey Steppe cattle, is found in the NW Turkey. They are being bred for milk and meat. Their body confirmation is very strong and resistant to hard conditions; they are also kept as beast of burden (Mason, 1996). They are famous with their horns' characteristic crescent-like shape. Their milk production is around 1000-1500 kg (Soysal *et al.*, 2003). According to Özdemir & Dogru (2009), TG

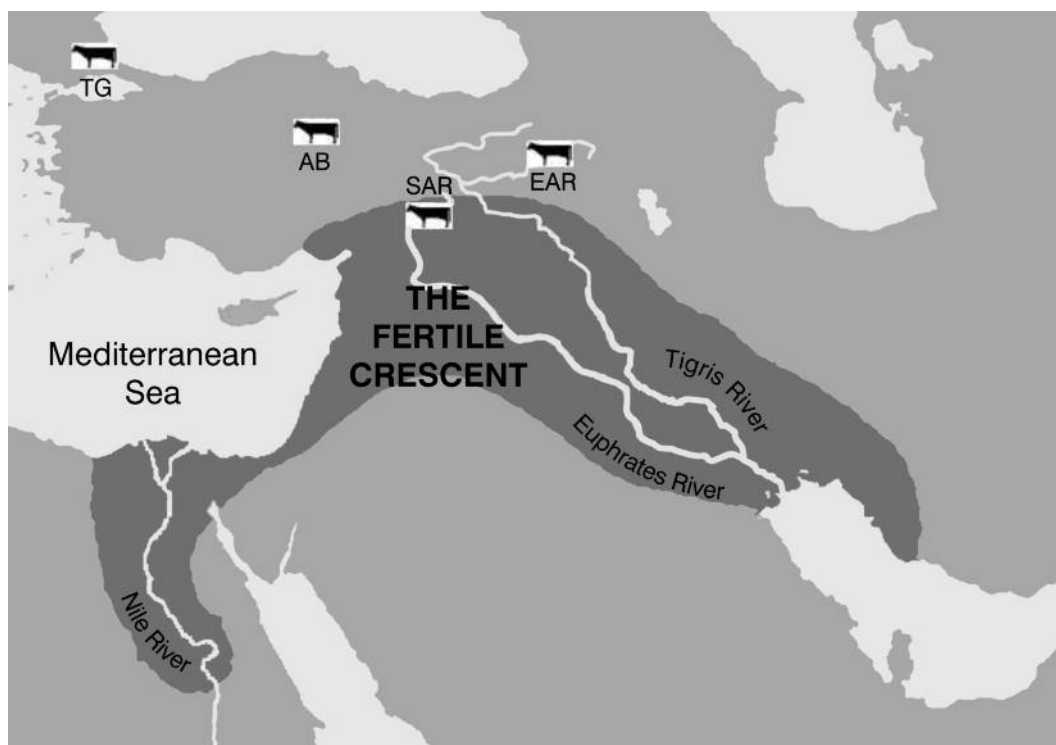


FIG. 1. Geographical distribution of the indigenous cattle breeds in Anatolia.

originated from the Balkan region of Europe, but Soysal & K ok (2004) suggested that the origin of this breed is the Ukrainian steppe. From Ukraine, it expanded into Italy, Hungary, the Balkans and Turkey; therefore, there are many similar local breeds in these countries (Soysal & K ok, 2004).

The AB cattle breed is strong, resistant to diseases and tolerant to poor care and poor diet. It is highly adaptable to all adverse climate conditions. They are used for their milk and also as beast of burden. The conformation of the breed tends to vary from typical beef to dairy (Mason, 1996). At present, almost no purebred animals of this breed have remained because of the wrong cross breeding policies implemented in the last fifty years (Soysal *et al.*, 2003).

