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Conserved Exon 2 but a Highly Polymorphic 5'-UTR of Tyrosinase Gene in Tianzhu White Yak (*Bos grunniens*)

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ABSTRACT

Domestic yak plays a critical role in supporting the livelihoods of nomads in the Central Asian Highlands. Tianzhu White yak is a unique breed developed from a very small number of mutant founders and its white hair has a special niche market value. In this study, the genetic polymorphisms in Tyrosinase (*TYR*) gene, which has been considered as a 'albino locus' in cattle, were identified and characterized to search for alleles associated with the white coat colour in yak. A total of 973 yak samples were collected, including 438 animals from five nucleus breeding herds and 365 individuals from four reproductive herds of the Tianzhu White yak. The reference *TYR* genomic DNA sequence derived from a Hereford bull was used to design all primers for screening and sequencing the exon 2 and the last partial 5'-untranslated region (5'-UTR) of the yak *TYR* gene. Both PCR-SSCP analysis and DNA sequences for their complete exon 2 in selected samples from the Tianzhu White yak herds and black yak populations identified a single conserved sequence identical to other cattle breeds. There were 14 genotypes and seven alleles defined by nucleotide polymorphisms present in the 215 bp long 5'-UTR of yak *TYR* gene among all yak samples, of which five alleles were specific to yak while the other two alleles were of a cattle origin. Although, current data suggested no association of these polymorphisms with the yak coat colour variations, they shed light on the potential function of the promoter on regulation of expression of yak *TYR* gene that is warranted to screen for additional polymorphisms in its extended 5'-UTR and other exons.

Key words: Tyrosinase, exon 2, 5'-UTR, polymorphism, yak, white coat

INTRODUCTION

Domestic yak (*Bos grunniens*) is a species of family Bovidae and distributed in the Central Asian Highlands around the Qinghai-Tibetan Plateau which is characterized by cold weather and high altitude typically above 3500 m. There are approximately 14 million domestic yak (13 million in China alone), which are considered as the most important livestock species supporting

the livelihoods of nomads in the region by providing meat, milk, hair, hide, dung fuel as well as pack energy. There are 13 officially recognized breeds of domestic yak in China based on their characteristics of distribution, coat colour, body conformation and local history (Cai, 1989; Ma *et al*., 2010; Qi *et al*., 2008, 2010; Xuebin *et al*., 2005; Rhode *et al*., 2007; Wiener *et al*., 2003, 2011; Zhang, 1989). While all other yak breeds or populations in China and elsewhere are predominantly black coated, the Tianzhu White yak, which is distributed in Tianzhu county of Gansu province, China (102°02'-103°29'E; 36°29'-37°41'N), has a white coat, which is unique and has a special market value locally. It is also worth to note that there are 2-3% white individuals in other yak breeds or populations (Wiener *et al*., 2003).

It is believed that herdsmen who migrated into the Tianzhu area had started the selection and breeding of pure white yak herds about 130 years ago. A few nucleus breeding herds have been developed since 1981 (Zhang, 1989). Currently, there are around 60,000 white yak with half of them being treated as pure white yak with white hair, skin and slightly red eye sockets. They are considered as typical albinos. The remaining animals are white coated but with some coloured spots mostly around their eye sockets, which can help reducing the heavy ultraviolet irradiation at high altitudes (Wiener *et al*., 2003, 2011). Compared to other yak breeds, the Tianzhu White yak has a moderate genetic variation in their mitochondrial DNA D-loop sequences in terms of haplotype distribution among the general yak haplogroups as well as both haplotype and nucleotide diversities within this breed (Guo *et al*., 2006; Lai *et al*., 2005, 2007; Qi *et al*., 2008; Wang *et al*., 2010). Microsatellite DNA markers also reveal a middle range of genetic diversity in the Tianzhu White yak and its admixed genetic relationship or differentiation among other yak breeds (Zhang *et al*., 2008; Zhong *et al*., 2006) but a very limited cattle introgression (Qi *et al*., 2010). However, a relatively low number of alleles at *Bogr-DRA* locus suggest that the Tianzhu White yak could have suffered from bottleneck events resulted from a very small number of mutant founders of either true albinos or animals with a white coat (An *et al*., 2012).

