Current Status of the Swine Leukocyte Antigen (SLA) System

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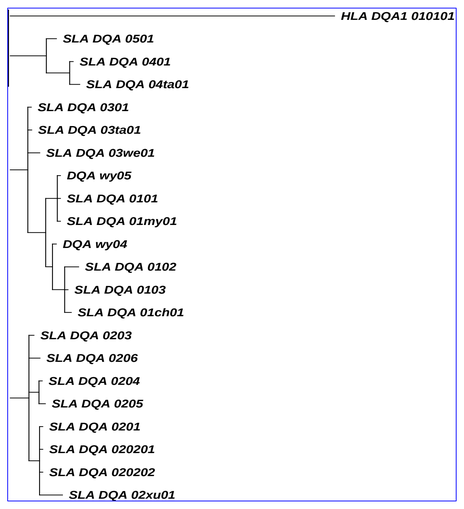
Abstract

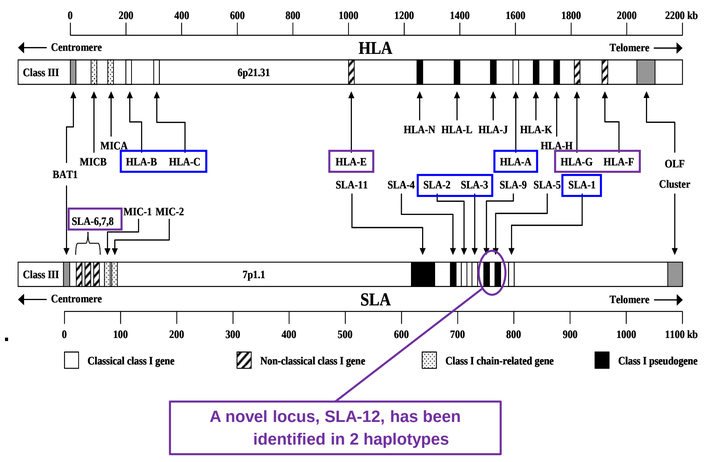
The swine leukocyte antigen (SLA) system is among the most well characterized major histocompatibility complex (MHC) systems in non-human animal species. The International Society for Animal Genetics (ISAG) and International Union of Immunological Societies Veterinary Immunology Committee (IUIS VIC), The SLA Nomenclature Committee was formed in 2002. The committee's primary objectives are: 1) to validate newly identified SLA sequences according to the guidelines established for maintaining high quality standards of the accepted sequences; 2) to assign appropriate nomenclatures for new alleles as they are validated; and 3) to serve as a curator of the IPD-MHC SLA sequence database (http://www.ebi.ac.uk/ipd/mhc/sla/), which is the repository for all recognized SLA genes, their allelic sequences and haplotypes. To date, there are 131 classical class I (SLA-1, SLA-2, SLA-3), 13 non-classical class I (SLA-6, SLA-7 and SLA-8) and 174 class II (DRA, DRB1, DQA, DQB1, DMA) alleles officially designated. There are 34 class I and 27 class II haplotypes at the high-resolution (allele) level designation. Recent evidence has suggested certain loci in the SLA system previously recognized as pseudogenes (e.g. SLA-9, SLA-11, DQB2 and DOB2) may be expressed at the transcript level for some haplotypes; the committee will determine if designation of the alleles of these loci is warranted as more evidence accumulates. A systematic nomenclature for the genes, alleles and haplotypes of the swine MHC is critical to the research in swine genetic diversity, immunology, health, vaccinology, and organ or cell transplantation. Continuous efforts on characterizing SLA alleles and haplotypes and studying of their diversity in various pig populations will further our understanding of the architecture and polymorphism of the SLA system and their role in disease, vaccine and allo- or xeno-grafts responses.

