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REVIEW ARTICLE

Nomenclature for factors of the swine leukocyte antigen class II system, 2005

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Abstract

A systematic nomenclature for the genes and alleles of the swine major histocompatibility complex (MHC) is essential to the development and communication of research in swine immunology. The Swine Leukocyte Antigen (SLA) Nomenclature Committee of the International Society for Animal Genetics (ISAG) has reviewed all of the DNA-sequence information for MHC class II genes, available in GenBank/EMBL/DDBJ databases, and the associated published reports to develop such a systematic nomenclature. This article summarizes the proposed nomenclature, which parallels the World Health Organization's nomenclature for factors of the human MHC. The SLA class II genes expressed on the cell membrane will be noted as SLA-DRA, SLA-DRB1, SLA-DQA, and SLA-DQB1. Nomenclature assignments for all SLA class II GenBank sequences are now noted. The committee will add new SLA class II allele designations, as they are discovered, and will maintain a publicly available list of all recognized genes and alleles using the Immuno Polymorphism Database (IPD). The sequences will be available from the IPD-MHC section of the database which contains non-human MHC sequences (http://www.ebi.ac.uk/ipd/mhc/sla/).

Introduction

The class II genes of the swine leukocyte antigen (SLA) complex play critical roles in the immune responses to foreign antigens. Swine with different SLA haplotypes have been shown to develop SLA-dependent titers of complement and antibodies to defined antigens and vaccines (1–4). Expression of SLA class II genes helps to differentiate myeloid dendritic cells (DCs) from natural interferon-producing cells or plasmacytoid DCs (5, 6). SLA class II genes also control infectious disease responses and influence vaccine efficacy and specificity (1, 7–12). SLA class II matching is required for acceptance of bone marrow cell and solid organ allografts (13–15). Novel approaches to expressing or preventing expression of SLA class II antigens in swine should lead to better understanding transplant rejection and tolerance (16–18). This article details the international effort to systematize the nomenclature for the swine class II antigens.

Due to the efforts of many investigators, there is now sufficient DNA-sequence information on the genes and alleles of the swine major histocompatibility complex (MHC) to propose a DNA-sequence-based nomenclature for SLA class II genes. The International Society for Animal Genetics (ISAG) Nomenclature Committee for Factors of the SLA System was formed at the 28th annual ISAG conference in Goettingen, Germany on August 12, 2002 to establish the principles of a systematic nomenclature system for SLA alleles that have been defined by DNA sequencing. A previous report details the nomenclature system for SLA class I alleles (19). This report summarizes the results of the committee's activities for SLA

class II gene nomenclature. Wherever possible, the committee has maintained the same naming conventions as proposed for the SLA class I nomenclature. The committee will add new SLA class II allele designations, as they are discovered, and will maintain a publicly available list of all recognized genes and alleles using the Immuno Polymorphism Database (IPD). The sequences will be available from the IPD-MHC section of the database which contains non-human MHC sequences (http://www.ebi.ac.uk/ipd/mhc/sla/) (20).

Naming of SLA class II loci

The SLA class II region has recently been fully sequenced (Renard et al., unpublished data). The SLA class II genes demonstrate much stronger sequence homology with their human leukocyte antigen (HLA) counterparts than they do with each other (21). Thus, it is not difficult to assign the locus names by sequence comparisons. The overall arrangement of genes in the class II region is very similar to the HLA class II region, except that the length of the region is much shorter, there are no *DP* genes, and it is separated from the class III region by the centromere (Figure 1) (22). Homologs of the *HLA-DM* and *DO* genes are also present. These proteins are involved in catalyzing or inhibiting the loading of antigenic peptides onto the DR and DQ proteins.

There are several class II β-chain pseudogenes, particularly for SLA-DRB. In humans, the number and location of *HLA-DRB* genes and pseudogenes vary considerably between HLA haplotypes [e.g., an HLA-DR17-containing haplotype has a *DRB3 (DR52)* gene and no *DRB4 (DR53)*, while a DR4-containing haplotype has a *DRB4* gene and no *DRB3*] (23). Only one SLA haplotype has been fully sequenced, H01 (Hp-1.1) (24–26). No SLA haplotype has been found that expresses a second *DRB* gene, but several pseudogenes have been found. We propose to denote the pseudogenes SLA-DRB2 through SLA-DRB5 (Table 1)

Naming convention 1

The names of expressed DR and DQ α- and β-chain genes will be named after their human homologs. The β-chain loci will be numbered 1 (i.e., SLA-DRB1). The α-chain genes will not be numbered unless a second α-chain gene or pseudogene is found. Other class II pseudogenes will be numbered sequentially.

Genes of the swine MHC class II region considered by the SLA Nomenclature Committee

The genes considered by the committee are listed in Table 1. All of the loci could be named relative to their closest homologs in the HLA class II region, except that the SLA class II region did not have a *DP* gene pair and two pseudogenes appear to be more homologous to the *DY* genes found in cattle, sheep, and goats (27). This is slightly different from the previous reports that had indicated the presence of a *DPA* gene and had classified the DY-like pseudogenes as DQ pseudogenes (28). The putative DY-like sequences are located within the DQ/DO segment and are not strictly orthologous to the cattle *DY* genes, which are located in the class IIb segment. However, the phylogenetic analysis of the DY sequences show that they cluster with the DY-like sequences of other species and show some sequence motifs that appear to be characteristic of DY sequences (Renard, unpublished data), thus we have named these loci SLA-wDYA and

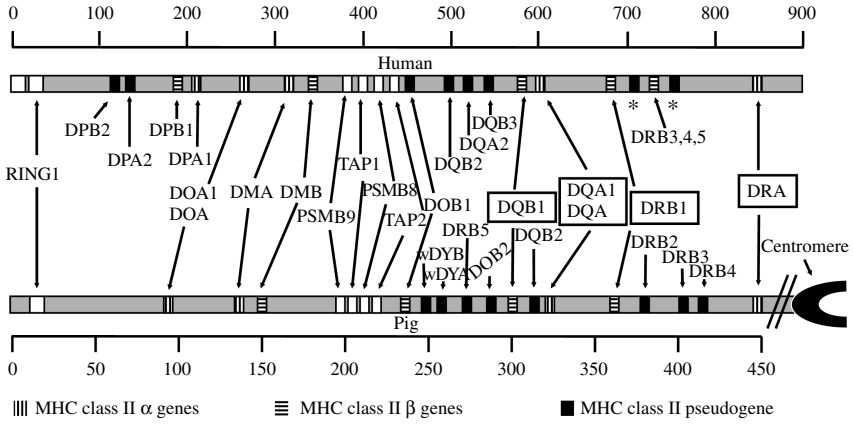

Figure 1 Comparative map of the pig and human major histocompatibility complex (MHC) class II regions, based on Barbosa et al. (21) and Renard et al. (unpublished data). (The map does not include all genes in this region). *The number and location of human leukocyte antigen (HLA)-DRB pseudogenes vary between haplotypes. Only one swine leukocyte antigen (SLA) haplotype has been fully sequenced. Boxed loci are the genes that encode the expressed SLA-DR and SLA-DQ proteins.

