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Distribution Characteristics of Alleles of Classical SLA-I and II Genes and Bioinformatic Analysis of Novel Alleles in Guizhou Miniature Pigs

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Abstract.- This article has systematically elucidated the alleles distribution characteristics of classical SLA class I and II genes, and analyzed novel alleles in Guizhou miniature pigs via bioinformatics. The frequency of twenty five allele sequences from seven SLA - I and II genes previously derived in this population were calculated. There existed five alleles in SLA-2, four alleles in SLA-1, three in QA, QB1 locus, and two in SLA-RA, RB1, respectively. The dominant alleles were evident; every locus had 1 or 2 dominant alleles, one in SLA-3, two in SLA-1 two in QA, QB1: SLA-RA and SLA-RB1 loci have only two alleles. Their distribution is relatively uniform. The comparison between novel SLA class I and II gene sequences and reference sequences showed highly polymorphic region of SLA-I focus on the α1 and α2 areas of amino acid sequence and the polymorphic region of SLA-II mainly expressed in α1 area. The novel alleles and the referenced sequences showed more than 92% homology in amino acid level. The highest amino acid homology percentage of novel alleles and HLA alleles in NCBI were more than 70%. Novel alleles have some functional sites of HLA. According to the analysis, Guizhou miniature pigs have obvious SLA characteristics, it could be the evidences for further haplotypes selection, pig breeding and xenotransplantation.

Key words: SLA, xenotransplantation, breeding, gene frequency, homology.

INTRODUCTION

The polymorphism of major histocompatibility complex (MHC) in swine, also known as swine leukocyte antigen (SLA) plays a vital role in immune system (Lumsden *et al.*, 1993), diseases (Blangero *et al.*, 1996; Geffrotin *et al.*, 2004), breeding (Soe *et al.*, 2008; Shehzadi *et al.*, 2013) and xenotransplantation, (Logan, 2000; Yamada *et al.*, 2005). SLA, mapped in a highly linked gene group with centromeres of the 7th chromosome (Rabin *et al.*, 1985; Smith *et al.*, 1995), also known as a polymorphic area, is divided into three classes *viz.*, SLA-I, SLA-II, SLA-III, of which the first two have been more investigation. From SLA-I antigen, only SLA-1, SLA-2, and SLA-3 have complete class I gene structure and could express persistently. SLA-II antigen has a lot of genes, but only DR and DQ can express at protein level (Lunney *et al.*, 2009). Plenty of SLA alleles have been discovered in many pig breeds all over the world. The systematic naming system of the SLA alleles and haplotypes were confirmed by SLA Nomenclature Committee of the International Society for Animal Genetics (ISAG) (Smith *et al.*, 2005; Ho *et al.*, 2009). Guizhou miniature pigs is one of precious pig breeds in China. At present, there are few reports on multiple functional genes with complete sequence, the systematic study of the haplotypes and analyze the complete gene sequence. In this paper, bioinformatics analysis has been carried out on 25 complete sequences of 7 genes obtained from 22 miniature pigs. These materials were taken from the Germplasm Resource Center of Chinese Laboratory Minipigs from Guiyang College of Traditional Chinese Medicine. The information will provide effective evidence for the later work of selecting specific haplotypes, breeding and immunological research.

MATERIALS AND METHODS

The early experiments obtained the entire CDS sequences, which were amplified using 7 sequence amplimers of SLA-I (SLA-1, 2, 3) and SLA-II (SLA-DRA, DRB, DQA, DQB), gained 25 alleles, and these have been submitted to the

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databank. This paper was based on these alleles. According to the previous assessment, there were 12 novel alleles of 25 alleles in SLA class I and II genes (Table I).

The population distribution characteristics and the gene frequency of 25 alleles of Guizhou miniature pigs have been analyzed. Novel sequences in 7 gene locus and the reference sequences which have a closer relationship to novel alleles have been compared. The homology between new sequences and the HLA alleles have been analyzed by using BLAST software in NCBI. The structure and characteristics of each allele and the differences of nucleotide and amino acid between novel alleles and reference genes have been analyzed. According to the published information of SLA gene sequence structure in NCBI, reported in the references and BLAT outcome on the UCSC website.