SLA Nomenclature System (Similar to HLA)

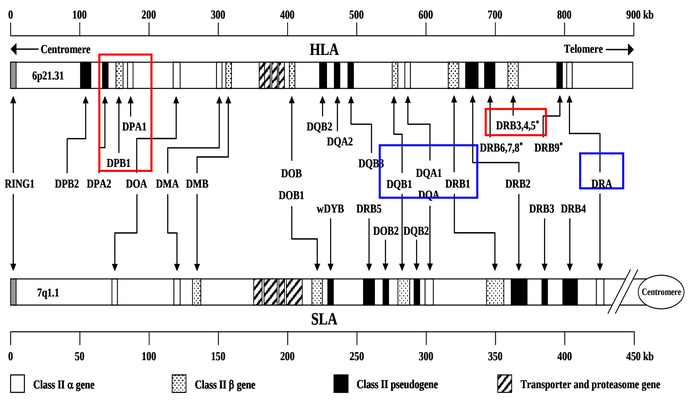
Designation	Indication
SLA-1	A particular SLA locus
SLA-1a, SLA-1b, SLA-1c	a = the most centromeric b = telomeric to a c = telomeric to b……etc
SLA-1*01	A group of alleles (by phylogeny and/or sequence motif)
SLA-1*0101	A confirmed allele
SLA-1*010101	A confirmed allele which differs by synonymous nucleotide substitution
SLA-1*0101N	Null allele
SLA-1*0101Q	Questionable expression
SLA-1*0101L	Low expression



Human MHC (HLA) vs Swine MHC (SLA) class I



Human MHC (HLA) vs Swine MHC (SLA) class II



SLA Genes Recognized

Gene	Description
SLA-1	Ia α-chain
SLA-2	Ia α-chain
SLA-3	Ia α-chain
SLA-4	Pseudogene
SLA-5	Pseudogene(?)
SLA-6	Ib α-chain
SLA-7	Ib α-chain
SLA-8	Ib α-chain
SLA-9	Pseudogene(?)
SLA-11	?
SLA-12	?
MIC-1	Pseudogene
MIC-2	Class I chain-related
DRA	α-chain
DRB1	β-chain
DRB2	Pseudogene
DRB3	Pseudogene
DRB4	Pseudogene
DRB5	Pseudogene
DQA	α-chain
DQB1	β-chain
DQB2	Pseudogene
DMA	α-chain
DMB	β-chain
DOA	α-chain
DOB1	β-chain
DOB2	Pseudogene
wDYA	Pseudogene
wDYB	Pseudogene
TAP1	Transporter
TAP2	Transporter

Nomenclature based on low resolution (Lr) typing

Because of the extensive polymorphic nature of SLA genes (Ho et al. 2009a), accurate and sensitive typing methods are crucial for studying their influences, particularly in outbred pigs with diverse genetic backgrounds.

The Low resolution (Lr) SLA typing method uses a PCR-sequence-specific primer (PCR-SSP) strategy to differentiate alleles by groups with similar sequence motifs.

1) is technically simple, rapid and inexpensive;
2) allows an effective and unambiguous detection of SLA class I and II alleles; and
3) facilitates the identification of common class I and II haplotypes in outbred pig populations.

Ho et al. (2009b) described a Lr typing system for characterizing SLA class I alleles of the SLA-1, -2 and -3 loci.

Ho et al. (2010) developed a similar molecular-based, Lr typing system for characterizing SLA class II alleles of the DRB1, DQB1 and DQA

High-Resolution Haplotype (Hp)

Allele level by sequence based typing (SBT)

e.g. Hp-1a.2

→ 39 class I, 31 class II designated to date

Hp- / Lr-	SLA-1	SLA-3	SLA-2
1a.0	0101	0101	0101
2.0	0201(a), 0701(b)	Null	0201

Hp- / Lr-	DRA	DRB1	DQA	DQB1
0.1	010101	0101	0101	0101
0.2	010101	0201	0201	0201

Low-Resolution Haplotype (Lr)

Allele-group level by SSP/SSOP, e.g. Lr-5.6

→ 71 class I, 42 class II designated to date

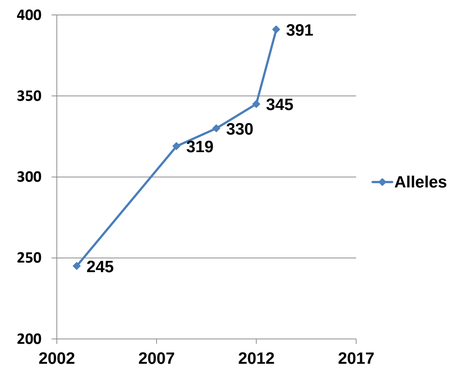
Hp- / Lr-	SLA-1	SLA-3	SLA-2
5.0	04XX	05XX	08XX
6.0	08XX	06XX	05XX