Table 1 Names for genes in the swine leukocyte antigen (SLA) class II region considered by the SLA Nomenclature Committee

Name	Molecular characteristics
SLA-DRA	Class II α-chain
SLA-DRB1	Class II β-chain
SLA-DRB2	Class II β-chain pseudogene
SLA-DRB3	Class II β-chain pseudogene
SLA-DRB4	Class II β-chain pseudogene
SLA-DRB5	Class II β-chain pseudogene
SLA-DQA	Class II α-chain
SLA-DQB1	Class II β-chain
SLA-DQB2	Class II β-chain pseudogene
SLA-wDYA	Class II α-chain pseudogene
SLA-wDYB	Class II β-chain pseudogene
SLA-DMA	Class II-related α-chain
SLA-DMB	Class II-related β-chain
SLA-DOA	Class II-related α-chain
SLA-DOB1	Class II-related β-chain
SLA-DOB2	Class II-related β-chain pseudogene

SLA-wDYB, with the 'w' used to indicate that this designation is still tentative.

Numbering of SLA class II alleles

In the HLA nomenclature, the first two digits are used to group alleles. Usually this corresponds to the serologic group to which the allele belongs. Although these groups are composed of alleles with similar sequences, most of the allelic differences can still be recognized by T cells. There are no serologic specificities for SLA class II antigens; therefore, the SLA Nomenclature Committee will assign allele groups based on similarities in DNA sequences.

Naming convention 1

The SLA class II loci will be named after the loci identified in the map of the SLA class II region (Renard et al., unpublished data) (Figure 1), based on demonstrated sequence or functional homology to HLA loci.

Naming convention 2

The first two digits will be used to designate groups of alleles that have similar DNA sequences (Table 2). Group names will be based upon phylogenetic analysis and the identification of DNA-sequence motifs that can be used to identify groups by polymerase chain reaction (PCR) methods. Groups that have at least one confirmed allele will receive a permanent number. If a group does not contain any confirmed alleles, it will be designated with a lower case 'w' to indicate a tentative (workshop) designation. Sequences that do not contain the full exon 2 region and do not match another full-length sequence will not be assigned a group number.

Table 2 Proposed assignment of names and numbers for swine leukocyte antigen (SLA) class II alleles

Nomenclature	Indicates
SLA	The SLA region and prefix for an *SLA* gene
SLA-DRB1	A particular SLA locus, i.e., SLA-DRB1
SLA-DRB1*01	A group of SLA alleles (based on DNA-sequence similarity)
SLA-DRB1*0101	A specific SLA allele
SLA-DRB1*0101N	A null allele (L = a low expression allele)
SLA-DRB1*010102	An allele that differs by a synonymous mutation
SLA-DRB1*01010102	An allele that contains a mutation outside the coding region
SLA-DRB1*01010102N	A null allele that contains a mutation outside the coding region

This convention draws heavily on the nomenclature system used for the naming of human *MHC* genes (29, 30).

Naming convention 3

The third and fourth digits will be used to designate alleles that differ in amino acid sequence, with the fifth and sixth digits being used to designate alleles that differ only by synonymous substitutions (Table 2).

Naming convention 4

The capital letters 'N' or 'L' will be used to designate alleles that have no expression or a low level of protein expression. If the mutation causing this altered expression occurs outside the protein-coding region of the gene, the allele will be named using the seventh and eighth digits (Table 2).

DNA-sequence requirements for naming a new allele

Strict quality standards for DNA sequencing are essential to prevent creation of large numbers of non-existent alleles. We will follow the same standard as previously proposed for SLA class I sequences (19), except that for all future submissions, the minimum requirement for the SLA class II sequence length will be that it must cover all of exon 2. In addition, any partial length sequences derived using locus-specific PCR amplification must show evidence that the primers used are specific for the designated locus. This means that there must be evidence from family studies that the primer set used does not amplify more than two alleles in any individual and that a single allele is inherited from each parent. The primer set should also have been used to amplify at least one known allele from that locus, which has been defined by its full coding sequence.

Naming convention 5

Sequences that do not meet all of these criteria may be accepted but will be given a provisional alphanumeric allele name containing two lower case letters (except 'L')

and two numerals (e.g., SLA-DRB1*ss08) (Table 3). If the allele can be assigned to an existing group, then the first two digits will be assigned for that group followed by a provisional alphanumeric allele name (e.g., SLA-DRB1*02sp02). Some groups of sequences may be assigned a provisional (workshop or 'w') group number if none of the sequences has been independently confirmed (e.g., SLA-DRB1*w11br02). Previously published allele sequences will be given a provisional alphanumeric allele name unless the sequence has been confirmed by more than one laboratory, in more than one breed, or by a unique PCR site-specific primer (PCR-SSP) or PCR-restriction fragment length polymorphism (PCR-RFLP) pattern.

These temporary designations will be phased out as more full-length and high-quality sequences are submitted. This should occur over the next few years. There are only a few laboratories actively sequencing new alleles; thus, it is difficult to predict exactly when we will have enough allele-sequence information to phase out these temporary designations.

We compared the sequences of published unconfirmed alleles against the GenBank expressed sequence tag (EST) database to see whether any EST sequences were exactly matched to the published sequences and could therefore be confirmed (e.g., DRA*020201). We also considered an EST sequence as confirming whether it matched all of exon 2 as well as all positions that differed from another sequence in the same group (e.g., DQA*0103).

Naming of SLA haplotypes

The SLA haplotypes that have previously been defined were limited to SLA class I alleles (31). Because there is very strong linkage between SLA class II loci, it is useful to designate haplotypes, particularly for SLA-DRB1 and SLA-DQB1 alleles. The strong linkage disequilibrium between these loci often allows one to surmise more information about the individual (e.g., in humans, the HLA-DRB1*1501 allele is almost always found in association with the HLA-DQB1*0602 allele in Caucasians;

Table 3 Swine leukocyte antigen (SLA)-DRA-sequence comparisons and allele assignments

Group	Allele	Previous designation	Comment	Breed	Accession number	Submitter
DRA*01	010101	z		Yucatan	AY285938	Martens et al
		M17		Sinclair	AY285933	Martens et al
		H01	BAC clone		BX088590	Sehra
		a		NIH	AY459302	Martens et al
			EST	LWD	AB215118	Uenishi et al (38)
	010102	d		NIH	AY285928	Martens et al
		LW1		Large White	AY247782	Lee et al (39)
		d	1 bp ≠ AY285928	NIH	M93028	Hirsch et al (40)
	0101we01	We1		Westran	AY247781	Lee et al (39)
	0101ta01			Taihu	AY243102	Tan et al
				Taihu	AY303990	Tan et al
DRA*02	0201	c		NIH	AY285929	Martens et al
		c		NIH	M92445	Hirsch et al (40)
	020201	m3		Sinclair	AY285935	Martens et al
			EST, 2 clones		BP463493	Uenishi et al (38)
	0202mw01	w		Yucatan	AY285937	Martens et al
	0202Lw02	LW2		Large White	AY247783	Lee et al (39)
	0202mm16	m16		Sinclair	AY285926	Martens et al
	020301	x		Yucatan	AY285936	Martens et al
		bs133		Banna	AY191779	Zeng et al (41)
			EST	LWD	AB215119	Uenishi et al (38)
	0203my01	y		Yucatan	AY285939	Martens et al
DRA*w03	w03ta01			Wuzhishan	AY243106	Tan et al