RESULTS

The alleles distribution in Guizhou miniature pigs

The alleles distribution of 7 SLA genetic locos in Guizhou miniature pigs (Fig. 1, Table I) showed that, the number of alleles in SLA-1, SLA-2, SLA-3, SLA-DRA, SLA-DRB, SLA-DQA, SLA-DQB locus were, as follows, 4, 5, 4, 2, 2, 4, 4.Although there existed big differences in the number of alleles on every locus, there was only 1 or 2 dominant alleles, they existed in 11-22 individuals of the 24 pigs, others only existed in 1-4 individuals. As shown in Figure 1 and Table I, the SLA-3 was the one locus which had one dominant allele, SLA-3*gz01 existed in 22 individuals with the highest frequency of 93.18%, while the other 3 alleles were shown separately in one animal. The other six locus had 2 dominant alleles, in SLA-1 locus, existed 2 dominant alleles, SLA-1*gz01 and SLA-1*gz02, distributed in 14 and 15 individuals with the frequency of 38.64%, 50.00%, respectively, moreover SLA-1*gz03 and SLA-1*gz04 only existed in 4 and 1 individual separately; In the 5 alleles in SLA-2 locus, SLA-2*gz01 and SLA-B*m both with a frequency of 43.18%, were the most widely distributed alleles, they existed in 15, 12 individuals, the rest of 3 alleles existed in 3, 2 **and** 1 individuals separately; In SLA-DRA and SLA-DRB1 locus, the alleles distributed relatively equally, the allele frequency of the 2 alleles in SLA-DRA was 56.82% and 43.18%, they existed in 17, 14 individuals; 2 alleles in SLA-DRB1 had the equally frequency also, with the data of 47.73% and 52.27%, existed in 14, 15 individuals separately; In the 4 alleles of SLA-DQA, SLA-DQA*0301 and SLA-DQA*0101 existed in 12, 14 individuals with the higher frequency of 38.64% and 45.45%, while SLA-DQA*yn and SLA-DQA*gz01 existed in 2, 4 individuals, respectively; In 4 alleles in SLA-DQB1 locus, SLA-DQB1*0801 and SLA-DQB1*0601 existed in 11, 14 individuals with the higher frequency of 36.36% and 50.00%, SLA-DQB1*113C3 and SLA-DQB1*0901 existed both in 3 individuals separately.

Homologous sequence analysis of novel SLA alleles

On the basis of the analysis about phylogenetic tree included all alleles in every locus obtained from Guizhou minipigs and alleles collected in IPD-MHC database(unpublished data), choosing the alleles have close relationship with the novels as the reference allele, we further assessed the homology between new allele sequence and the reference sequence, HLA alleles sequence in NCBI. The results were shown in Table II. In this population, 11 novel alleles from SLA- I genes and only one novel allele from SLA- II genes were detected, SLA class I genes have more extremely polymorphisms than class II genes. Based on the data from Table II, the homology between novel alleles and reference alleles were consistently matches at nucleotide and amino acid level, the highest percentage in SLA-1,SLA-2,SLA-3 locus were 99.36%, 97.90%, 99.72% and 98.06%, 96.15%, 99.45%, besides, the information in SLA-DRA were 99.60% and 99.21%,accordingly. The highest homology between novel alleles and HLA alleles in SLA-1,SLA-2,SLA-3 locus at nucleotide and amino acid level were 85.50%, 86.10%, 85.90% and 72.70%, 74.86%, 74.65%, the data in SLA-DRA were 88.37% and 83.07%, respectively. These data revealed a high degree of homology between these alleles, but differences between these allele sequences were evidently, that could be the theoretical basis for immunological research, breeding, xenograft and other biological study.

