Review Article

Cytogenetic and Genome Research

Cytogenet Genome Res 2009;126:63–76
DOI: 10.1159/000245907

Accepted after revision: June 15, 2009
by M. Schmid

Molecular Cytogenetics and Gene Mapping in Sheep (*Ovis aries*, 2n = 54)

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Key Words
Chromosome structure · Genome analysis · Linkage mapping · QTL · Sheep cytogenetic map

Abstract
The development of a completely annotated sheep genome sequence is a key need for understanding the phylogenetic relationships and genetic diversity among the many different sheep breeds worldwide and for identifying genes controlling economically and physiologically important traits. The ovine genome sequence assembly will be crucial for developing optimized breeding programs based on highly productive, healthy sheep phenotypes that are adapted to modern breeding and production conditions. Scientists and breeders around the globe have been contributing to this goal by generating genomic and cDNA libraries, performing genome-wide and trait-associated analyses of polymorphism, expression analysis, genome sequencing, and by developing virtual and physical comparative maps. The International Sheep Genomics Consortium (ISGC), an informal network of sheep genomics researchers, is playing a major role in coordinating many of these activities. In addition to serving as an essential tool for monitoring chromosome abnormalities in specific sheep populations, ovine molecular cytogenetics provides physical anchors which link and order genome regions, such as sequence contigs, genes and polymorphic DNA markers to ovine chromosomes. Likewise, molecular cytogenetics can contribute to the process of defining evolutionary breakpoints between related species. The selective expansion of the sheep cytogenetic map, using loci to connect maps and identify chromosome bands, can substantially contribute to improving the quality of the annotated sheep genome sequence and will also accelerate its assembly. Furthermore, identifying major morphological chromosome anomalies and micro-rearrangements, such as gene duplications or deletions, that might occur between different sheep breeds and other *Ovis* species will also be important to understand the diversity of sheep chromosome structure and its implications for cross-breeding. To date, 566 loci have been assigned to specific chromosome regions in sheep and the new cytogenetic map is presented as part of this review. This review will also summarize the current cytogenomic status of the sheep genome, describe current activities in the sheep cytogenomics research sector, and will discuss the cytogenomics data in context with other major sheep genomics projects.

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The number of domestic sheep (*Ovis aries*, 2n = 54) in the world is steadily growing and currently amounts to about 1.3 billion animals. Extremely large numbers of sheep can be found in China, Australia, India, Iran, Sudan, and New Zealand [Wint and Robinson, 2007]. Sheep production plays an important economic and agricultural role in developed and developing countries. Several products are obtained from sheep, such as wool, milk, meat, leather, and fertilizer. In less developed and poor countries, sheep often provide the only economic basis for survival of many rural people. Although nearly 60 sheep breeds are known to be extinct, and an additional 120 breeds are at risk of extinction, the existence of more than 1,400 known breeds make sheep an ideal model for studying biodiversity or genome variation [Scherf, 1995, 2000]. The relatively close phylogenetic relationship between sheep and humans means that sheep also serve as biomedical models [e.g. Goetz et al., 2008; Neddermann et al., 2009].

Over the past 10 years, the interests of breeder associations, whose goal is to produce healthy, highly productive sheep in a cost-efficient manner, and of scientists studying ovine genomics have merged, leading to a powerful symbiotic alliance that is focusing on the complete analysis of the sheep genome. In addition, automated cytogenetic and molecular genetic tools have become more affordable, which has tremendously accelerated sheep genome analysis. The International Sheep Genomics Consortium (ISGC, www.sheephapmap.org) is an informal network of sheep genomics researchers that is playing a major role in coordinating many of the sheep genomics activities and ensuring that the results from these initiatives are placed in the public domain.