BAC, bacterial artificial chromosome; EST, expressed sequence tag; PSI, primer sequence included in GenBank entry; La, landrace; LW, Large White; Me, Meishan; Go, Goettingen; Du, Duroc; LWD, (Landrace × Large White) × Duroc.
MARC1 library was created from a mixture of mRNA from Yorkshire × Landrace pigs, and the MARC2 library was created from a mixture of mRNA predominantly Yorkshire × Landrace sows and 11% Meishan × Chester White-Landrace-Yorkshire boar. 1 bp ≠ accession number: denotes sequences that differ by 1 or 2 bp. When such an allele is listed with another confirmed allele, it was judged by the authors to represent a sequencing artifact. If it is listed separately, the authors could not rule out a separate allele. Also = allele name: these are partial sequences that match more than one allele. Stop codon: indicates a null allele cause by a mutation that creates a premature stop codon.

however, it is almost always found in association with the HLA-DQB1*0601 allele in Asians). Thus, where sufficient family data are available to assign haplotypes, these will be assigned numbers (Table 9).

We have previously decided that the first number would represent the class I haplotype and the second would represent the class II haplotype.

Naming convention 6

Haplotypes defined by high-resolution DNA sequencing will be named with a prefix 'Hp-' and a number for the class I haplotype followed by a number for the class II haplotype separated by a period (i.e., Hp-1.1). If no typing is available for the associated class I or class II alleles, it will be indicated by using the number 0 (i.e., 1.0).

Because some SLA typing will be performed at less than high resolution (group-specific typing rather than allele specific), it would be helpful to be able to denote the similarity of some haplotypes. Therefore, we propose to use a modifier that would denote haplotypes that have very similar SLA class II alleles.

Naming convention 7

The number designation of an SLA haplotype may be modified with a lower case letter (i.e., 1.1a *vs* 1.1b) to designate a second haplotype that has the same group-specific allele typing for SLA-DRB1 and DQB1.

Numbering of base pairs and codons in SLA DNA sequences

The numbering of base pairs and codons in the SLA DNA sequences is assigned relative to the DNA sequence of the alleles of the Hp-1.1 haplotype. This haplotype was used for the full sequencing of the SLA region, and we have numbered each of these alleles 0101. The base-pair numbering starts with the 'A' of the start codon (32), and the codons are numbered based on the first amino acid in the mature protein, with the codons of the leader peptide given negative numbers. The only difference in length of SLA class II alleles that occurs within a locus group is in the DQA alleles where all of the alleles in group DQA*01 are 3 bp shorter than the alleles of all other groups.

Summary of published DNA-sequence data and assignment of allele names

SLA-DRA alleles

The limited polymorphism in the SLA-DRA locus is of interest because the DRA locus in most species does not show any polymorphism in the peptide-binding portion of the protein, the α1 domain (33). One such polymorphism has been found in water buffalo (34). In the SLA-DRA locus, only two polymorphic sites are found in the α1 domain (exon 2). One occurs at bp c.286, which can be an A, C, or G (the G has only been found in one allele that has not yet been confirmed). This results in a substitution of a methionine, leucine, or valine at residue 73, respectively. A second polymorphic site occurs at bp c.297, which can be either a C or a T; however, both code for an arginine. Because polymorphisms in this region of DRA are rarely seen in other species, we decided to confirm these polymorphisms with a PCR-SSP assay. We were able to confirm the A and C polymorphisms at bp 286 (we did not have DNA from the allele that has a G at bp 286) and the C and T polymorphism at bp 297 (Smith et al., unpublished data). Therefore, we assigned alleles to three groups based upon the substitution at residue 73 (Table 3). All of the alleles in group 01 code for the same protein and the group 02 alleles code for three unique proteins, which only differ outside of the α1 domain. Group 03 contains a single allele that has not yet been independently confirmed.

SLA-DRB1 alleles

This is a highly polymorphic locus with 135 published full or partial DNA sequences that represent alleles belonging to at least 10 confirmed groups (Table 4). Each of these groups has at least one confirmed allele, and four groups have more than one confirmed allele. Two additional provisional groups have multiple DNA sequences but no confirmed alleles. There are also 11 sequences that do not appear to belong to these established groups, making it likely that additional groups will be designated. Many of the published DRB1 DNA sequences were determined from PCR products derived from genomic DNA, and they do not include all of the second exon sequence. Because phylogenetic analysis must be performed on DNA sequences of equal length, either we must compare sequences that do not include all of exon 2 or we must remove the shorter sequences from our analysis. We performed our analysis both ways and found that all allele groups that were represented in the analysis using full exon 2 sequence were in the same groups as in the analysis using maximum available overlapping sequences. We have displayed the results of the maximum overlapping sequence analysis in Figure 2.

Two allele sequences that are very similar to each other appear to be null alleles. SLA-DRB1*kb03N and kb04N have a premature stop signal in codon 52 of the mature protein.

The SLA-DRB1*02zs13 allele is unusual. The beginning of exon 2 matches the DRB1*02 group for the first 164 bp, then matches the DRB1*05 group for the remainder of the exon. This type of hybrid allele can represent a true allele that has arisen because of a crossover between two alleles, or it can represent a sequencing artifact that arises during amplification of the DNA template. This type of artifact is

Table 4 Swine leukocyte antigen (SLA)-DRB1-sequence comparisons and allele assignments