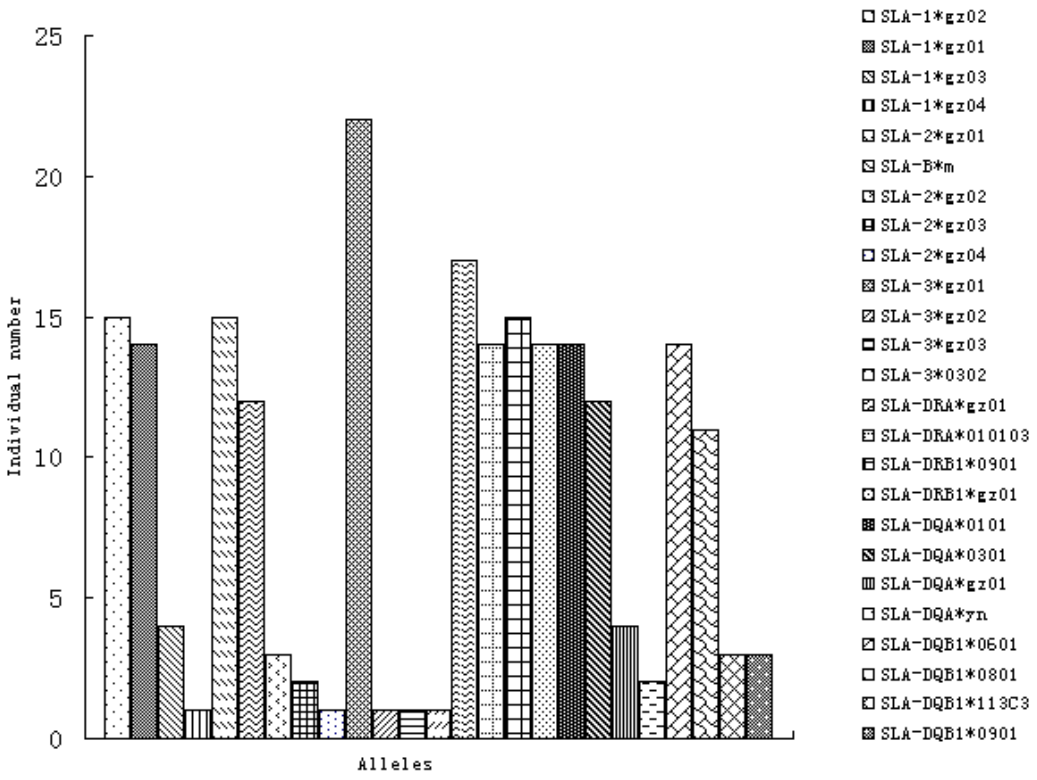

Fig. 1. Distribution of individual number of alleles in seven SLA loci.

DISCUSSION

The population distribution characteristics of alleles

Among Guizhou miniature pigs, there existed rich alleles in SLA class I genes, but only one or two dominant alleles in every locus; In SLA class II locus, existed fewer DRA and DRB1 alleles, but these alleles distributed equally, there were rich DQA and DQB alleles and they both had two dominant alleles. This phenomenon had been reports in other reference as well, which was about the rich alleles in population and dominant alleles or dominant haplotypes/genotype obviously. Yeom *et al*. (2010) typed 6 SLA locus (SLA-1,2, DRA, DRB1, DQA, DQB1) in 12 SNU miniature pigs and detected 17 defined alleles, according to the results of analysis these alleles, found two dominant alleles in SLA-1 locus, two in SLA-2 locus and one in SLA-DQB1 locus are the dominant alleles, respectively. Park *et al.* (2010) genotyped the SLA-DQB1 locus and identified 11 alleles in 350 individuals from 7 pig breeds, one allele showed the highest allelic frequency, which is also the major allele in Duroc pigs. Thong *et al.* (2011) typed the SLA-DRB1 gene in 415 individuals from 7 populations, identified 18 alleles, two alleles appeared as common alleles for the most breeds, while one alleles was unique to SNU minipigs, two to Duroc, two to Yorkshire, two to KNP. This phenomenon might be caused by some advantageous genes or haplotypes related SLA complex, or natural selection and inbreeding (Ho *et al.*, 2009), these dominant alleles may used for as the candidate genes which could improve the immune effect, and provide the evidence for breeding the specific alleles or haplotypes pigs.

Analysis of mutation site of the new allele sequences

New allele sequences of SLA-1 gene

Four new SLA-1 alleles all have whole open reading framework, including 1086 nucleotides, which encodes 361 amino acid residues. According to the structure and expression of SLA-1 gene reported in reference literature (Satz *et al.*, 1985),

Table I.- Distribution, name and NCBI accession number of 25 alleles from SLA I and SLA II gene.