GENETIC ANALYSES ON ANATOLIAN BREEDS USING AUTOSOMAL GENES

As an outcome of the studies made in recent years, a database has started to be established using the results of research on Anatolian indigenous breeds, especially SAR and EAR cattle (Oztabak *et al.*, 2008;  n *et al.*, 2008; Yardibi *et al.*, 2009; Akis *et al.*, 2010). This database can have a contribution to the insights about the domestication processes of the taurine and zebu breeds. Until today, results of several studies have been published separately and only a few of these studies interpreted the allele frequencies as zebu introgression. We evaluated allele distributions of some autosomal genes together to discuss the presence of *Bos indicus* associated alleles in SAR and EAR cattle. In Table 1, genotype and allele distributions of *PRL*, *IGF-1*, *PIT-1*, *GH*, *GHRH-R*, *PRNP* and *DGAT-1* genes in SAR and EAR cattle are compared with the data from taurine and indicine cattle. All of these genes mentioned here displayed zebu-associated alleles in SAR and EAR cattle breeds, in different levels. Especially for *PRNP* and *DGAT-1* genes, the indications of zebu introgression are not as strong as they are for the other five genes. Further studies are needed in order to gather support evidence.

PRL

Bovine *PRL* gene is located on BTA23 and has a silent A/G transition in exon 3, which can be detected with *RsaI* restriction enzyme. PCR-RFLP method reveals two alleles (A and B). According to the results of Udina *et al.* (2001), B allele of the bovine prolactin gene has a very low frequency in two taurine breeds, Gorbатов Red and Ayrshire Red. Researchers sugge-

sted that the polymorphism in exon 3 might be an ancient polymorphism. It is also possible that this polymorphism has originated from *Bos indicus* and the low frequency might point to a zebu introgression in the past. B allele frequency in Anatolian cattle breeds was found to be higher than those in the other taurine breeds, with a frequency of 0.26 and 0.44 in EAR and SAR breeds, respectively. BB genotype frequencies are calculated as 0.13 in EAR and 0.15 in SAR (Oztabak *et al.*, 2008), which seems to be controversial compared to the earlier studied taurine breeds. Mitra *et al.* (1995) and Chrenek *et al.* (1998) found that BB genotype was absent in taurine cattle breeds.

IGF-1

The single nucleotide polymorphism (SNP) identified as a T/C transition in the 5' flanking region of *IGF-1* gene on BTA5, can be determined by RFLP with *SnaBI* digestion (Ge *et al.*, 2001). It has been suggested that allele A is characteristic of taurine breeds because of the absence of allele A in Nellore cattle (*Bos indicus*) (Curi *et al.*, 2005). The researchers supported this suggestion by the A allele frequencies observed for Canchim breed (5/8 Charolais + 3/8 Zebu), 1/2 Simmental and 1/2 Angus cattle, which were 0.35, 0.20 and 0.32, respectively. In Girolando breed (5/8 Holstein + 3/8 Zebu), allele A had a frequency of 0.36. Curi *et al.* (2005) suggested that the fixation of B allele in indicine cattle might be the result of genetic drift, selection or mutation. In a study on SAR and EAR cattle, frequency of allele B was found to be much higher (0.77 and 0.62, respectively) than those of European taurine breeds (Akis *et al.*, 2010).

PIT-1

The bovine *PIT-1* gene is located on BTA1 and has a SNP (A/G transition) in exon 6 which can be detected by RFLP analysis with *HinfI* enzyme. In a study on *PIT-1* gene of Indian zebu cattle, a comparison has been made between the allele frequencies of taurine and indicine cattle. A near fixation of B allele in Indian zebu cattle was very obvious with a frequency of 0.94 (Mukesh *et al.*, 2008). The B allele had a higher frequency than the A allele in both of the SAR and EAR breeds, with frequencies of 0.57 and 0.71, respectively (Oztabak *et al.*, 2008). Especially the frequency of AA genotype was found to be very low (0.05) in the EAR breed.