Group	Allele	Previous designation	Comment	Breed	Accession number	Submitter
DRB1*01	0101	Verb4			AF464046	Martens et al
		H01	BAC clone		BX088590	Sehra et al
		73I3	Single clone	MARC1	AY135579	Martens et al
		73I3	EST	MARC1	BE232509	Fahrenkrug et al (42)
			EST	LWD	AB215120	Uenishi et al (38)
	0102	72G24	Single clone	MARC2	AY135580	Martens et al
		72G24	EST	MARC2	BF191401	Fahrenkrug et al (42)
		Consensus of G01		Goettingen	AB016746	Kanai et al (43)
		G03			AB016748	Kanai et al (43)
		G04			AB016749	Kanai et al (43)
		G08			AB016753	Kanai et al (43)
		G10			AB016755	Kanai et al (43)
		G11			AB016756	Kanai et al (43)
		G13			AB016758	Hosokawa et al
		G14			AB016759	Kanai et al (43)
		G15			AB016760	Hosokawa et al
		S06			U10027	Shia et al (44)
DRB1*02	0201	a		NIH	AF464031	Martens et al
		a		Hanford	AY135582	Martens et al
		b		Sinclair	AY135583	Martens et al
		d		NIH	AY962314	Ho et al
		d	d $\neq$ 2bp	NIH	M55166	Gustafsson et al (45)
		We1		Westran	AY247784	Lee et al (39)
		LW1		Large White	AY247785	Lee et al (39)
				Landrace	Z26641	Vage et al (46)
		K07G		Landrace	D87424	Kawakami et al
			EST	LWD	AB215121	Uenishi et al (38)
	0201br05	5		Yorkshire	L36571	Brunsberg et al (47)
	02ka05	K05C		Large White	D87416	Kawakami et al
	02ka06	K06G		Duroc	D87421	Kawakami et al
	02ka08	K08G		Large White	D87425	Kawakami et al
	02sp02	P02			AF272725	Shiels et al
	02sp08	P08			AF272731	Shiels et al
	02zs13	S13	PSI		U52528	Zhang et al
DRB1*03	0301	c		NIH	M55165	Gustafsson et al (45)
		c		NIH	AY962313	Ho et al
		Consensus of G02		Goettingen	AB016747	Kanai et al (43)
		G05			AB016750	Kanai et al (43)
		G07			AB016752	Kanai et al (43)
		G12			AB016757	Hosokawa et al
DRB1*04	0401	n		Meishan	AF464051	Martens et al
		n		Hanford	AY126721	Martens et al
	04ta01			Wuzhishan	AY243107	Tan et al
	0402	bs133		Banna	AY191776	Zeng et al (41)
		3		Yorkshire	L36569	Brunsberg et al (47)
		Consensus of K10G,		La $\times$ LW	D87427	Kawakami et al
		K05C		LW	D87417	Kawakami et al
		K11G		La $\times$ LW	D87428	Kawakami et al
	04ga01		Same as 0402 except in the signal peptide		AB205163	Gao et al

	0403	m15		Hanford	AF464037	Martens et al
		P03			AF272726	Shiels et al
		P04	P04 ≠ 1bp		AF272727	Shiels et al
		K04C		Meishan	D87414	Kawakami et al
		K12G	K12G ≠ 1bp		D87429	Kawakami et al
			EST	Meishan	AB215122	Uenishi et al (38)
DRB1*05	0501	wx		Yucatan	AF464032	Martens et al
		wx		Yucatan	AF464035	Martens et al
		K02G	Also = 05ch01	Landrace	D87411	Kawakami et al
			EST	LWD	AB215123	Uenishi et al (38)
	0502	S11	PSI	Yorkshire	U47277	Zhang et al
		1			L36567	Brunsberg et al (47)
	05ch01	gx	1 aa ≠ 0501 in the signal peptide		AY102479	Chen et al
	05np01	12-3		Nippon (wild boar)	D78150	Kawakami et al
	05ka01	K01G		Me × Go	D87409	Kawakami et al
	05ka03	K03G		Me × Go	D87413	Kawakami et al
	05sp06	P06			AF272729	Sheils et al
DRB1*06	0601	y		Yucatan	AF464033	Martens et al (48)
		C16a03			AY135578	Martens et al (48)
				Landrace	Z26639	Vage et al (46)
	060201	t		Sinclair	AF464060	Martens et al
		t		Sinclair	AY135584	Martens et al
		t-1	Single clone	MARC1	AY135576	Martens et al
		K07C (a)	Also = 65N19	Large White	D87422	Kawakami et al
		K07C (b)	Also = 65N19	Large White	D87423	Kawakami et al
	060202	65N19		MARC1	AY135581	Martens et al
		65N19		MARC1	BE232674	Fahrenkrug et al (42)
		UMNMPM3	EST		CB286464	Dvorak et al
	06zs12	S12	PSI		U52526	Zhang et al
	06sL47				L08847	Shia et al (44)
DRB1*07	0701	yn			AY102481	Chen et al (49)
		S09			U10033	Shia et al (44)
	07ka03	K03C		Large White	D87412	Kawakami et al
DRB1*08	0801	z		Yucatan	AF464034	Martens et al (48)
		1-7	Also = G06		L36573	Brunsberg et al (47)
			Also = G06	Landrace	Z26638	Vage et al (46)
		S07	Also = G06		U10028	Shia et al (44)
				Clawn	AB193509	Ando et al (50)
			EST	LWD	AB215124	Uenishi et al (38)
	0801hg06	G06		Goettingen	AB016751	Kanai et al (43)
	08hg09	G09		Goettingen	AB016754	Kanai et al (43)
	08ka92	9-2	0801 ≠ 1bp (first base)	Kakeruma (wild boar)	D78149	Kawakami et al
	08ka83	8-3	0801 ≠ 1bp	Amani (wild boar)	D78146	Kawakami et al
	08sp05	P05			AF272728	Sheils et al
DRB1*09	0901	m		Meishan	AF464050	Martens et al
		m		Sinclair	AY135575	Martens et al
		m-1			AY135585	Martens et al
		gz			AY102480	Chen et al
		KB01	Also = 09ta1	Berkshire	AB082382	Li et al
		K01C	Also = 09ta1	Meishan	D87408	Kawakami et al
		S04	Also = 09ta1		U09952	Shia et al (44)
		K06C	Also = 09ta1	Large White	D87420	Kawakami et al
					L08849	Shia et al (44)
	0901br04	4		Yorkshire	L36570	Brunsberg et al (47)
	09ta01		1 aa ≠ 0901 in signal peptide	Taihu	AY243103	Tan et al
				Taihu	AY303991	Tan et al

Table 4 Continued

Group	Allele	Previous designation	Comment	Breed	Accession number	Submitter
	09sL48				L08848	Shia et al (44)
DRB1*10	1001	8			L36574	Brunsberg et al (47)
				Landrace	Z26637	Vage et al (46)
		S04	Also = P07		U09569	Shia et al (44)
		K02C	Also = P07	Landrace	D87410	Kawakami et al
		rjej04b_d24.y1.abd	EST		DN595186	Jianga et al
		UTR01B030101	EST, multiple clones		CJ030292	Uenishi et al (38)
10sp07	P07			AF272730	Shiels et al	
10ka06	K06C		Large White	D87419	Kawakami et al	
DRB1*w11	w11br02	2		Yorkshire	L36568	Brunsberg et al (47)
	w11zs10	S10	PSI		U46216	Zhang et al
	w11sp01	P01			AF272724	Shiels et al
	w11ac21	c21		Clawn	AB180664	Ando et al (50)
	w11an01			Duroc	AB211036	Ando et al
DRB1*w12	w12ka02	7-2		Amami (wild boar)	D78145	Kawakami et al
	w12ka05	20-5		Iriomote (wild boar)	D78147	Kawakami et al
	w12ka12	21-12		Iriomote (wild boar)	D78148	Kawakami et al
DRB1*Misc	–ss08	S08			U10032	Shia et al (44)
				Landrace	Z26640	Vage et al (46)
		1-6			L36572	Brunsberg et al (47)
DRB1*Misc	–ka14	K14G		Landrace	D87431	Kawakami et al
DRB1*Misc	–ka13	K13G		Meishan	D87430	Kawakami et al
DRB1*Misc	–oj01	J01		Pittman-Moore	AB038988	Omi et al
DRB1*Misc	–ka04	K04G		Goettingen	D87415	Kawakami et al
DRB1*Misc	-ka05	K05G		Goettingen	D87418	Kawakami et al
DRB1*Misc	–ka09	K09G		La × LW	D87426	Kawakami et al
DRB1*Misc	–oj02	J02		Crown	AB038989	Omi et al
DRB1*Misc	–kb02	KB02		Berkshire	AB082383	Li et al
DRB1*Misc	–kb03N	KB03	Stop codon	Berkshire	AB082384	Li et al
	–kb04N	KB04	Stop codon	Berkshire	AB082385	Li et al