Cytogenetic Analysis of the Sheep Genome

Many cytogenomics resources have provided information about chromosome structure in sheep, in the context of related species. These resources include the following. A comparative Zoo-FISH map has been created and gives an overview of evolutionarily conserved syntenic chromosome segments and breakpoints between ovine and human chromosomes [Burkin et al., 1997; Iannuzzi et al., 1999]. Comprehensive cytogenetic maps corresponding to the sheep ISCNDB 2000 chromosome standard [Di Berardino et al., 2001] contain about 450 loci [Di Meo et al., 2003, 2007]. High-resolution or targeted-cytogenetic mapping has also linked trait-associated genome regions and candidate genes to chromosome bands for traits such as scrapie susceptibility [Cosseddu et al., 2002; presenilin 1 *(PSEN1)* and dihydrolipoamide S-succinyltransferase *(DLST)*, in this review], and apoptosis [Lyahyai et al., 2005]. Several studies have used modern cytogenetic techniques such as fiber-FISH or region-specific chromosome painting probes, generated by chromosome microdissection, for sex chromosome analysis in sheep [e.g. Di Berardino et al., 2004; Chaves et al., 2005; Bugno et al., 2008]. Zoo-FISH using bovine painting probes has also been used to investigate the differences in chromosome abnormalities of in vitro and in vivo generated ovine embryos [Coppola et al., 2007] which in the long term will help with improving the production of in vitro embryos. Ovine chromosome-specific painting probes have been produced and used for comparative studies between sheep, pig, and javelina *(Pecari tajacu)* [Adega et al., 2006]. Research has also been performed to analyze distinctive features of sheep chromosome morphology, such as translocations or fragile sites [e.g. Chaves et al., 2003; Ali et al., 2008].

Genetic and Physical Analysis of the Sheep Genome

A range of other genomics resources have been developed for sheep and are summarized schematically in figure 1. Sheep genetic maps of increasing resolution have been assembled [http://rubens.its.unimelb.edu.au/~jillm/jill.htm; Crawford et al., 1995; de Gortari et al., 1998; Maddox et al., 2001, 2008; Maddox, 2005]. Several studies have been published on the use of polymorphic markers in the discovery of genetic associations and chromosomal locations associated with quantitative trait loci (QTL). A QTL database for the sheep genome, Sheep QTLdb, has been developed in association with the AnimalQTLdb project that summarizes mapped QTL and displays QTL chromosome linkages based on map information of a suitable format given in published manuscripts [http://sphinx.vet.unimelb.edu.au/cgi-bin/QTLdb/OA/viewmap; Hu et al., 2007]. Numerous new unlisted QTL for milk, growth or health parameters have recently been identified in several sheep breeds, e.g. milk fat content [Calvo et al., 2006], carcass [Johnson et al., 2005], muscle depth [Hadjipavlou et al., 2008], facial eczema [Phua et al., 2009], scrapie incubation time [Moreno et al., 2008], or resistance to internal parasites such as *Haemonchus contortus* [Marshall et al., 2009].

An ovine bacterial artificial chromosome (BAC) library of 10–12-fold genome coverage, comprising more than 200,000 clones, was developed from a Texel ram

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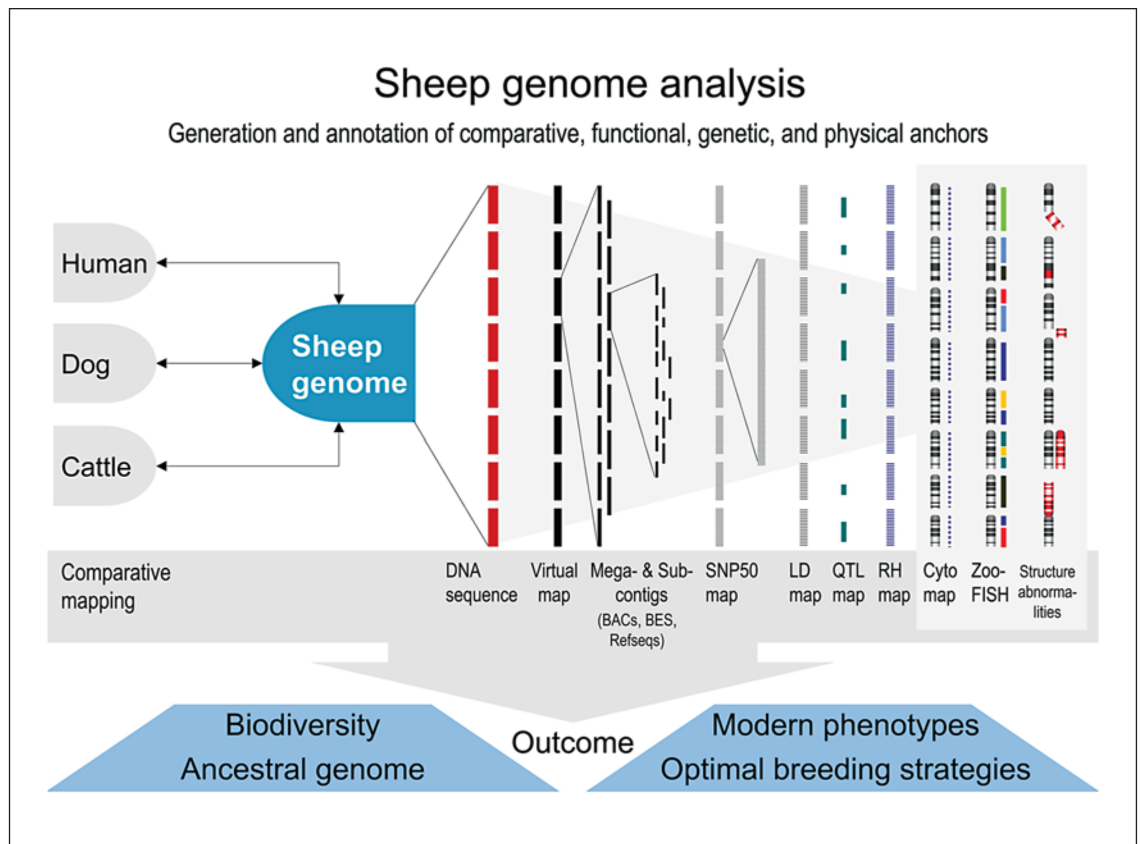