Hp- / Lr-	DRA	DRB1	DQA	DQB1
0.4	01XX	02XX	02XX	04XX
0.6	02XX	05XX	01XX	08XX

Number of SLA Alleles Designated to date

Class I	n
SLA-1	62
SLA-2	61
SLA-3	32
SLA-5	4
SLA-6	9
SLA-7	3
SLA-8	4
SLA-12	5
Pseudogenes	7
TOTAL	187

Class II	n
DRA	14
DRB1	88
DQA	22
DQB1	51
DMA	7
DMB	1
DOA	2
DOB1	3
Pseudogenes	16
TOTAL	204



Background

The Swine Leukocyte Antigen (SLA) Nomenclature Committee was established in 2002 at the 28th International Society of Animal Genetics (ISAG) Conference in Göttingen, Germany. It subsequently became affiliated with the Veterinary Immunology Committee of the International Union of Immunological Societies (VIC IUIS). It is now a standing committee of both, ISAG and VIC IUIS.

Objectives & Responsibilities

- To validate newly identified SLA sequences according to the guidelines established for maintaining high quality standards of the accepted sequences
- To assign appropriate nomenclatures for new alleles as they are validated
- To serve as a curator of the IPD-MHC SLA Database and the Repository of SLA Sequences and Haplotypes http://www.ebi.ac.uk/ipd/mhc/sla/index.html

SLA Committee Nomenclature Committee Members

North America

Chak-Sum Ho - Gift of Life MI **(Chair)**
Joan Lunney - USDA ARS BARC
Larry Schook - Univ. Illinois
Doug Smith - retired; Univ. Michigan

Europe

Claire Rogel-Gaillard - INRA, Jouy-en-Josas, France
Sabine Essler - Univ. Vet. Medicine Vienna, Austria

Asia

Asako Ando - Tokai Univ,. Japan
Jun-Heon Lee - Chungnam National Univ., Korea

Ho Lunney Schook Smith

Rogel-Gaillard Essler

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Presented at the North American Porcine Reproductive and Respiratory Syndrome Symposium, and the Conference of Research Workers in Animal Diseases (CRWAD) meetings in Chicago IL USA Dec. 7-10, 2013.

Challenges with Designation of New SLA Alleles and Haplotypes

Swine MHC region remains largely unknown in many haplotypes and in outbred pig populations

- 3 class I, 2 class II haplotypes completely sequenced to date (Renard et al. 2006, Tanaka-Matsuda et al. 2009, Groenen et al.,2012)
- Some SLA regions may harbor haplotype-specific loci (e.g. SLA-12), or gene duplication (e.g. SLA-1)
- Locus-specificity of primers for Lr typing = difficult to confirm

Validation of new sequences = tedious & time consuming

Mounting evidence suggests certain loci previously annotated as pseudogenes may in fact be transcriptionally active, e.g., SLA-5, SLA-9, SLA-11 (Gao et al. 2012; Gao et al. 2010; Tanaka-Matsuda et al. 2009)

Common Problems with Sequence Submission

Submitted sequences not meeting length requirements . Conditions for Acceptance of New Alleles are noted at the IPD MHC website http://www.ebi.ac.uk/ipd/mhc/sla/guidelines.html

Locus-specific primers are not specific; Primer sequences not removed from submitted sequence

Multiple very similar alleles (w/ individual “SNPs” at different places) identified w/in a small cohort of animals, e.g. 10 very similar SLA-6 alleles in a cohort of 4 pigs

More than 2 alleles identified for a given locus in one pig, e.g. 5 DQB alleles identified in one pig

Summary

The SLA system is among the most well characterized MHC systems

Systematic nomenclature for swine MHC genes is critical to research in swine immunology, health, vaccine improvement, and the use of pigs as large animal model in transplantation studies

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