TABLE 1. *Bos indicus* associated allele frequencies in South Anatolian Red and East Anatolian Red cattle breeds

Locus	allele ^a	Allele frequencies				References
		SAR ^b	EAR ^c	<i>Bos taurus</i>	<i>Bos indicus</i>	
<i>PRL</i>	B	0.44	0.26	0.05-0.20	0.51	Udina <i>et al.</i> , 2001 ¹ Mitra <i>et al.</i> , 1995 ² Oztabak <i>et al.</i> , 2008 ³
<i>IGF-1</i>	B	0.77	0.62	0.35-0.48	1.00	Ge <i>et al.</i> , 2001 ⁴ Curi <i>et al.</i> , 2005 ⁵ Siadkowska <i>et al.</i> , 2006 ⁶ Akis <i>et al.</i> , 2010 ⁷
<i>PIT-1</i>	B	0.57	0.71	0.06	0.94	Mukesh <i>et al.</i> , 2008 ⁸ Oztabak <i>et al.</i> , 2008 ³
<i>GH</i>	(-)	0.33	0.41	0.10	0.87	Lagziel <i>et al.</i> , 1999 ⁹ Mitra <i>et al.</i> , 1995 ² Yardibi <i>et al.</i> , 2009 ¹⁰
<i>GHRH-R</i>	A	0.53	0.45	0.00	1.00	Connor <i>et al.</i> , 1999 ¹¹ Eken, 2010 ¹² Eken <i>et al.</i> , 2011 ¹³
<i>PRNP</i>	12in	0.69	0.72	0.45	0.87	Brunelle <i>et al.</i> , 2008 ¹⁴ Ün <i>et al.</i> , 2008 ¹⁵
<i>DGAT1</i>	K	0.21	0.25	0.00-0.69	0.88-0.99	Kaupe <i>et al.</i> , 2004 ¹⁶

^a*Bos indicus* associated allele, ^bSouth Anatolian Red cattle, ^cEast Anatolian Red cattle

Number of animals: ¹81, ²57, ³80, ⁴760, ⁵374, ⁶262, ⁷100, ⁸723, ⁹473, ¹⁰100, ¹¹175, ¹²100, ¹³100, ¹⁴2371, ¹⁵100, ¹⁶1748

GH

The bovine *GH* gene located on BTA19 has a polymorphism which leads to an *Msp*I restriction site in intron 3. The allele frequencies in zebu cattle breeds show a near fixation of the *Msp*⁻ allele with the frequency 0.87 in zebu (Mitra *et al.*, 1995), 0.10 in North European and North American taurine cattle (Lagziel *et al.*, 1999). Dybus (2002) suggested that there is an increase of zebu originated allele of *GH* in European breeds as it gets closer to Anatolia. The Eastern European cattle have a *Msp*⁻ allele frequency of 0.39. The SAR and EAR breeds have intermediate values between zebu and taurine (Yardibi *et al.*, 2009).

GHRH-R

GHRH-R gene is located on BTA4 and has a polymorphism, which can be detected with *Eco*57I restriction enzyme. RFLP method reveals two alleles, A and B. A allele has a fixation in zebu cattle breeds with a frequency of 1.00 (Connor *et al.*, 1999). No individual with allele A in *Bos taurus* breeds could be observed in previous studies. Intermediate levels of A allele

frequency was found in SAR and EAR cattle (Eken, 2010; Eken *et al.*, 2011).

PRNP

Polymorphisms in open reading frames of the *PRNP* gene have been studied in almost all breeds of cattle because of the importance of the prion disease susceptibility. One of the insertion/deletion (indel) mutations related to Bovine Spongiform Encephalopathy (BSE) susceptibility is the 12 bp indel in intron 1 of *PRNP* gene. *Bos taurus* and *Bos indicus* show different patterns in terms of disease resistance. Brunelle *et al.* (2008) compared the frequencies of polymorphisms associated with BSE resistance between *Bos taurus*, *Bos indicus* and composite cattle and observed a significant difference. 12 bp in allele of *PRNP* gene has a very high frequency in *Bos indicus* breeds (0.87). Ün *et al.* (2008) found that 12 bp in allele frequency is 0.80 in TG cattle, which is one of the highest frequencies among taurine cattle. The frequencies of this allele in SAR and EAR cattle are closer to zebu cattle than the mean value in *Bos taurus* cattle.