It is well known that the synthesis and distribution of melanins from melanosomes in the cytoplasm of melanocytes determine the basic colour in skin, hair bulbs and eyes in mammals. Eumelanin and pheomelanin are the two major types of melanins. Melanocortin receptor 1 (*MC1R*) or the *Extension* locus *MC1R*, mapped to bovine chromosome 18 (Werth *et al*., 1996), plays a major role in regulation of the switch between eumelanin (black pigment) and pheomelanin (red pigment) in cattle (Olson, 1999; Klungland and Vage, 2003; Seo *et al*., 2007). Tyrosinase (*TYR*) is identified as the most essential rate-limiting enzyme in the melanogenesis pathway with its high level for the production of eumelanin while a low level for the production of pheomelanin (Gutierrez-Gil *et al*., 2007; Seo *et al*., 2007). To search for genes or alleles associated with the white coat colour in yak, the complete *MC1R* coding sequence in 954 bp was sequenced, however, none of the five identified nucleotide substitutions or three defined haplotypes is specific to black or white phenotype of the yak breeds studied, indicating possible involvement of other genes in the coat colour determination in yak (Chen *et al*., 2009).

An insertion of a cytosine within exon 2 at the 926th nucleotide in coding sequence of the *TYR* locus, located on bovine chromosome 29 (Schmidtz *et al*., 2001), was detected in an albino Braunvieh calf. This mutation caused a frame shift mutation turning its 317th codon into a premature stop codon that reduces the normal sequence encoding 530 amino acids down to 316 residues. The mutation may eventually eliminate one of the two copper binding sites, the CuB

(Oetting and King, 1999) and thus result in an impaired function of the *TYR*. This evidence was therefore considered to support the assumption of *TYR* gene as the 'albino locus' in cattle (Foreman *et al*., 1994; Schmutz *et al*., 2004). In this study, we screened and characterized the genetic polymorphisms in genomic DNA sequences of the complete exon 2 and also of the last partial 5'-untranslated region (5'-UTR) of the *TYR* gene with a large sample size of Tianzhu White yak. The objectives of this study were to identity possible causative and functional mutations in the *TYR* gene responsible for the white coat colour in yak for marker-assisted selection to facilitate future breeding program.

MATERIALS AND METHODS

This experiment was conducted at the CAAS-ILRI Joint Laboratory on Livestock and Forage Genetic Resources, Institute of Animal Science, Chinese Academy of Agricultural Sciences (CAAS) in China from September 2010 to March 2012.

Samples: A total of 803 blood samples were collected from the Tianzhu White yak for this study, of which 438 yak were collected from five nucleus breeding herds with animals selected for a pure white coat while other 365 yak having predominantly a white coat and some coloured spots in different parts of bodies of animals from four reproductive herds. A population of Gannan yak (53) with a pure black coat was sampled in Gansu and two populations of local Dangxiong yak (117) with predominantly a black coat were collected in Tibet for comparison purpose (Table 1). DNA extraction was performed following the routine phenol-chloroform protocol (Sambrook *et al*., 1989).

Primer design: The complete *TYR* genomic DNA sequence was retrieved from the *Bos taurus* chromosome 29 genomic scaffold, alternate assembly Btau_4.6.1 Chr29.scaffold8 derived from the Hereford bull L1 Domino 99375 and released in October 2011 (GenBank accession No. NC_007330; The Bovine Genome Sequencing and Analysis Consortium, 2009; Zimin *et al*., 2009). It was used to design all primers for this study. Two pairs of primers were designed for screening and sequencing the exon 2 and another three pairs were used for the last partial 5'-UTR of the yak *TYR* gene using the Primer program version 5.0 (Premier Biosoft International, Palo Alto, CA, USA) (Table 2).