EST, expressed sequence tag; PSI, primer sequence included in GenBank entry; LWD, (Landrace × Large White) × Duroc.

most often seen when the PCR products are cloned. We have assigned this allele to the DRB1*02 group because a longer portion of the sequence matches this group rather than the DRB1-05, but this allele will need confirmation.

SLA-DRB pseudogenes

The results of full-length sequencing of the H01 (Hp-1.1) haplotype (Figure 1) showed four SLA-DRB pseudogenes. Two series of alleles for DRB pseudogenes have been published that have characteristic deletions in the second exon that match the DRB2 and DRB3 loci of the H01 BAC clone sequence. We have assigned these sequences to these loci (Table 5). The DRB4 and DRB5 loci also contain a region homologous to exon 2 and therefore must be considered when designing SSPs or probes; however, only the alleles of the H01 haplotype have been published. One sequence (L36581) has a unique deletion that does not match any of the pseudogenes in the H01 haplotype; therefore, it may represent another locus present in only some haplotypes or a cloning artifact.

Because sequencing from genomic DNA does not depend on expression of mRNA, there is a possibility that some of the sequences that appear to be SLA-DRB1

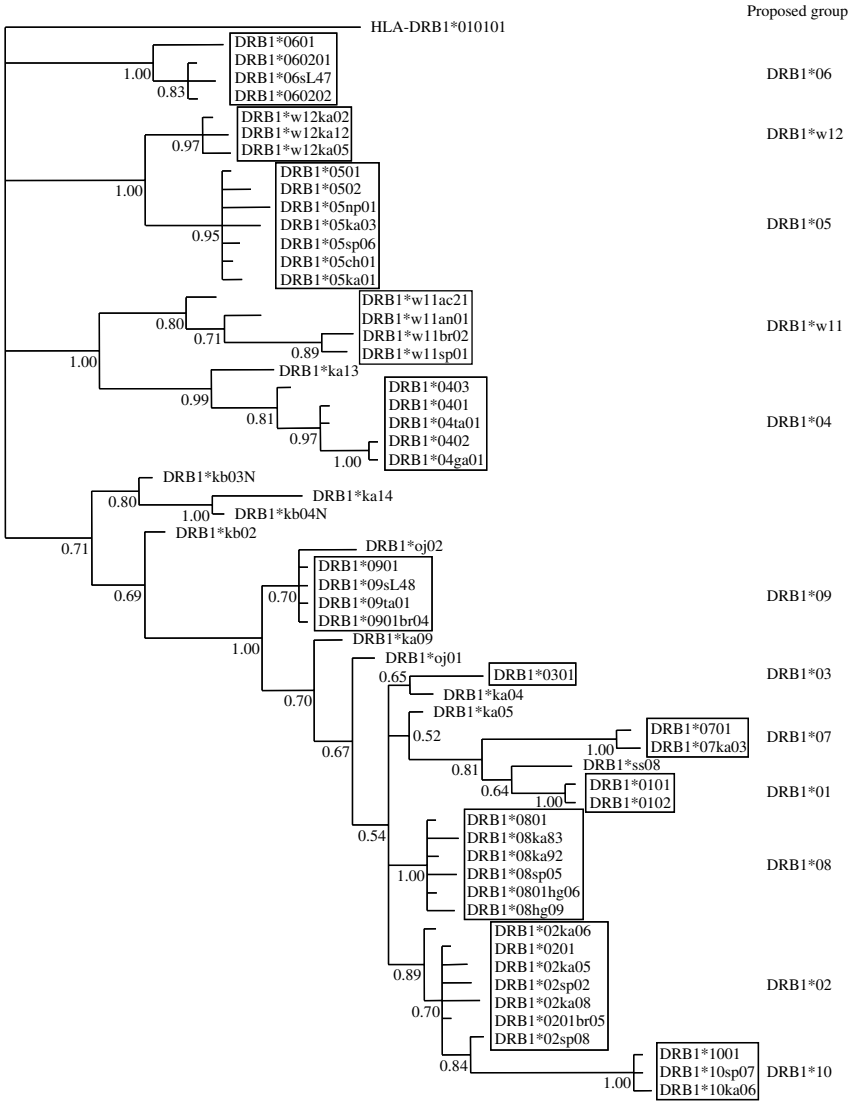

Figure 2 Phylogenetic analysis of exon 2 sequences of swine leukocyte antigen (SLA)-DRB1 alleles using the maximum overlapping sequence of exon 2. Phylogeny of each locus was analyzed by the Bayesian Inference of Phylogeny (MrBayes version 3.0, http://morphbank.ebc.uu.se/mrbayes/info.php), based on the Metropolis-coupled Markov Chain Monte Carlo method. In each case, 3.5 million generations of four simultaneous Markov Chain Monte Carlo chains were employed, and the human homolog was used as the out-group for rooting the trees. The resulting consensus tree was derived from a total of 30,000 trees saved, and the probability value near each node estimates the reliability of a particular grouping. For DRB1, the maximum available overlap of exon 2 sequences was used, +112–321 (210 bp).

alleles could be derived from a DRB pseudogene. However, they do not contain the characteristic deletions in exon 2 that characterize DRB2 and DRB3, and the sequences of DRB4 and DRB5 are quite divergent. Thus, it is relatively unlikely that any of these sequences are derived from DRB pseudogenes.

SLA-DQA alleles

This is a moderately polymorphic locus. There are 29 published full or partial DNA sequences that represent alleles belonging to at least four groups and one tentative group (Table 6, Figure 3). Four groups have a confirmed allele. One partial sequence, SLA-DQA*ka01, does not appear to belong to any of these established groups.

Alleles in group 1 are one amino acid shorter than alleles from the other groups. This deletion is located in the $\alpha 2$ domain and should not affect the peptide-binding cleft.

