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Full Length Research Paper

Characterization, single nucleotide polymorphism (SNP) identification and variation of goat *c-Kit* gene in different populations

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Effects of *C-kit* mutations on coat color has been reported in human, pig and mouse, little is known about it in goat. In this paper, a total of 22472 bp of goat *c-Kit* gene sequence (HM130675) was determined and 20 variable sites were detected, of which only one (*g.40545G>A*) existed in exon 16 resulting in *p.Gly763Glu*, the others all existed in introns. The variation of *g.40545G>A* and *g.35818_35819insTCTC* was analyzed in different goat populations with different coat color. The results showed that allele A at *g.40545G>A* and T at *g.35818_35819insTCTC* was favour of white, while allele G at *g.40545G>A* and C at *g.35818_35819insTCTC* was favour of darker coat color. Haplotype AT and GC have close relationship with white coat color and dark coat color, respectively. The phylogenetic relationship of populations not only reflacts breed forming history, but also basically was consistent with the coat color variation. Higher deficiency of heterozygotes existed in Liaoning Cashmere Goat, Leizhou Black Goat at *g.40545G>A* and *g.35818_35819insTCTC*, indicating their high inbreeding coefficients within populations.

Key words: *c-Kit*, goat population, coat color, variation.

INTRODUCTION

C-kit gene encodes Mast/stem cell growth factor receptor (also called as C-kit receptor, KIT or CD117), expressed on the surface of hematopoietic stem cells, neural crest-derived melanocyte precursors as well as other cell types. This receptor binds to stem cell factor (a substance that causes certain types of cells to grow). It has a tyrosine-protein kinase activity. Binding of the ligands leads to the autophosphorylation of KIT and its association with substrates such as phosphatidylinositol 3-kinase (Pi3K). Altered forms of this receptor affect melanogenesis, gametogenesis and hematopoiesis during development and in adult life, and may be associated with some types of cancer (Edling and Hallberg, 2007; Fleischman et al., 1991; Nocka et al., 1990). The *c-Kit* mutations cause pigmentation disorders as well as other effects on hematopoietic cells, primordial germ cells, interstitial cells in the small intestine in animals (Chabot et al., 1988; Fleischman et al., 1991; Geissler et al., 1988; Giebel and Spritz, 1991). Deng et al. (2005) found that the mutation of G2465C in *c-Kit* gene was the cause of clinical phenotype of piebaldism in human. Marklund et al. (1998) described that the dominant white phenotype in domestic pigs is caused by two mutations in the *c-Kit* gene, one gene duplication associated with a partially dominant phenotype and a splice mutation in one of the copies leading to the fully dominant allele. Xue et al. (2007) reported that a nonsense mutation of *c-Kit* in W^{-3Bao} mouse resulted in dominant spotting phenotype. The complete open reading frame (ORF) of the goat *c-kit* cDNA was first cloned by Tanaka et al. (1997). To extend our knowledge of *c-Kit* gene and provide some useful information for goat breeding, we determined partial goat *c-Kit* gene (HM130675), identified some variable sites, and carried out the distribution analysis of two variable sites

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Table 1. Gene frequency of *g.40545G>A* and *g.35818_35819insTCTC* and haplotype frequency in goat populations.

Population	Coat color	Size	Frequency of *g.40545G>A*		Frequency of *g.35818_35819insTCTC*		Haplotype frequency			
			G	A	T	C	GC	GT	AC	AT
TSD	White	52	0.000	1.000	0.490	0.510	0.000	0.000	0.521	0.479
LNC	White	36	0.083	0.917**	0.403	0.597	0.083	0.000	0.500	0.417
JNG	Gray	48	0.104	0.896**	0.385	0.615	0.107	0.002	0.502	0.389
CDM	Yellow-brown	33	0.500	0.500	0.000	1.000	0.500	0.000	0.500	0.000
NJH	Tan	36	0.611	0.389	0.028	0.972**	0.594	0.010	0.385	0.011
NJF	Tan	36	0.639	0.361	0.028	0.972**	0.636	0.010	0.343	0.011
NJB	Black	35	0.657	0.343	0.043	0.957**	0.688	0.000	0.292	0.021
LZB	Black	30	0.367	0.633**	0.113	0.883**	0.322	0.028	0.628	0.022
CDP	Black	35	0.357	0.643**	0.000	1.000	0.333	0.000	0.667	0.000