Table 1: Sampling information of 12 yak populations

Populations	Names of herds	No. of samples	Locations	Coat colours
Tianzhu White	LZH	116	Songshan town, Tianzhu	White
	WYCH	108 (19)	Songshan town, Tianzhu	White
	JDL	80 (24)	Zhuaxixiulong town, Tianzhu	White
	ZML	81	Xidatan town, Tianzhu	White
	MJF	53 (20)	Huazangsi, Tianzhu	White
	LJL	73 (37)	Songshan town, Tianzhu	With coloured spots
	JZMJ	118 (46)	Zhuaxixiulong town, Tianzhu	With coloured spots
	JDW	102	Zhuaxixiulong town, Tianzhu	With coloured spots
	CQG	72 (21)	Duoshi town, Tianzhu	With coloured spots
Gannan	GN	53 (22)	Maqu county, Gansu	Black
Dangxiong	DQ	70 (20)	Daquka town, Dangxiong, Tibet	Predominantly black
Dangxiong	GT	47 (21)	Gongtang town, Dangxiong, Tibet	Predominantly black
Total		973 (230)		

No. in brackets are the samples selected for screening the exon 2

Table 2: Names, sequences and positions of the primers used for amplification of the complete exon 2 and last partial 5'-UTR in yak *TYR* gene

Names	Sequences (5' to 3')	Positions	Expected sizes of PCR products (bp)
TYR-E2sF	TCCAAATAAGGAATCCCAACC	53-73 bp before exon 2	290
TYR-E2sR	CTTCCAGGGTATTTCTAAAGCTG	Last 23 bp in exon 2	
TYR-E2lF	GCAAGACTAGAACTGTGGTCTGAA	180-203 bp before exon 2	564
TYR-E2lR	CGTTCTGCTAGAGTGATTGGT	124-144 bp after exon 2	
TYR-5UsF	TAGGCCTATCCCACTGATGG	212-231 bp before exon 1	267
TYR-5UsR	ACTCCACAGTAGGCAGTACAGG	15-36 bp in exon 1	
TYR-5UlF	TACTACCAATGCCTTGGCCTATTT	463-486 bp before exon 1	1424
TYR-5UlR	CATTTTCTAGGCTTGGCAGGAGAA	96-119 bp after exon 1	
TYR-5USF	TGCCAGGACGTCATTCTGT	163-181 bp in exon 1	For sequencing reactions of 1424 bp long 5'-UTR
TYR-5USR	CCGCAATTGAATCCCATGAAG	282-302 bp in exon 1	

PCR-SSCP analysis: Polymerase Chain Reaction (PCR) and Single-strand Conformational Polymorphism (SSCP) were used to screen for possible polymorphisms within the amplified fragments of 290 bp long exon 2 in 230 selected samples from six Tianzhu White yak herds and the three black yak populations as well as of 267 bp long last partial 5'-UTR in all 973 samples (Table 1, 2). Similar PCR system and conditions were followed (Zhang *et al*., 2011) with exceptions of the annealing temperatures at 55.7 and 61.6°C for the exon 2 and 5'-UTR fragments, respectively. The SSCP conditions were also similar to Musa *et al*. (2007), Qiong *et al*. (2011) and Zhang *et al*. (2011) but a 10% non-denaturing acrylamide gel (Acr:Bis = 39:1) was run for 15 to 20 h at 150-190 V.

DNA sequencing: After screening polymorphisms in the two small fragments, a set of selected DNA samples, in particular those representing the different genotypes based on the SSCP data (three each from GT and DQ, seven from GN, six each from LZH and JZML and four from JDL), were amplified for longer exon 2 (564 bp) and 5'-UTR (1424 bp) fragments using respective primer pairs (Table 2). The PCR reactions were increased to a 50 μL volume with same concentrations of the reagents. Similar PCR conditions were applied but an annealing temperature at 56.7°C for the exon 2 fragments and 58.8°C for the 5'-UTR. The PCR products were purified and sequenced using either the PCR primers for the exon 2 fragment or specific sequencing primers (Table 2) for the 5'-UTR on an ABI 3730 DNA Sequencer.

Statistical analysis: Genotype data from the PCR-SSCP analysis were analyzed for the number of observed alleles (Na), allele and genotype frequencies, Polymorphic Information Content (PIC), observed (Ho) and expected (He) heterozygosity using the Excel Microsatellite Toolkit version 3.1 (Park, 2001) and Hardy-Weinberg Equilibrium (HWE) tests using the Genepop'007 package (Rousset, 2008) based on a Markov chain simulation with 10000 of dememorizations and 10000 iterations for each of the 1000 batches. DNA sequences were aligned and analyzed using the MEGA software version 5.0 (Tamura *et al*., 2011).