SLA-DQB1 alleles

This is a highly polymorphic locus. There are 95 published full or partial DNA sequences that represent alleles belonging to at least nine groups (Table 7, Figure 4). Each of these groups has at least one confirmed allele, and four groups have multiple confirmed alleles. Four additional sequences do not appear to belong to any of these nine groups and may represent additional allele groups. A large number of additional SLA-DQB sequences have recently been submitted to GenBank by Li et al. (35) (AY626069–AY626136 and AY769642–AY769670). The PCR primers used in their study were not locus specific for SLA-DQB1 and resulted in sequences for alleles from at least two loci. Phylogenetic analysis does not allow us to distinguish alleles belonging to each locus, and the sequences are not full coding sequences; hence, we are not able to tell whether one of

Table 5 Swine leukocyte antigen (SLA)-DRB pseudogene sequences

Locus	Allele	Previous designation	Comment	Breed	Accession number	Submitter
DRB2	0101	H01	Characterized by deletion of 1 bp at +249		BX088590	Sehra
	0102	DRB2*02		Landrace	Z26643	Vage et al (46)
		DRB2*2A			L36576	Brunsberg et al (47)
	01vz42	DRB2*01		Landrace	Z26642	Vage et al (46)
	01bL80	DRB2*3	Missing exon 1 and 6		L36580	Brunsberg et al (47)
	01bL77	DRB2*2B		Yorkshire	L36577	Brunsberg et al (47)
	01bL78	DRB2*2C		Yorkshire	L36578	Brunsberg et al (47)
	vz44	DRB2*03		Landrace	Z26644	Vage et al (46)
	bL75	DRB2*1			L36575	Brunsberg et al (47)
	bL79	DRB2*2D		Yorkshire	L36579	Brunsberg et al (47)
DRB3	0101	H01	Characterized by deletion of 14 bp at +249		BX088590	Sehra
	01bL82	DRB3*1			L36582	Brunsberg et al (47)
	01bL83	DRB3*1B		Yorkshire	L36583	Brunsberg et al (47)
	01bL84	DRB3*1C		Yorkshire	L36584	Brunsberg et al (47)
	01bL85	DRB3*1D	Missing exon 1 and 6	Yorkshire	L36585	Brunsberg et al (47)
DRB4	0101	H01	Missing partial exon 1		BX088590	Sehra
DRB5	0101	H01	Missing exon 1 and 6		BX323833	Sehra

Table 6 Swine leukocyte antigen (SLA)-DQA-sequence comparisons and allele assignments

Group	Allele	Previous designation	Comment	Breed	Accession number	Submitter
DQA*01	0101	H01	BAC clone 1 bp ≠ 01my01	EST	BX088590	Sehra
					AB215110	Uenishi et al (38)
	01my01	y		Yucatan	AY285931	Martens et al
	0102	c		NIH	M29938	Hirsch et al (51)
		c		NIH	AY962312	Ho et al
	0103	w		Yucatan	AY285927	Martens et al
			EST		DN595524	Jianga et al
	01ch01	gx			AY102473	Chen et al (52)
DQA*02	0201	a	1 aa ≠ 0202 in signal peptide	NIH	AY285925	Martens et al
		b		Sinclair	AY906855	Ho et al
	020201	d		NIH	M29939	Hirsch et al (51)
		d		NIH	AY285932	Martens et al
			EST	LWD	AB21511	Uenishi et al (38)
	020202	x		Yucatan	AY285934	Martens et al
		LW1		Large White	AY247777	Lee et al (39)
		bs133		Banna	AY191777	Zeng et al
			EST	LWD	AB215112	Uenishi et al (38)
	0203	z		Yucatan	AY459303	Ho et al
			EST, multiple clones		BP160216	Uenishi et al (38)
	02xu01	DQA1*0101		Large White	DQ003300	Xu et al
DQA*03	0301	m5		Sinclair	AY285930	Martens et al
				Taihu	AY243100	Tan et al
	03ta01			Taihu	AY303988	Tan et al
	03we01	We1		Westran	AY247776	Lee et al (39)
DQA*04	0401	yn			AY102475	Chen et al (49, 52)
			EST		DN595570	Jianga et al
	04ta01			Wuzhishan	AY243104	Tan et al
DQA*w05	w05ch01	gz			AY102474	Chen et al (52)
Misc	–ka01				D17740	Kawakami et al

EST, expressed sequence tag; LWD, (Landrace × Large White) × Duroc.

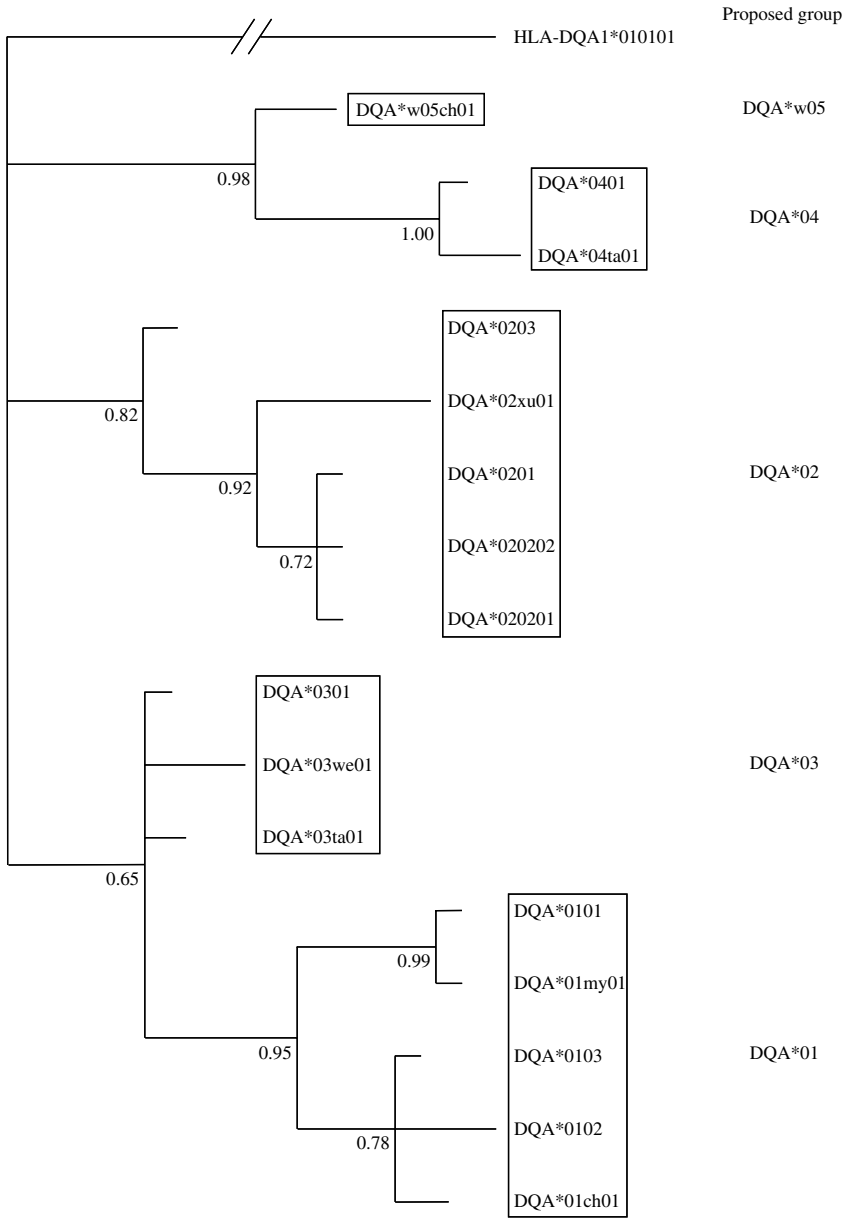

Figure 3 Phylogenetic analysis of exon 2 sequences of swine leukocyte antigen (SLA)-DQA alleles using the complete sequence of exon 2 (249 bp).

the loci is a pseudogene. Therefore, we have not included these SLA-DQB sequences in our analysis.