TSD, LNC, JNG, CDM, NJH, NJF, NJB, LZB and CDP are short for Tangshan Dairy Goat, Liaoning Cashmere Goat, Jining Gray Goat, Chengdu Ma Goat, Nanjiang Yellow Goat high fertility strain, Nanjiang Yellow Goat fast growth strain, Nanjiang Yellow Goat black strain, Leizhou Black Goat and Chengde Polled Goat, respectively. ** represents disequilibrium of population at variation site at 0.01.

(*g.40545G>A* and *g.35818_35819insTCTC*) in different coat color populations.

MATERIALS AND METHODS

Involved goat populations with different coat color

A total number of 341 individuals from nine goat breeds/strains with different coat color was sampled, including Chengdu Ma Goat (CDM, yellow-brown), Nanjiang Brown Goat fast grow strain (NJF, tan), Nanjiang Brown Goat high fertility strain (NJH, tan) and Nanjiang Brown Goat black strain (NJB, black) from Sichuan province of China; Jining Gray Goat (JNG, gray) from Shandong province of China; Leizhou Black Goat (LZB, black) from Guangdong province of China, Chengde Polled Goat (CDP, black) and Tangshan Dairy Goat (TSD, white) from Hebei province of China; Liaoning Cashmere Goat (LNC, white) from Liaoning province of China (Table 1).

DNA extraction, primer design, and PCR amplification

Genomic DNA from blood samples of goat was isolated according to the standard phenol:chloroform extraction method. Pairs of primers were designed using Primer Premier 5 version 5.00 (Table 2) according to the conserved genomic domain of cattle (NC_007304) and goat *c-Kit* mRNA sequence (D45168). PCR amplification was carried out on a programmable thermal controller (German Biometra) with a total volume of 25 µL solution containing 50~100 ng genomic DNA, 2.5 µl 10 × PCR reaction buffer (Mg^{2+} plus), 400 pmol/l each forward and reverse primer, 200 pmol/µl dNTPs, and 2 U Taq DNA polymerase from Tiangen Biotech (Beijing). For those PCR primers with products longer than 1.5 kb, we used Taq10 DNA polymerase from Zexing Biotech (Beijing). The PCR protocols were as follows: denaturation at 95℃ for 4 min, followed by 35 amplification cycles (28 cycles for long fragment) of denaturation at 94℃ for 30 s, annealing at the corresponding temperature (shown in Table 2) for 30 s and extension at 72℃ for times that were developed based on the product length (basically 1 kb/min), followed by an extended elongation at 72℃ for 10 min. PCR products were detected on a 1 to 1.5% agarose gel including 0.5 lg/ml of ethidium bromide, photographed under UV light, and sequenced by Shanghai Sangon Biological Engineering Technology and Services (Shanghai).

DNA sequence structure analysis and SNP identification

The sequenced fragments were connected using SeqMan software (version 7.1.0) as implemented in the DNAStar software package. Exons and introns were determined and numbered by aligning the connected sequence to *c-Kit* mRNA sequence (D45168) using the Spidey program (http://www.ncbi.nlm.nih.gov/IEB/Research/Ostell/Spidey/). To identify SNPs of the goat *c-Kit* gene, we mixed PCR products from three individuals of each of the following breeds: Chengdu Ma goat, Jining gray goat and Tangshan dairy goat, and got them sequenced; then heterozygous sites were screened and determined by ABI chromatogram of BioEdit software (version 4.7.0).