RESULTS

No polymorphism in the exon 2 of yak *TRY* gene: Screening of the complete exon 2 fragment (217 bp) amongst 230 selected samples from six Tianzhu White yak herds and the three black yak populations did not yield any polymorphism (Fig. 1). Further sequencing of the same exon 2

fragment in 13 black yak and 16 white yak (some of them were selected as for representatives of different genotypes in the 5'-UTR) also did not show any variation. The single yak *TYR* exon 2 sequence was identical to those of the reference Hereford, White Galloway (GenBank accession No. AY046527.2) and Holstein (NM_181001.2), indicating its conservative property.

A highly polymorphic 5'-UTR of yak TRY gene: Opposite to the exon 2, there were 14 genotypes defined by seven alleles (A to G) in the last partial 5'-UTR among the 973 yak samples (Fig. 2). A total of 29 representative samples of different genotypes, including 14 homozygote samples (AA, BB, CC, DD and GG) and 15 heterozygote samples (AB, AC, AD, BD, BC, AE, BE, DE and DF), were selected for sequencing the same fragment. DNA sequences of the homozygote samples confirmed the presence of five alleles identified from the PCR-SSCP results. Heterozygote samples of AB, AD, AE, AF, BD and CG genotypes carried a Single Nucleotide Polymorphism (SNP) between the two alleles, therefore their allele reconstructions were easily achieved and confirmed using the homozygote sequences of A, B, D, C and G alleles. Because sequences of BE and BF genotypes suggested the presence of two SNPs while DE and DF genotypes of three SNPs, their allele constitutions were first deduced using the sequences of B, E and F alleles. Six samples each of the AE, AD, BC, BE, DE and DF genotypes were selected to follow the routine cloning and sequencing procedures to validate the relevant and deduced sequences from two to 10 clones per sample.

It is confirmed that there were seven alleles in the last partial 5'-UTR of yak *TYR* gene based on the PCR-SSCP and DNA sequencing data. After excluding the TYR-5UsF primer sequence region and the first partial exon 1 sequence from further analysis, a fragment of 215 nucleotides were present in the A, B, D, E and F alleles. Sequence alignment showed that there was an insertion/deletion of four base pairs from the 3rd to the 6th nucleotides between the A, B, D, E and F alleles and C and G alleles. Comparison with the homology region in the reference Hereford genome showed that the sequence of C allele was identical to the reference Hereford genome while G allele had only a single mutation from adenosine in allele C to cytosine at their 158th nucleotide, thus suggesting their probable origin of a taurine (*Bos taurus*) genetic background.

For genotype frequency distribution, a predominant AA (0.492-0.906) followed by AB (0.057-0.267) were found in all 12 yak populations, less frequent AD and AE in seven populations each and AC and BB in five populations each and the least frequent (<6%) remaining eight genotypes in only one or two populations. A similar pattern was observed in allele frequency distribution with a predominant A (0.6907-0.9528) followed by B (0.0278-0.1698) in all 12 yak populations, less frequent D and E in seven populations each, then C ranging from 0.0068 to 0.0938 in six populations and the least frequent F and G (<3%) in one population each. There was no significant difference in both genotype and allele frequency distribution patterns either between the five nucleus breeding and four reproductive herds of the Tianzhu White yak in particular or between the Tianzhu White yak and other three black yak populations in general (Table 3). Furthermore, all genetic diversity parameters did not detect any specific difference between the herds and populations although four out of the five nucleus breeding herds had a relatively low genetic variation with only 2 or 3 observed alleles at this locus, a result from the selective program to maintain their white coats. The GT population showed a significant deviation from the expected Hardy-Weinberg equilibrium due probably to its rich genetic variation with six alleles at this locus but in a relatively small size (Table 1, 4).