SLA-DMA alleles

Only one study has been published regarding polymorphisms of the SLA-DMA locus (36). That study showed limited polymorphism with four polymorphic sites in the third exon. Three of these sites were confirmed by PCR-RFLP. In addition, one of the alleles was confirmed from the sequence of the BAC clone XX-1044B7 (BX324144). Two alleles were also confirmed by finding ESTs that had identical sequences. Because no polymorphisms were found in the second exon, all of these alleles have been designated as belonging to one group (Table 8).

SLA-DMB, DOA, DOB alleles

There are few published DMB, DOA, or DOB alleles. The sequencing of the BAC clone XX-1044B7 (BX324144) from the H01 (Hp-1.1) haplotype contains alleles for DOA and DMB. A partial sequence of the same DMB allele is submitted as AF074417. A similar DOA allele is submitted as AB012858 (37). The sequencing of the BAC clone XX-554F3 (BX323833) from the H01 (Hp-1.1) haplotype contains a DOB1 allele and a DOB2 pseudogene. A partial sequence of a DOB allele from the

Table 7 Swine leukocyte antigen (SLA)-DQB1-sequence comparisons and allele assignments

Group	Allele	Previous designation	Comment	Breed	Accession number	Submitter
DQB1*01	0101	H01	BAC clone		BX088590	Sehra
					L08592	Shia et al (44)
		S11	PSI		U52527	Zhang et al
			EST	LWD	AB215113	Uenishi et al (38)
	01sh01				L08843	Shia et al (44)
DQB1*02	0201	a		NIH	AF464024	Martens et al (48)
		x		Yucatan	AF464028	Martens et al (48)
		ax		Hanford	AY135569	Martens et al
		ax-1		Sinclair	AY135570	Martens et al
		P02			AF272712	Shiels et al
					AF272717	Shiels et al l
					AF272716	Shiels et al
		G07		Goettingen	AB016741	Hosakowa et al
		10	PSI		U44797	Zhang et al
		ax		Meishan	AY459300	Ho et al
			EST	LWD	AB215114	Uenishi et al (38)
	02kg02	G02		Goettingen	AB016736	Kanai et al (43)
	0202	z		Yucatan	AF464030	Martens et al
		LW2		Large White	AY247780	Lee et al (39)
		S09	PSI		U53205	Zhang et al
		bs133		Banna	AY191778	Zeng et al
			EST	LWD	AB215115	Uenishi et al (38)
	0203	J01		Ohmini	AB012093	Omi et al (53)
		P01	Last 2 bp ≠ J01	La × Du	AF113970	Huett et al
	02zs16	S16	PSI	Ohmini	AF027171	Zhang et al
	02sh02				L08844	Shia et al (44)
DQB1*03	0301	c		NIH	AF464025	Martens et al
		c		NIH	M32117	Gustafsson et al (54)
		c		NIH	M31497	Gustafsson et al (54)
		Consensus of G03,		Goettingen	AB016737	Kanai et al (43)
		G08, G04, G05, G10			AB016742	Hosakowa et al
					AB016738	Kanai et al (43)
					AB016739	Kanai et al (43)
					AB016744	Kanai et al (43)
		Consensus of P03,			AF272713	Shiels et al
		P08, P04			AF272718	Shiels et al
					AF272714	Shiels et al
	0302	P35			AF272722	Shiels et al
		S15	PSI		U86111	Zhang et al
	0303	m2			AF464047	Martens et al
			EST, 2 clones	Hanford	DN595956	Jianga et al
			EST	Meishan	AB215116	Uenishi et al (38)
DQB1*04	0401	d		NIH	M31498	Gustafsson et al (54)
				NIH	M32120	Gustafsson et al (54)
				NIH	AF464026	Martens et al (48)
		LW1		Large White	AY247779	Lee et al (39)
		P09			AF272719	Shiels et al
	04hg09	G09	1 aa ≠ 0401 signal peptide	Goettingen	AB016743	Hosakowa et al
	0402	m18		Sinclair	AF464048	Martens et al
			EST, 2 clones		DN595729	Jianga et al
	0402we01	We1		Westran	AY247778	Lee et al (39)
	04sp16	P16			AF272721	Shiels et al

DQB1*05	0501	113C3	EST	MARC2	AY135574	Martens et al
		Consensus of 113C3, 121F11, 69L11	EST	MARC2	BI342662	Fahrenkrug et al (42)
		Consensus of G11, G01, G06			BI345059	Fahrenkrug et al (42)
					BF192170	Fahrenkrug et al (42)
				Goettingen	AB016745	Kanai et al (43)
					AB010577	Hosokawa et al (55)
					AB016740	Kanai et al (43)
				Wuzhishan	AY243105	Tan et al
				Wuzhishan	AY102478	Chen et al (49, 52)
		yn		Goettingen	AB012728	Omi et al (53)
		J02			AF272723	Sheils et al
		P36		Clawn	AB193511	Ando et al (50)
	0502	gz			AY102477	Chen et al (52)
		S07	PSI		AF027170	Zhang et al
	05sp06	P06			AF272715	Sheils et al
	05an01			Duroc	AB211037	Ando et al
DQB1*06	0601	y		Yucatan	AF464029	Martens et al
		S08		Ohmini	AB009659	Omi et al
		S08	PSI		U41325	Zhang et al
				Clawn	AB193510	Ando et al (50)
			EST	LWD	AB215117	Uenishi et al (38)
	06sp10	P10			AF272720	Sheils et al
DQB1*07	0701	t		Sinclair	AF464061	Martens et al
		t		Sinclair	AY135571	Martens et al
		42P15		MARC1	AY135572	Martens et al
		42P15		MARC1	AW786624	Fahrenkrug et al (42)
		CCH040	EST	UNL	AY459305	Ho et al
		CCH040	EST	UNL	BI183698	Caetano et al (56)
		S06	PSI		U40456	Zhang et al (44)
DQB1*08	0801	w		Yucatan	AF464027	Martens et al (48)
		w		Hanford	AY135568	Martens et al
				Taihu	AY243101	Tan et al
				Taihu	AY303989	Tan et al
					L08842	Shia et al (44)
				Meishan	AY459301	Ho et al
	08ch01	gx	Mature protein = 0801		AY102476	Chen et al (52)
DQB1*09	0901	Verb3	EST, multiple clones		AF464038	Martens et al
					CJ000766	Uenishi et al (38)
	−09zh01	NAU		Wuzhishan	AY281361	Zhou et al
DQB1*Misc	−zs13	S13	PSI		U86109	Zhang et al
	−sh03	S10			L08841	Shia et al (44)
	−zs12	S12	PSI		U53206	Zhang et al
	−zs14	S14	PSI		U86110	Zhang et al

EST, expressed sequence tag; PSI, primer sequence included in GenBank entry; LWD, (Landrace × Large White) × Duroc.
MARC2 library was created from a mixture of mRNA predominantly from Yorkshire × Landrace sows and 11% Meishan × Chester White-Landrace-Yorkshire boar.