SLA locus	Name of allele	Frequency of allele	New gene (Yes/No)	NCBI accession number
SLA-1	SLA-1*gz01	38.64%	Yes	JQ361648
	SLA-1*gz02	50.00%	Yes	JQ361649
	SLA-1*gz03	9.09%	Yes	JQ361650
	SLA-1*gz04	2.27%	Yes	JQ361651
SLA-2	SLA-2*gz01	43.18%	Yes	JQ361652
	SLA-2*gz02	6.82%	Yes	JQ361653
	SLA-2*gz03	4.55%	Yes	JQ361654
	SLA-2*gz04	2.27%	Yes	JQ361655
	SLA-B*m	43.18%	No	AF464049.2
SLA-3	SLA-3*gz01	93.18%	Yes	JQ361656
	SLA-3*gz02	2.27%	Yes	JQ361657
	SLA-3*gz03	2.27%	Yes	JQ361658
	SLA-3*0302	2.27%	No	EU432097.1
SLA-DRA	SLA-DRA*gz01	56.82%	Yes	JQ361659
	SLA-DRA*010103	43.18%	No	EU432070.1
SLA-DRB1	SLA-DRB1*0901	47.73%	No	EU432073.1
	SLA-DRB1*gz01	52.27%	No	AK347078.1
SLA-DQA	SLA-DQA*yn	11.36%	No	AY102475.1
	SLA-DQA*0301	38.64%	No	EU722913.1
	SLA-DQA*0101	4.55%	No	DQ883218.1
	SLA-DQA*gz01	45.45%	No	AK230483.1
SLA-DQB1	SLA-DQB1*0801	6.82%	No	DQ303219.1
	SLA-DQB1*113C3	6.82%	No	AY135574.1
	SLA-DQB1*0901	36.36%	No	EU432063.1
	SLA-DQB1*0601	50.00%	No	DQ883219.1

Table II.- Homology comparison between novel alleles discovered in Guizhou mininpigs and reference sequence HLA alleles of GeneBank.

SLA locus	Allele	Reference allele	Homology between new alleles and reference alleles		The highest homology between new alleles and HLA alleles in NCBI	
			Nucleotide	Amino acid	Nucleotide	Amino acid
SLA-1	SLA-1*gz01	SLA-1*11jh02	99.08%	97.23%	84.74%	70.75%
	SLA-1*gz04	SLA-1*11mp11	99.36%	98.06%	84.44%	71.31%
	SLA-1*gz03	SLA-1*0401	98.90%	97.23%	85.33%	71.75%
	SLA-1*gz02	SLA-1*08sk11	99.26%	98.06%	85.50%	72.70%
SLA-2	SLA-2*gz01	SLA-2*0502	97.90%	96.15%	84.84%	72.65%
	SLA-2*gz02	SLA-2*w08sw01	97.44%	95.05%	86.10%	73.40%
	SLA-2*gz03	SLA-2*110101	96.07%	92.58%	85.10%	72.80%
	SLA-2*gz04	SLA-2*0201	95.98%	92.58%	85.57%	74.86%
SLA-3	SLA-3*gz01	SLA-3*0401	99.72%	99.45%	85.38%	73.26%
	SLA-3*gz03	SLA-3*0401	99.26%	98.06%	85.90%	74.65%
	SLA-3*gz02	SLA-3*05sw01	99.54%	98.89%	85.29%	73.54%
SLA-DRA	SLA-DRA*gz01	SLA-DRA*010101	99.60%	99.21%	88.37%	83.07%

the sequences were analyzed through NCBI and consulted the spreading of the exons. In amino acid level, the amino acid residue 1-21 was signal peptide area, the aa 22-111 was α1 functional area, the aa 112-217 was α2 functional area, the aa 218-303 was α3 functional area, the aa 304-361 was transmembrane and cytoplasmic region.

Compared to the referenced sequence, the differences of SLA-1*gz01 and SLA-1*11jh02 concentrated on the exon2, and there were 6 amino acid residue mutations in the corresponding amino acid sequence. The differences of the genes SLA-1*gz02 and SLA-1*08sk11 concentrated on the exon3, in the corresponding amino acid residue belonging to α2 area. The variations of SLA-1*gz03 and SLA-1*0401 concentrated on the exon3, in the corresponding amino acid residue belonging to α2 area. The differences of SLA-1*gz04 and SLA-1*11mp11 concentrated on the exon3, the corresponding amino acid residue was α2 area and the functional areas.