Table 3: Genotype and allele frequencies of 5'-UTR of *TYR* gene in 12 domestic yak populations

	Genotypes														Alleles						
Herds	AA	BB	CC	DD	GG	AB	AC	AD	AE	BC	BD	BE	DE	DF	A	B	C	D	E	F	G
LZH	0.724					0.267			0.009						0.8621	0.1336	0	0	0.0043	0	0
WYCH	0.796	0.028				0.176									0.8843	0.1157	0	0	0	0	0
JDL	0.675	0.025	0.025			0.100	0.113	0.025	0.013	0.025					0.8000	0.0875	0.0938	0.0125	0.0063	0	0
ZML	0.889					0.111									0.9444	0.0556	0	0	0	0	0
MJF	0.906					0.057			0.038						0.9528	0.0283	0	0	0.0189	0	0
LJL	0.822					0.096	0.014	0.068							0.9110	0.0479	0.0068	0.0342	0	0	0
JZMJ	0.492	0.017		0.034		0.203		0.220	0.008		0.025		0.008	0.008	0.6907	0.1314	0	0.1653	0.0085	0.0042	0
JDW	0.775					0.147	0.039	0.010	0.010	0.020					0.8775	0.0833	0.0294	0.0049	0.0049	0	0
CQG	0.903					0.056	0.014	0.028							0.9514	0.0278	0.0069	0.0139	0	0	0
GN	0.585	0.038				0.189	0.038	0.019	0.057		0.057	0.019			0.7358	0.1698	0.0189	0.0377	0.0377	0	0
DQ	0.900	0.014				0.086									0.9429	0.0571	0	0	0	0	0
GT	0.660		0.043		0.022	0.170		0.064	0.043						0.7979	0.0851	0.0426	0.0319	0.0213	0	0.0213

Table 4: Observed (Ho) and expected (He) heterozygosity, number of observed alleles (Na), Polymorphic Information Content (PIC) and p-values for Hardy-Weinberg Equilibrium (HWE) test for the 5'-UTR of *TYR* gene in 12 yak populations

Herds	Ho	He	Na	PIC	p-values for HWE
LZH	0.2400	0.2759	3	0.2124	0.3216
WYCH	0.2056	0.1759	2	0.1837	0.1447
JDL	0.3455	0.2750	5	0.3219	0.1422
ZML	0.1056	0.1111	2	0.0994	1.0000
MJF	0.0918	0.0943	3	0.0889	1.0000
LJL	0.1678	0.1781	4	0.1608	1.0000
JZMJ	0.4803	0.4576	5	0.4348	0.3604
JDW	0.2233	0.2255	5	0.2101	0.3842
CQG	0.0945	0.0972	4	0.0920	1.0000
GN	0.4305	0.3774	5	0.3916	0.1746
DQ	0.1085	0.0857	2	0.1019	0.1906
GT	0.3562	0.2766	6	0.3384	0.0014**

** Significnt at $p<0.01$

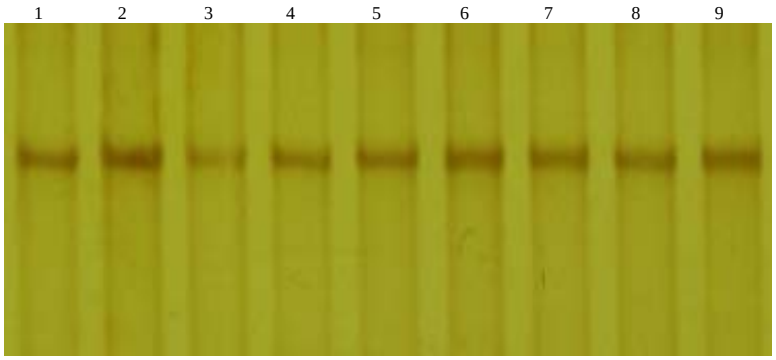

Fig. 1: Single-strand conformational polymorphism (SSCP) analysis of polymerase chain reaction (PCR) products of exon 2 fragment in yak *TYR* gene (Lanes 1-9 represented nine samples from MJF population)