DGATI

DGATI gene is located on BTA14, which has a lysine/alanine (K232A) substitution, affecting milk production in cattle. This polymorphism has two alleles: A and K. It has been suggested that *DGATI^K* is an ancestral allele and the substitution occurred after the divergence of indicine and taurine lineages (Lofthus *et al.*, 1994; Grisart *et al.*, 2002; Winter *et al.*, 2002). The results obtained from 1748 DNA samples of 38 different *Bos taurus* and *Bos indicus* cattle breeds from 13 countries of five continents, showed a fixation of *DGATI^A* in some *Bos taurus* breeds and a fixation of *DGATI^K* in one *Bos indicus* breed. Anatolian breeds (SAR, EAR, TG and AB) were found to have intermediate frequencies (0.21, 0.25, 0.36 and 0.38, respectively). *DGATI^K* allele frequency varied from 0.88 to 0.99 in three zebu cattle studied, and from 0.00 to 0.69 in taurine cattle (Kaupe *et al.*, 2004). The frequency of 0.69 belongs to the Jersey Island breed and this breed may have been derived from the early cattle strains coming to Europe, being heterozygous for *DGATI* gene. The constant milk fat selection of this breed in later years might have increased the *DGATI^K* allele frequency.

CONCLUSIONS AND FUTURE PERSPECTIVES

The results from several studies on autosomal genes of Anatolian cattle breeds have established a genetic database. Assessment of this database as a whole by taking zebu introgression into account depicts the genetic relationship between zebu cattle and SAR and EAR cattle. Studies on autosomal genes that affect trait characteristics and resistance to diseases show that *Bos indicus* alleles are present in Anatolian breeds with different levels. A basic problem of indigenous Anatolian breeds is that their production traits are very low compared to high trait European cattle breeds. But their adaptation to climatic conditions, resistance to poor breeding and feeding conditions and parasitic diseases are their advantages. It can be considered that the alleles affecting these characteristics are inherited from zebu through several events. This gene flow might have had positive contributions to the success of Anatolian breeds during natural selection. Future research conducted on the analyses of genes associated with climate adaptation in Anatolian cattle breeds, will shed light on functional genomics as well as on evolutionary processes.

A better understanding of genotypic characteris-

tics of Anatolian cattle breeds will not only contribute to the development of livestock breeding in the region, but it will also contribute to the knowledge about the history of cattle domestication. Until recent years, there have been relatively limited genetic studies on Anatolian cattle breeds in spite of their importance for the history of domestication and conservation of genetic diversity. Most of the substantial research efforts had limited sample sizes and only a few of them discussed the possible zebu introgression. It is necessary to conduct studies on large samples of indigenous Anatolian breeds with different genetic markers such as mtDNA sequences, Y-chromosomal haplotypes, nuclear microsatellites and large panels of SNPs (Edwards *et al.*, 2007b; Gibbs *et al.*, 2009). The results obtained from various analyses should be compared with the data of taurine and indicine cattle. It is also useful to increase the number of studies on genes under selection for economically important traits to understand the characterization of livestock domestication. Progress in ancient DNA studies and multidisciplinary approaches will make a great contribution to the knowledge about evolution and domestication of animals (Troy *et al.*, 2001; Singh *et al.*, 2011). Making ancient DNA studies in the Near East is challenging because of the hot climatic conditions. Thus, improved techniques should be applied to the remains found in Anatolia. All of the results obtained from Anatolian cattle breeds would contribute to world-wide molecular data and provide new insights for animal and human histories.

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