PCR-RFLP analysis

The *g.40545G>A*, only one SNP located in exon 16 found in this paper, was analyzed using PCR-RFLP. PCR products (303 bp) amplified with primers of P17 in Table 2 were digested by restriction enzyme AluⅠ, which could recognize and cut the consensus sequence AG↓CT. The restriction endonuclease reaction was carried out in a total reaction volume of 10 µl solution containing 3 µl PCR product, 0.2 µl restriction enzyme (5 U/µl, TaKaRa Biotechnology Co., Ltd. Dalian, China), 1 µl 10 × L buffer and 5.8 µl ddH2O at 37℃ for 3 h. The digested products were analyzed on 12% polyacrylamide gels of size 16 × 18 cm. Electrophoresis was carried out at 150 V for 3 h at room temperature in 1 × TBE buffer. After silver stain, the gels were detected under white light by gel photography system (GeneSnap from SynGene). Homozygote GG was defined (one 303 bp band) when base G existed at position 40545 forming GGCT not recognized by AluI. Homozygote AA was defined (one 278 bp band and one 25 bp band) when base A existed at position 40545 forming AGCT recognized by AluI. Heterozygote GA was defined (one 303 bp band, one 278 bp band and one 25 bp band) when allele G and A both existed at the same position of the homologous chromosomes.

Table 2. Primers used for amplification of goat *C-kit* gene.

Primer no.	Primer sequence	Region	Annealing temp. (℃)	Product (bp)
P1	F 5' GTCAGTGTTGGCGACGAGAT 3' R 5'CAGATCAACAGTGAATCAAGGAGT3'	exon2-exon3	62	3972
P2	F 5' GTCTGCACTGCTCAGCGAATC 3' R5'ATCCACATAGAGTCCACGGAACTAG3'	exon3-exon4	62	1266
P3	F 5'GTGTCTAGTTCCGTGGACTCTATGT 3' R 5' GCCTTTCCTGACGGAGATAACT 3'	exon4-exon5	62	4298
P4	F 5' CAAAACCAGAAATCCTGACAC 3' R 5' CCCCAAAGTAAACACTCAAC 3'	exon8-intron8	56	899
P5	F 5' AAGCCCAGTGTAACATC 3' R 5' TTTCCAAATGGTGAGAC 3'	intron8-exon9	56	1122
P6	F 5' CGTATTACTACCCCAGTTTTACAG 3' R 5' GCATTTGAGGGCGAGAAC 3'	intron8-exon10	56	1848
P7	F 5' TTCACGCCGTTGCTGAT 3' R 5' TTAGGGCTTCTCGTTCTGTT 3'	exon10-exon13	56	796
P8	F 5' TTGCTCACCGTCAGTGTCC 3' R 5' GGACCCTGGCTCAACAGTAT 3'	intron12-intron14	60	1989
P9	F 5' CGTCTTCATTCAAAGGAGTC 3' R 5' GGTCTTGCCTTCTCAAAATAC 3'	exon14-intron14	60	960
P10	F5'GGCCCACCCTGGTCATTACAGAATAT3' R 5' TGTCTGCCGCCTTGGTTGGTAC 3'	exon14-exon15	64	2159
P11	F 5' TAAATCCCTGGTGTCGAGAG 3' R 5' CATCAAGCACTGCAACTACAAG 3'	intron14-inton16	54	1309
P12	F 5' AGACGTGACTCCTGCTATC 3' R 5' TTGATGTCTCTGGCTAGAC 3'	exon16-exon17	56	1221
P13	F 5' GGCAGCCAGAAATATCCTCCTT 3' A 5' CCCATAGGACCAGACATCACTTTC 3'	exon17-exon18	62	3095
P14	F 5' GAAAGTGATGTCTGGTCCTAT 3' R 5' ATCCCAGCAGGTCTTCAT 3'	exon18-exon20	56	639
P15	F 5' CAGGGCATTGAGGAGTGATAAT 3' R 5' AGTCGGGGTTGTCAGGAGAC 3'	exon20-exon21	60	1408
P16	F 5' CCTTCGTGATGATTCTTAC 3' R 5' AACTCAGCCTGTTCCTG 3'	exon10-exon11	56	253
P17	F 5' TGCGTTCATCCACCATTC 3' R 5' ACAAGTCCTCCAGGTCCAG 3'	intron15-exon16	56	303

F and R represent forward and reverse primer used in PCR, respectively.