National Institutes of Health (NIH) pig 'c' haplotype is submitted as M29944.

Discussion

A systematic nomenclature for SLA class II alleles is critical to the further development of research in swine immunology and disease responses and in transplantation using swine models. It allows investigators to communicate more effectively about SLA alleles and haplotypes, particularly in outbred pigs, where there are few molecularly defined SLA haplotypes and few or no serologic reagents. MHC class II proteins play a central role in the presentation of antigenic peptides to $CD4^+$ T cells, and powerful new technologies, such as MHC/peptide multimers, will be extremely useful in the study of cell-mediated immunity to pathogens and vaccine responses. Full sequence comparisons will further the definition of the peptide-binding motifs of

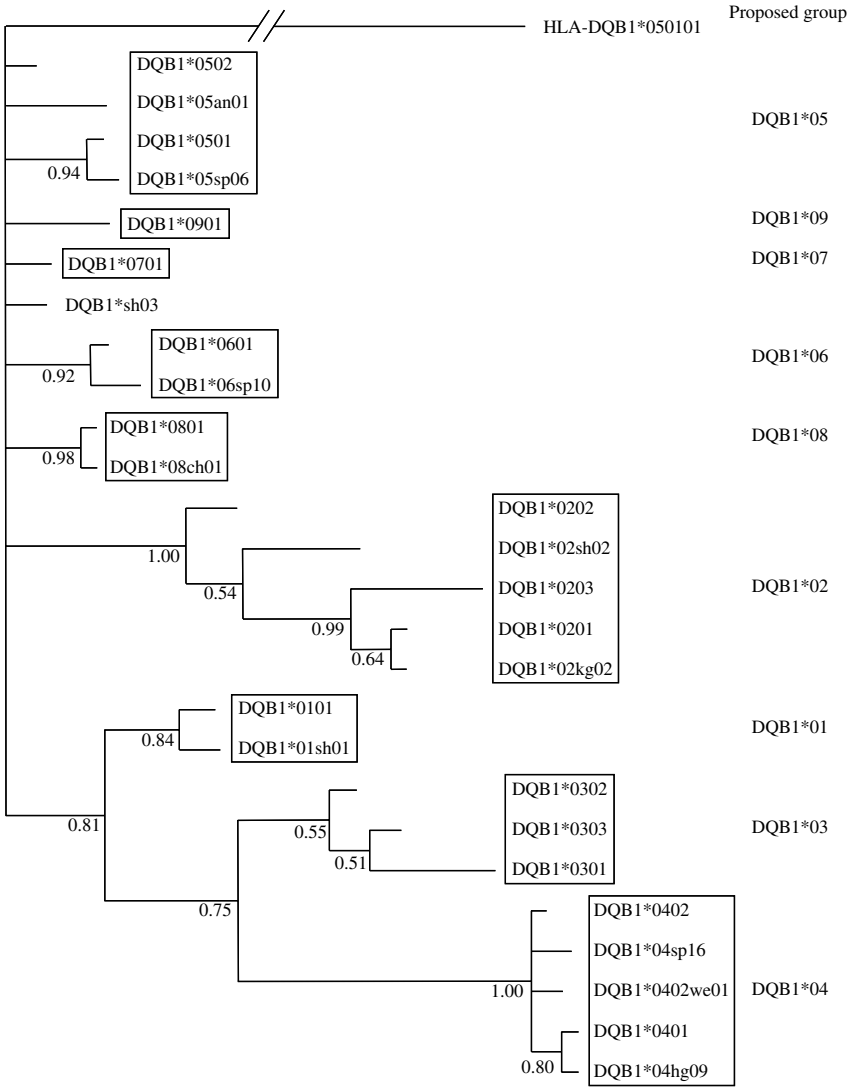

Figure 4 Phylogenetic analysis of swine leukocyte antigen (SLA)-DQB1 alleles using the maximum available overlapping sequence. 264 bp of exon 2 maximum overlap (+112 to +375).

Table 8 Swine leukocyte antigen (SLA)-DMA-sequence comparisons and allele assignments

Group	Allele	Previous designation	Comment	Breed	Accession number	Submitter
DMA*01	0101	02		Goettingen	AB117618	Ando et al (36)
				Clawn		Ando et al (36)
				Meishan		Ando et al (36)
				Mexican		Ando et al (36)
				Hairless		Ando et al (36)
		H01	BAC clone		BX324144	Beasley
	0102	01		Goettingen	AB032169	Ando et al (36)
	0103	03	Confirmed by PCR-RFLP	Mexican	AB117619	Ando et al (36)
			EST	Hairless	BP170164	Uenishi et al
	0104	04	Confirmed by PCR-RFLP	Yorkshire	AB117620	Ando et al (36)
			EST		BP464759	Uenishi et al
	0105	05	Confirmed by PCR-RFLP	Yorkshire	AB117621	Ando et al (36)
				Meishan		Ando et al (36)

EST, expressed sequence tag; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

Table 9 Swine leukocyte antigen (SLA) class II haplotype assignments

Name	Breed	Previous designation	DRA	DRB1	DQA	DQB1
0.1	Large White	H01	0101	0101	0101	0101
0.2	NIH	a	0101	0201	0201	0201
	Sinclair	b				
	Hanford					
0.3	NIH	c	0201	0301	0102	0301
0.4	NIH	d	0101	0201	0202	0401
0.5	Yucatan	x	0203	0501	0203	0201
0.6	Yucatan	w	0202	0501	0103	0801
0.7	Yucatan	y	0203	0601	01my01	0601
0.8	Yucatan	z	0101	0801	0204	0202
0.9	Westran		0101	0201	03we01	0402
0.10	Sinclair	a	0401		0801	
	Hanford					
0.11	Sinclair	c	0202	0901		0402
0.12	Sinclair	d	0202	0602	0301	0701
0.13	Hanford	e		0403		0303
0.14	Meishan	m		0901		0801
0.15	Meishan	n		0401		0201
0.16	Clawn	c1		w11ac21		0601
0.17	Clawn	c2		0801		0501

individual SLA class II alleles. This will inform the discovery of T cell epitopes in viral or bacterial proteins, particularly those that derive from conserved portions of viral genomes. Overall, such information will be very useful for designing vaccines that produce effective protective immunity for infectious diseases in pigs.

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