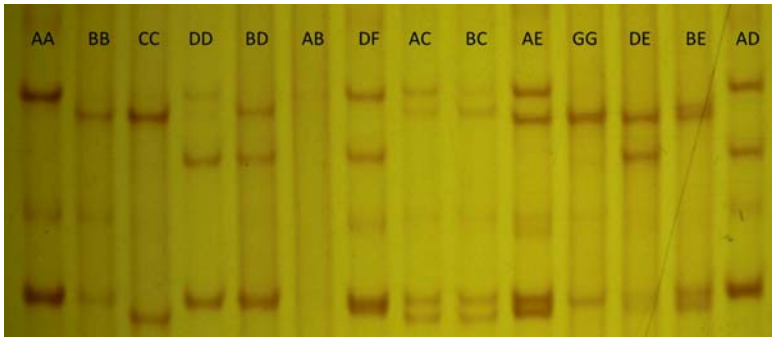

Fig. 2: SSCP patterns of different genotypes in the 5'-UTR in yak *TYR* gene (Order of the samples and their genotypes in brackets: LZH02 (AA), JDL30 (BB), JDL12 (CC), JZML91 (DD), JZML38 (BD), JZML85 (AB), JZML06 (DF), JDL29 (AC), JDL31 (BC), GN116 (AE), GT45 (GG), JZML21 (DE), GN270 (BE) and JZML50 (AD)

DISCUSSION

Considering the possible impact of *TYR* gene as the 'albino locus' in cattle (Foreman *et al*., 1994; Schmutz *et al*., 2004) and its very complicated genomic DNA sequence structure with five exons ranging from 148 to 819 bp and four introns from 820 to 46945 bp (The Bovine Genome Sequencing and Analysis Consortium, 2009), this study was initially attempted to detect the frame shift mutation in the exon 2 of *TYR* gene (Schmutz *et al*., 2004) in Tianzhu White yak. However, the PCR-SSCP screening of 230 Tianzhu White yak and black yak as well as the DNA sequences of 29 white and black yak revealed no polymorphism in the exon 2. This rather conserved exon 2 fragment was identical to those of other cattle breeds with normal coat colours. In fact, the albino Holstein calf carrying an exon 2 sequence identical to other normally pigmented cattle (Schmutz *et al*., 2004) and the new data from this study imply that the frame shift mutation in the albino Braunvieh calf (Schmutz *et al*., 2004) was most likely case or breed specific.

The Albinism Database (Oetting and King, 1999; http://albinismdb.med.umn.edu /oca1mut.html, last updated in September 2009) documented several polymorphisms in the 5'-UTR

or promoter region in human *TYR* gene. The high polymorphisms of seven alleles in the 215 bp long last partial 5'-UTR of yak *TYR* gene shed light on the potential function of the promoter on regulation of its expression (Ponnazhagan *et al*., 1994). Although, five alleles with the insertion of four nucleotides were specific to yak, the lack of distribution pattern of the predominant A allele between either the nucleus breeding herds (0.89±0.11) and reproductive herds (0.86±0.12) of the Tianzhu White yak or the Tianzhu White yak (0.88±0.09) and other black yak populations (0.83±0.11) suggested that these alleles defined in this limited 5'-UTR fragment of *TYR* gene played no functional role in coat colour differentiation in yak. Furthermore the presence of cattle derived C and G alleles in six yak populations including one of the nucleus breeding herds and three out of the four reproductive herds of Tianzhu White yak implied that today the genetic variations in coat colours of yak may have already been complicated by the gene flow from different taurine or indicine cattle breeds (Cai, 1989; Qi *et al*., 2010; Wiener *et al*., 2003; Zhang, 1989).

The relatively low number of alleles present in the last partial 5'-UTR of *TYR* gene in the nucleus breeding herds of Tianzhu White yak confirmed that the long term selection for the white coat colour trait has led to a reduced genetic variation in this breed (Wiener *et al*., 2003; An *et al*., 2012). However, the presence of important enhancer elements between -2020 and -550 bp in promoter region for the transcription control of human *TYR* gene (Ponnazhagan *et al*., 1994), hundreds of the nonsense, frameshift and splice site mutations identified in human *TYR* gene associated with oculocutaneous albinism (Oetting and King, 1999; http://albinismdb.med.umn.edu/oca1mut.html, last updated in September 2009; Preising *et al*., 2011; Renugadevi *et al*., 2010; Wu *et al*., 2012) and the highly polymorphic last partial 5'-UTR (215 bp) of yak *TYR* gene detected for the first time in this study all warrant a further intensive search for additional polymorphisms in the extended 5'-UTR and other exons of the yak *TYR* gene, which could eventually lead to a depth understanding of the association of TYR function with the coat colours of the yak.

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