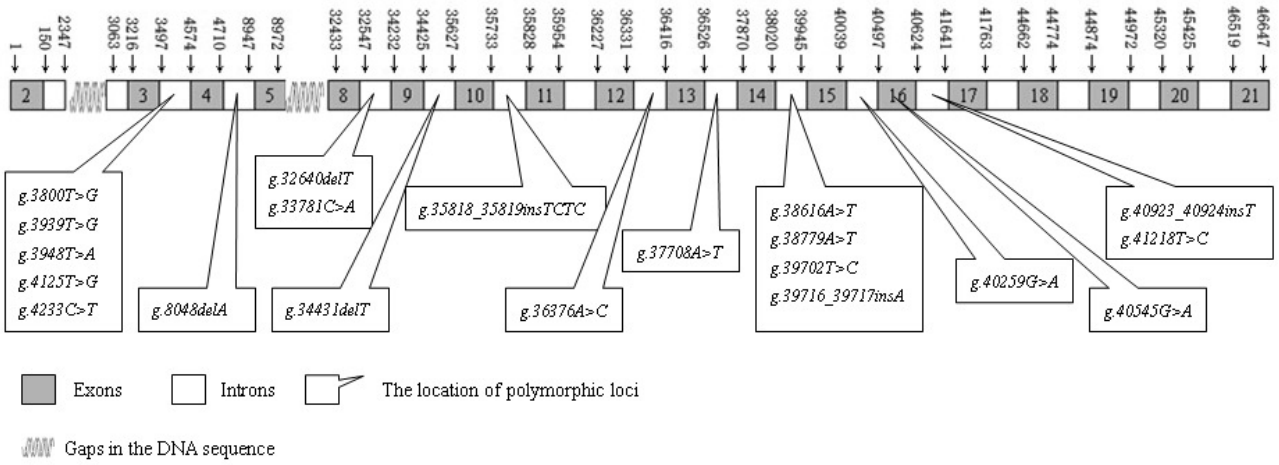

Figure 1. Structural diagram of part sequenced goat *c-Kit* gene (not shown in proportion) Exon 2, 5 and 21 are not complete; Exons and gaps are specified by the base position numbers above the bar according to our submitted HM130675.

PCR-SSCP analysis

Meanwhile, the variable sites of *g.35818_35819insTCTC* in intron 10 were also analyzed using PCR-SSCP. Every 3 µl PCR product (about 250 bp) obtained with P16 primers in Table 2 was mixed with 7 µl denaturing buffer. Denatured at 99°C for 10 min beforehand, the mixture were cooled rapidly on ice for another 10 min, and then loaded on 12% polyacrylamide gels of size 16 × 18 cm. Electrophoresis was carried out at 150 V for 14 h at 4°C in 1 × TBE buffer. After silver stain, the gels were detected under white light by gel photography system (GeneSnap from SynGene). For *g.35818_35819insTCTC*, the wild-type allele was designated as C, while the allele with TCTC insertion was designated as T.

Statistical analysis

PopGene32 software (Version 1.32) was used to do Hardy-Weinberg equilibrium test for *g.40545G>A* and *g.35818_35819insTCTC*, of which genetic diversity within and among populations were also investigated, including heterozygosity (Het) computed using the algorithm of Levene (1949) and Nei's (1973) expected heterozygosity, and Wright's fixation Index (*FIS*). Estimates of the population haplotype frequency at *g.40545G>A* and *g.35818_35819insTCTC* were got via Bayesian statistics method implemented in Phase 2.1 program (Stephens et al., 2001). The phylogenetic tree of populations was constructed by the UPGMA method based on Nei's distance using Mega 4 software.