Fig. 1. Sheep genome analyses at different resolutions using different genomic resources.

[Osoegawa et al., 1998] as an ISGC project and is distributed as the CHORI-243 library through BACAPAC Resources (http://bacpac.chori.org/library.php?id=162). End sequencing from both ends of approximately 180,000 BAC clones from the CHORI-243 library allowed generation of comparative genome contigs (BAC-CGCs) covering 91.2% of the human genome. The BAC end sequences were combined with a comparative mapping approach using human, dog and cattle genome data as a framework and used to construct a virtual sheep genome (VSG) [www.livestockgenomics.csiro.au/perl/gbrowse.cgi/vsheep2/; Dalrymple et al., 2007]. Two publicly available cell lines have also been made from the Texel ram [Chitko-McKown et al., 2008] which will ensure both a ready supply of DNA from this animal and be useful for functional studies.

Two ovine whole-genome radiation hybrid panels have been produced allowing different resolutions for physi-cal mapping of the sheep genome. A 5,000-rad panel, USUoRH5000 has been used to generate a comparative and comprehensive RH map with 3,227 loci that spans the sheep genome by mapping markers that were a mix of monomorphic markers such as BAC end sequences, genes, and polymorphic markers [Cockett, 2006; Wu et al., 2007, 2008a, b, 2009]. A 12,000-rad panel was produced at the Institut National de la Recherche Agrono-mique (INRA) and has been used to generate a high-resolution map in a scrapie-associated chromosome region from *Ovis aries* (OAR) chromosome 18 [Laurent et al., 2007].

More than 200,000 ovine ESTs from different sources have been deposited in public genome databases (http://compbio.dfci.harvard.edu/tgi/cgi-bin/tgi/T_release.pl?gudb=sheep) and several high-density sheep cDNA and oligo microarrays have been developed [e.g. Keane et al., 2006; Pariset et al., 2008; Sgorlon et al., 2008]. In addition, the close evolutionary relationship between sheep and cattle has allowed several groups to use bovine microarrays for functional studies in sheep with some success [e.g. Tao et al., 2004; Diez-Tascón et al., 2005; Cao et al., 2006].

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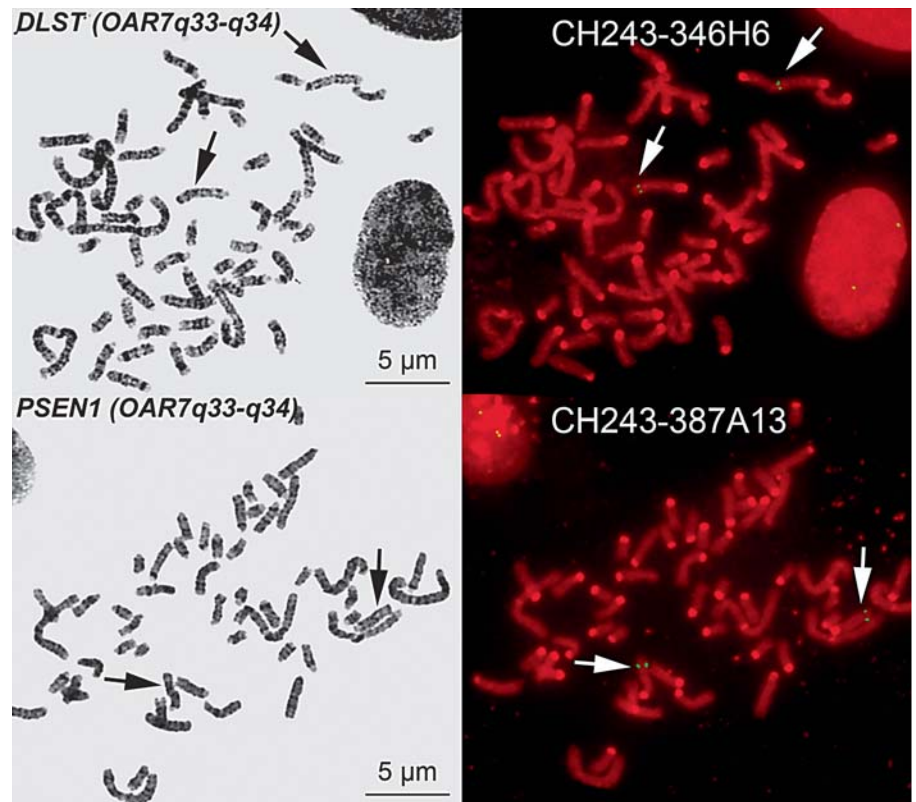