The nucleotide polymorphisms in SLA-1 new alleles mainly within exon2 and 3, the differences of amino acid sequence was mainly in the α1, α2 area. Previous research showed that, people's CD8+T cells and NK cells can directly recognize SLA class I molecules in pig to human xenotransplantation (Ando *et al.*, 2003), α1 and α2 are primary regions of peptide binding area that owned peptide ARS, α3 included the binding sites of the CD8+ molecules (Lunney *et al.*, 2009). Compared the alleles of SLA-1 locus with the HLA alleles in NCBI, the highest homology percentage of amino acid sequence were nearly more than 70%. Compared the new alleles with the highest homology HLA sequence, among the 8 essential amino acids (Y7, Y59, Y84, T143, K146, W147, Y159, Y17) that combine HLA-A2 with antigenic peptide (Hirsch *et al.*, 1992), SLA-1*gz01 and SLA-1*gz03 were consistent with human, SLA-1*gz02 and SLA-1*gz04 all have the same one site change (143:T-S). In the 3 essential amino acids (Gln, Asp, Glu) (Chardon *et al.*, 1999) that combine HLA-A2 with CD8+ molecule in α2 domain, the four sequences were all consistent with HLA allele sequence; Among the essential amino acids (199-205,211and 221 amino acid residues)that combine MHC class I with CD8+ molecule in α3 domain (Matsumura *et al.*, 1992; Ando *et al.*, 2003), there were 2 mutations in each new alleles (199:A-V, 211: A-K).

New allele sequences of SLA-2 gene

Four new SLA-2 alleles all have the complete open reading framework, which consisted of 1095 nucleotides and encodes 364 amino acid residues. According to the structure and expressing of SLA-2 gene reported in reference literature (Satz *et al.*, 1985), the sequences were evaluated through NCBI and consulted the spreading of exons, the aa 1-24 was signal peptide area, the aa 25-114 was α1 area, the aa 115-220 was α2 area, the aa 221-306 was α3 area, the aa 307-364 was transmembrane and cytoplasmic region.

The difference sites of SLA-2*gz01 and SLA-2*0502 concentrated on exon4, 8 amino acid residue mutations in the amino acid sequence. The variations that compared SLA-2*w08sw01 with SLA-2*gz02 concentrate on exon3 and 6, the amino acid residues belongs to α2 and α3 functional area. Comparison of SLA-2*gz03 and SLA-2*110101 showed that the difference sites concentrated on the exon3 and 4, the corresponding amino acid residues existed in α1 and α2 functional area. Compared SLA-2*gz04 with SLA-2*0201, the difference sites concentrated on the exon3,4 and 6, the corresponding amino acid residues existed in α1 , α2 , transmembrane and cytoplasmic region.

The difference sites of the alleles amino acid sequence in SLA-2 gene were mainly on the α1、α2 area of peptide-binding groove and α3 immunoglobulin-like region, the highest homology percentage of the four alleles in SLA-2 locus and HLA in NCBI were all more than 72%. The comparison of the new alleles and the highest homology HLA sequence showed that among the 8 essential amino acids (Y7, Y59, Y84, T143, K146, W147, Y159, Y17) which combined HLA-A2 with antigenic peptide (Hirsch *et al.*, 1992) and 3 essential amino acids (Chardon *et al.*, 1999) which combined HLA-A2 with CD8+ molecule, the four new alleles and HLA were all consistent, compared to the essential amino acids (199-205,211and 221 amino acid residues) which combined MHC-I with CD8+ molecule in α3 area (Matsumura *et al.*, 1992;

Ando *et al.*, 2003), the four genes all had 2 mutations (199: A-V, 211: A-K).

New allele sequences of SLA-3 gene

Three new SLA-3 alleles all have the complete open reading framework, including 1086 nucleotides, which encodes 361 amino acid residues. According to the structure and expressing of SLA-2 gene reported in reference literature (Satz *et al.*, 1985), the sequences were estimated through NCBI and consulted the spreading of exons, the amino acid residue 1-21 was signal peptide area, the aa 22-111 was α1 area, the aa 112-217 was α2 area, the aa 218-303 was α3 area, the aa 304-361 was transmembrane and cytoplasmic region.