RESULTS AND DISCUSSION

Structure and variable sites of determined goat *c-Kit* gene

First, we connected the sequenced fragments using SeqMan software (version 7.1.0) as implemented in the DNAStar software package. A total of 22472 bp sequence was obtained, which has been submitted to GenBank (HM130675). Through aligned to the published *c-Kit* mRNA sequence (D45168), the sequence was verified to be part of *c-Kit* gene, and its introns and exons were determined and numbered (Figure 1). All the involved exon-intron boundaries were in accord with the canonical GT–AG rule. Based on alignment of sequencing results, a total of 20 variable sites were detected along goat *c-Kit* gene (Figure 1). Among these variable sites, only one (*g.40545G>A*) existed in exon 16, resulting in *p.Gly763Glu*, the others all existed in introns. In the sequenced partial *c-Kit* gene, we did not detect any simple sequence repeats (SSR) motif with repeat number above 4.

Distribution of g.40545G>A and g.35818_35819insTCTC in different populations

The gene frequency for g.40545G>A and g.35818_35819insTCTC in different populations was shown in Table 1. It was obvious that the frequency of allele A for g.40545G>A was extremely superior in TSD (1.0000) and LNC (0.9167) with while coat color, and in JNG (0.8958) with grey coat color due the dilution of black, and then slightly superior in LZB (0.6333) and CDP (0.6429) with black coat color. The allele G frequencies in LZB (0.367) and CDP (0.357) were significantly higher than that in TSD (0.000), LNC (0.083) and JNG (0.104). The disequilibrium of LNC, JNG, LZB, and CDP at *g.40545G>A* also indicated that selection for white and black coat color changed gene frequency. The white TSD has lost G after long artificial selection. So it could be inferred that in LZB and CDP, besides the aforementioned allele G effect for darker coat color, there must have been other factors that contributed to their absolute black coat color.

Meanwhile, the frequency of allele A was relatively lower in three strains of Nanjiang Yellow goat (NJH, 0.389; NJF, 0.361; NJB, 0.343), which was close to one of their original ancestors, CDM (0.500). On the other hand, the allele G was superior in NJH (0.6111), NJF

Table 3. The heterozygosis of *g.40545G>A* and *g.35818_35819insTCTC* in goat populations.

Population	Size	Heterozygosis of *g.40545G>A*				Heterozygosis of *g.35818_35819insTCTC*			
		Observed Het	Expected Het	Nei's	F_{IS}	Observed Het	Expected Het	Nei's	F_{IS}
TSD	52	0.000	0.000	0.000	0.000	0.635	0.505	0.450	-0.270
LNC	36	0.000	0.155	0.153	1.000	0.250	0.488	0.481	0.480
JNG	48	0.208	0.189	0.187	-0.116	0.438	0.479	0.474	0.077
CDM	33	0.455	0.508	0.500	0.091	0.000	0.000	0.000	0.000
NJH	36	0.611	0.482	0.475	-0.286	0.056	0.055	0.054	-0.029
NJF	36	0.556	0.468	0.461	-0.204	0.056	0.055	0.054	-0.029
NJB	35	0.400	0.457	0.451	0.112	0.086	0.083	0.082	-0.045
LZB	30	0.200	0.472	0.464	0.569	0.100	0.210	0.206	0.515
CDP	35	0.600	0.466	0.459	-0.307	0.000	0.000	0.000	0.000

TSD, LNC, JNG, CDM, NJH, NJF, NJB, LZB and CDP are short for Tangshan Dairy Goat, Liaoning Cashmere Goat, Jining Gray Goat, Chengdu Ma Goat, Nanjiang Yellow Goat high fertility strain, Nanjiang Yellow Goat fast growth strain, Nanjiang Yellow Goat black strain, Leizhou Black Goat and Chengde Polled Goat, respectively. Expected heterozygosity was computed using the algorithm of Levene (1949). Nei's (1973) expected heterozygosity. The F_{IS} represents Wright's fixation Index.