Fig. 2. Assignment of *PSEN1* and *DLST* to OAR7q33–q34, a chromosome region known to be associated with scrapie susceptibility. The FISH experiment was done on G-banded ovine metaphase chromosomes. DNA sequencing with gene-specific primer sets confirmed gene specificity within ovine BAC probes. Primer sets for PCR and DNA sequencing: *DLST* (5′-GCTCCTGCTAAGGCCAG-3′/5′-CCGA-TGTTCTGAACGCAGAC-3′) and *PSEN1* (5′-CATTATTGCTCCTCGCCATT3′/AAGATGAAGAGTCCTGTTTGGT-TT-3′). Arrows indicate the position of hybridization signals.

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Recently, 1.5K and 50K SNP chips for sheep genotyping have been created under the auspices of the ISGC [Kijas et al., 2009]. The 50K SNP chip is being used for generating the most comprehensive map of haplotypes (HapMap) for livestock species from 2,890 domestic sheep representing 64 breeds (http://www.sheephapmap.org/hapmap.php).

A first draft of the sheep genome sequence assembly (version 1.0) that corresponds to 2,784.6 Mbp of DNA sequence generated from 6 diverse animals has been produced in another ISGC project and has been made available at http://www.livestockgenomics.csiro.au/perl/gbrowse.cgi/oar1.0/.

Most of the mapping and sequencing data generated for sheep have been made publically available and can be found at the listed websites. It can be suggested that the sheep genome will soon become a reference genome for the annotation of genomes of phylogenetically related species, such as goats and other *Ovis* species.

Although the international cooperative research within the last few years has made significant progress in the field of sheep genomics, more work remains to be done. Challenges such as limited funding and personnel have impeded the development of a high-quality annotated sheep genome sequence. However, once completed, the reference sequence will serve as a useful tool for the development of modern breeding plans, or to answer phylogenetic questions, or for the identification of causal mutations for specific traits. Another obstacle, which is the focus of this review, is the relatively low number of cytogenetic anchors that can be used to bridge between the different types of maps and chromosome morphology in sheep. We present here the current status of the cytogenetic map and discuss these data in the light of completing a sheep genome sequence assembly.

The 2009 Cytogenetic Map of the Sheep Genome

For sheep, the average number of cytogenetic loci per sheep chromosome is 20, which is similar to the number of loci that have been assigned to specific chromosome bands or segments in other farm animals, such as cattle with an average of 21 loci per chromosome or goat with about 14 loci (http://locus.jouy.inra.fr/). However, the resolution of the cytogenetic sheep map is low compared