SLA-3*gz01 and SLA-3*gz03 had a closer evolution relationship with SLA-3*0401, taken SLA-3*0401 as the referenced sequence, SLA-3*gz01 and SLA-3*0401 only had 3 difference sites in exon5, that means, in amino acid level, they belongs to α3 area. There existed 8 differences in nucleotide sequence between SLA-3*gz03 and SLA-3*0401, and they existed separately in the exon2,3,4,5,6, that corresponds to α1, α2, α3 area, transmembrane and cytoplasmic region of amino acid sequence. Compared SLA-3*gz02 with SLA-3*05sw01, there were 5 differences in the nucleotide sequence, existed in the exon1,3,6 separately, that corresponds to signal peptide domain, α2 area, transmembrane and cytoplasmic region of amino acid sequence.

The mainly polymorphism area of the new alleles nucleotide sequences in SLA-3 locus concentrated on exon5 and 6 corresponded to the α3 immunoglobulin-like region, and fewer mutations in signal peptide domain, α1, α2 and transmembrane region. The highest percentage of three new alleles in SLA-3 and the HLA alleles homology in NCBI were all more than 73%, the comparison of the new alleles and the highest homology HLA sequence showed that, among the 8 essential amino acids (Y7, Y59, Y84, T143, K146, W147, Y159, Y17) which combined HLA-A2 with antigenic peptide (Hirsch *et al.*, 1992), the three allele sequences all had the same one mutations (147:W-R). In the 3 essential amino acids (Gln, Asp, Glu) (Chardon *et al.*, 1999) which combined HLA-A2 with CD8+ molecule of α2 area, the three new allele sequences were all consistent with HLA allele sequence, among the essential amino acids (199-205, 211 and 221 amino acid residues) which combined MHC-I with CD8+ molecule in α3 area (Matsumura *et al.*, 1992; Ando *et al.*, 2003), the four allele sequences all had 2 mutations(199: A-V, 211: A-K).

New allele sequences of SLA-DRA

The new SLA-DRA*gz01 allele which was found in SLA-DRA locus has the complete open reading framework, including 759 nucleotides, encodes 252 amino acid residues. According to the structure and expressing of SLA-DRA gene reported in reference literature (Sun *et al.*, 1995), the sequences were analyzed through NCBI and consulted the spreading of exons, the amino acid residue 1-23 was signal peptide area, the aa 24-107 was α1 area, the aa 108-201 was α2 area, the aa 202-252 was transmembrane and cytoplasmic region.

Compared the SLA-DRA*gz01 with SLA-DRA*010101, there were 3 differences in nucleotide sequence, they all existed in exon2, corresponds to 2 differences of amino acid residues in α1 functional area.

The highly allelic polymorphism area in SLA-DRA gene locus mainly in α1 functional area, previous research showed that the 124 to the 136 amino acid residues in DR α chain can interact with human CD4+ molecule (Salter *et al.*, 1990), and they existed in relatively conservative α2 area. The highest homology percentage between new alleles and the HLA-DRA allele sequences in NCBI are 83.07%, compared the CD4+ molecule binding domain of these two sequences found 2 mutations in amino acid sequence(125: R-G, 129: V-I).

CONCLUSIONS

Our data demonstrated that rich alleles existed in Guizhou minipig breeds, there were twenty five alleles discovered from the seven SLA classical gene loci and twelve of them are novel. In this population, although the dominant alleles were obviously, every locus has 1 or 2 dominant alleles, These dominant alleles were more easier to reserve during the breeding evolution process, while lacking alleles are easily to be lost, the existence of these

dominate alleles provided evidence for selecting haplotypes and pig breeding. Sequences of SLA alleles in Guizhou miniature pigs existed rich polymorphic sites, the homology in amino acid level between new alleles of the SLA-1, 2, 3, DRA locus and the reference sequence were more than 97%, 92%, 98% and 99%,respectively.The highest homology between new alleles and the HLA alleles were more than 70%, 72%, 73% and 83%, respectively. Although the homology between Guizhou miniature pigs and human is not very high, the differences of necessary amino acid residues for HLA recognize or combine SLA molecular is small, these novel alleles still preserve the conditions as xeotransplanatation candidate donor, The aims could achieved through breeding breeds with specific alleles or haplotypes and gene artificial transformation. In summary, this paper supplied basis information for further related research via bioinformatics analysis, it is convenient for further study of SLA and breeding in the future.

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