(0.6389) and NJB (0.6571), which was also close to their one of original ancestors, CDM (0.500). It could be implied that allele G, could be in favor of melanin formation, resulting in darker coat color. For g.35818_35819insTCTC, the allele C (wild-type) was extremely superior in dark coat color populations, including CDM (1.0000), NJH (0.9722), NJF (0.9722), NJB (0.9571), LZB (0.8833) and CDP (1.0000), but relatively lower in white coat color populations, including TSD (0.5096), LNC (0.5972), the JNG (0.6146) with grey coat color was in between. The disequilibrium of NJH, NJF, NJB, and LZB at g.35818_35819insTCTC also indicated that selection for dark coat color changed gene frequency. The black CDP and yellow-brown CDM have lost T after long term artificial selection for dark coat color. It could be inferred that the allele C (wild-type) was in favour of expression of dark coat color, while the allele T, the insertion mutation, could disrupt KIT expression, eventually resulting in lighter coat color.

Haplotype frequency at g.40545G>A and g.35818_35819insTCTC in different populations

The estimated haplotype frequency for each population was also shown in Table 1. It was shown that the frequency of GC in dark coat color populations (0.322 to 0.688) was higher than that of white and grey coat color populations (0.000 to 0.107), while the frequency of AT in dark coat color populations (0.000 to 0.022) was lower than that of white and grey coat color populations (0.389 to 0.479). From the analysis of distribution of *g.40545G>A* and *g.35818_35819insTCTC* in different populations, it was obvious that allele A at *g.40545G>A* and allele T at *g.35818_35819insTCTC* was favour of white, while allele G at *g.40545G>A* and allele C at *g.35818_35819insTCTC* was favour of darker coat color. So haplotype AT and GC should have higher frequency in white coat color and dark coat color populations, respectively. This prediction was consistent with the result of estimated haplotype frequency in different coat color populations (Table 1).

Phylogenetic relationship of populations based on two variation sites

The phylogenetic tree of populations constructed by the UPGMA method based on Nei's distance (Table 4) using Mega 4 software was shown in Figure 2. It was obvious from Table 4 and Figure 2 that the goat population of TSD, LNC and JNG with white and grey coat color has smaller genetic distance (0.002 to 0.012) and closer relationship (Figure 2). The goat population of LZB and CDP with black coat color also has smaller genetic distance (0.004) and closer relationship. Meanwhile, three strains (NJH, NJF and NJB) from same breed, Nanjiang Yellow Goat, were clustered together, and then were put together with one of their original ancestors, CDM. These results were not only consistent with the breed forming history, but also basically consistent with the variation of g.40545G>A and g.35818_35819insTCTC in different coat color populations.

Genetic diversity of *g.40545G>A* and *g.35818_35819insTCTC* in different populations

Genetic diversity for each population was summarized in Table 3. The observed heterozygosity ranged from 0.000 (TSD and LNC) to 0.611 (NJH) for g.4055G>A, and from 0.000 (CDM and CDP) to 0.635 (TSD) for g.35818_35819insTCTC, which were all lower than that based on mtDNA of Chinese indigenous goat breeds

Table 4. Genetic distance between 9 goat populations.

Population	TSD	LNC	JNG	CDM	NJH	NJF	NJB	LZB
TSD								
LNC	0.007							
JNG	0.012	0.002						
CDM	0.394	0.263	0.238					
NJH	0.501	0.346	0.317	0.006				
NJF	0.537	0.375	0.343	0.011	0.001			
NJB	0.553	0.388	0.355	0.015	0.002	0.002		
LZB	0.211	0.124	0.108	0.017	0.045	0.055	0.062	
CDP	0.275	0.174	0.155	0.011	0.042	0.052	0.060	0.004

TSD, LNC, JNG, CDM, NJH, NJF, NJB, LZB and CDP are short for Tangshan Dairy Goat, Liaoning Cashmere Goat, Jining Gray Goat, Chengdu Ma Goat, Nanjiang Yellow Goat high fertility strain, Nanjiang Yellow Goat fast growth strain, Nanjiang Yellow Goat black strain, Leizhou Black Goat and Chengde Polled Goat, respectively.

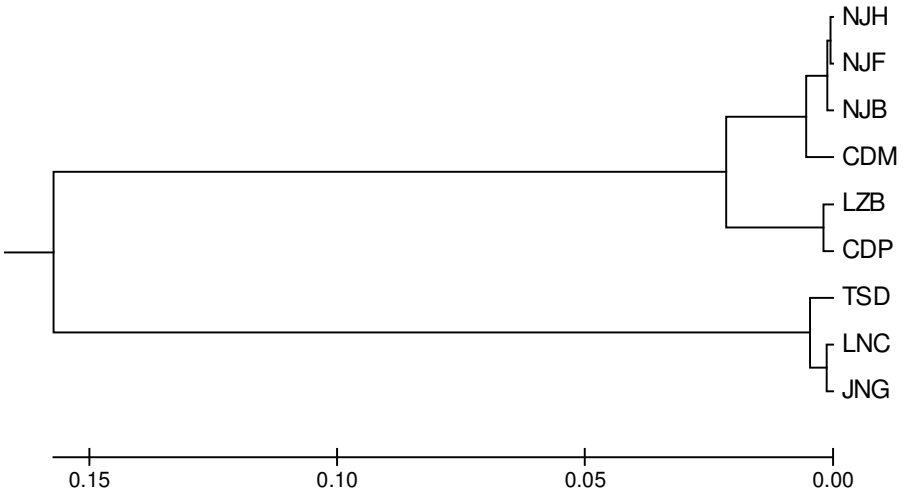

Figure 2. Phylogenetic tree of populations constructed by the UPGMA based on Nei's distance TSD, LNC, JNG, CDM, NJH, NJF, NJB, LZB and CDP are short for Tangshan Dairy Goat, Liaoning Cashmere Goat, Jining Gray Goat, Chengdu Ma Goat, Nanjiang Yellow Goat high fertility strain, Nanjiang Yellow Goat fast growth strain, Nanjiang Yellow Goat Black Strain, Leizhou Black Goat and Chengde Polled Goat, respectively.

(0.676 ± 0.191) (Li and Alessio, 2004). The levene's expected heterozygosity (Levene, 1949) ranged from 0.000 (TSD) to 0.508 (CDM) for g.40545G>A, and from 0.000 (CDM and CDP) to 0.505 (TSD) for g.35818_35819insTCTC. The Nei's expected heterozygosity (Nei, 1973) ranged from 0.0000 (TSD) to 0.500 (CDM) for g.40545G>A, and from 0.000 (CDM and CDP) to 0.500 (TSD) for g.35818_35819insTCTC. The two kinds of expected heterozygosity accorded with each other well, with little difference from observed heterozygosity. Average heterozygosity of g.40545G>A was significantly higher than that of g.35818_35819insTCTC. Wright's fixation Index values (F_{IS}) reflacts the heterozygosis deficiency of populations. The higher value of F_{IS} for LNC (1.000), LZB (0.569), NJB (0.112) at g.40545G>A indicated that they were deficient in heterozygotes, inferring higher inbreeding within their population. Same as the situation of g.40545G>A, the higher F_{IS} for LZB (0.515) and LNC (0.480) also shown the deficiency of heterozygosis and higher inbreeding at g.35818_35819insTCTC. The deficiency of heterozygosis and higher inbreeding for population LNC and LZB was accord with that of Li and Alessio (2004) based on microsatellite analysis.

Conclusion

A total of 22472 bp goat *c-kit* gene sequence was obtained (HM130675), in which 20 variable sites were detected, and only one (*g.40545G>A*) existed in exon 16, resulting in *p.Gly763Glu*, the others all existed in introns.

The allele A at *g.40545G>A* and T at *g.35818_35819insTCTC* was favour of white, while allele G at *g.40545G>A* and C at *g.35818_35819insTCTC* was favour of darker coat color. The haplotype AT and GC have close relationship with white coat color and dark coat color, respectively. The phylogenetic relationship of populations not only reflacts the breed forming history, but also basically was consistent with the coat color variation. Higher deficiency of heterozygotes existed in Liaoning Cashmere Goat, Leizhou Black Goat at *g.40545G>A* and *g.35818_35819insTCTC*, indicating their high inbreeding coefficients within populations.

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