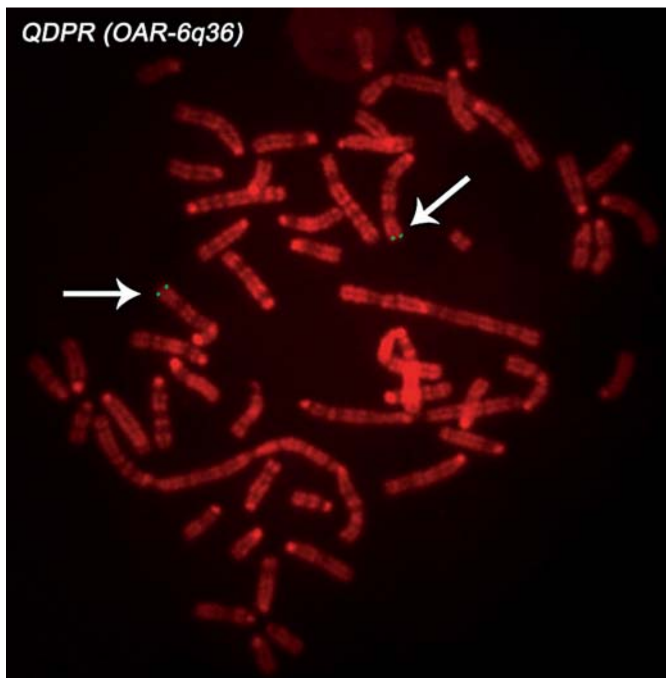

Fig. 3. Assignment of *QDPR* to OAR6q36. This FISH experiment was done on RBPI-banded (R-banding by late BrdU incorporation and propidium iodide staining) ovine metaphase chromosomes with simultaneous visualization of FITC signals (arrows). The majority of loci shown in figure 4 has been mapped to the sheep genome using this approach. Iannuzzi and Di Berardino [2008] have described this mapping approach in more detail.

to more completely analyzed genomes, such as the human genome with more than 11,000 cytogenetically assigned loci [http://www.ncbi.nlm.nih.gov/genome/cyto/hbrc.shtml; The BAC Resource Consortium et al., 2001] or the mouse genome with more than 1,400 mapped loci [http://www.informatics.jax.org/; Bult et al., 2008]. One reason for the low number in sheep is that cytogenetic mapping approaches require appropriate expertise, have lower throughput, and are seen as relatively expensive technologies when compared to sequence and bioinformatics approaches so that cytogenetic research in sheep is limited to a very small number of labs. Recent contributions to the sheep cytogenetic map have mainly focused on mapping trait-associated candidate genes [e.g. Cosseddu et al., 2002; Lyahyai et al., 2005; shown for *PSEN1* and *DLST* in fig. 2], or on the analysis of evolutionary breakpoint regions between sheep and other bovids or human [e.g. Perucatti et al., 2007, 2009; Chessa et al., 2009]. The most current ovine cytogenetic map (table 1) contains 566 loci, which is 112 more than for earlier cytogenetic maps [e.g. Di Meo et al., 2007]. 375 are type I loci (known genes) and 191 are type II loci (SSRs – simple sequence repeats, microsatellite markers, STSs – sequence tagged sites). All of these loci have been assigned to specific chromosome regions or bands. Most data have been obtained by using simultaneous visualization of FITC-signal hybridization and RBPI-banding (fig. 3). A new cytogenetic map for the whole ovine genome is shown in figure 4 and presents the actual number of cytogenetic loci assigned to specific chromosome regions on the sheep R-band ideogram according to the ISCNDB 2000 standard [Di Berardino et al., 2001].

The cytogenetic data presented in figure 4 have been analyzed in context with other recent and relevant data sets from the sheep genome analysis. From this, we conclude that various genomic maps, such as the SNP, genetic or RH maps, of the sheep genome have reached an appropriate density, and a first build of the sheep genome sequence assembly has been produced, but only a relatively small number of cytogenetic anchors link these maps to specific chromosome bands. This clearly impedes a deeper analysis of morphological and structural chromosome rearrangements.

The 566 loci on the cytogenetic map result in an average distance of 5.1 Mbp per locus based on the first draft of the ovine genome sequence assembly. In order to visualize the correspondence between cytogenetic location and DNA sequence position, we have constructed diagrams for OAR7 and OARX, 2 chromosomes having 2.6 and 2.1 mapped loci in average per chromosome band, respectively. Both sheep chromosomes have assignments of more than 40 DNA sequences and the average distance between cytogenetic loci was calculated as 2.5 and 2.9 Mbp, respectively (fig. 5). In general, the relative positions derived from the FISH mapping data and sequencing data are consistent. However, OAR7 and OARX contain chromosome bands where physical anchors are missing and there are order discrepancies be-

(For figure 4 see next pages.)

Fig. 4. The ovine cytogenetic map as of May 2009. 566 loci assigned to specific chromosome regions and chromosome bands are presented on the sheep R-band standard ideogram of the ISCNDB 2000 [Di Berardino et al., 2001]. Standard characters indicate type I loci (375) and italicized characters indicate type II loci (191). If more than 1 locus has been found for a gene (e.g. *CYP19A1* or *IL2*), the most precise position has been included in the drawing.

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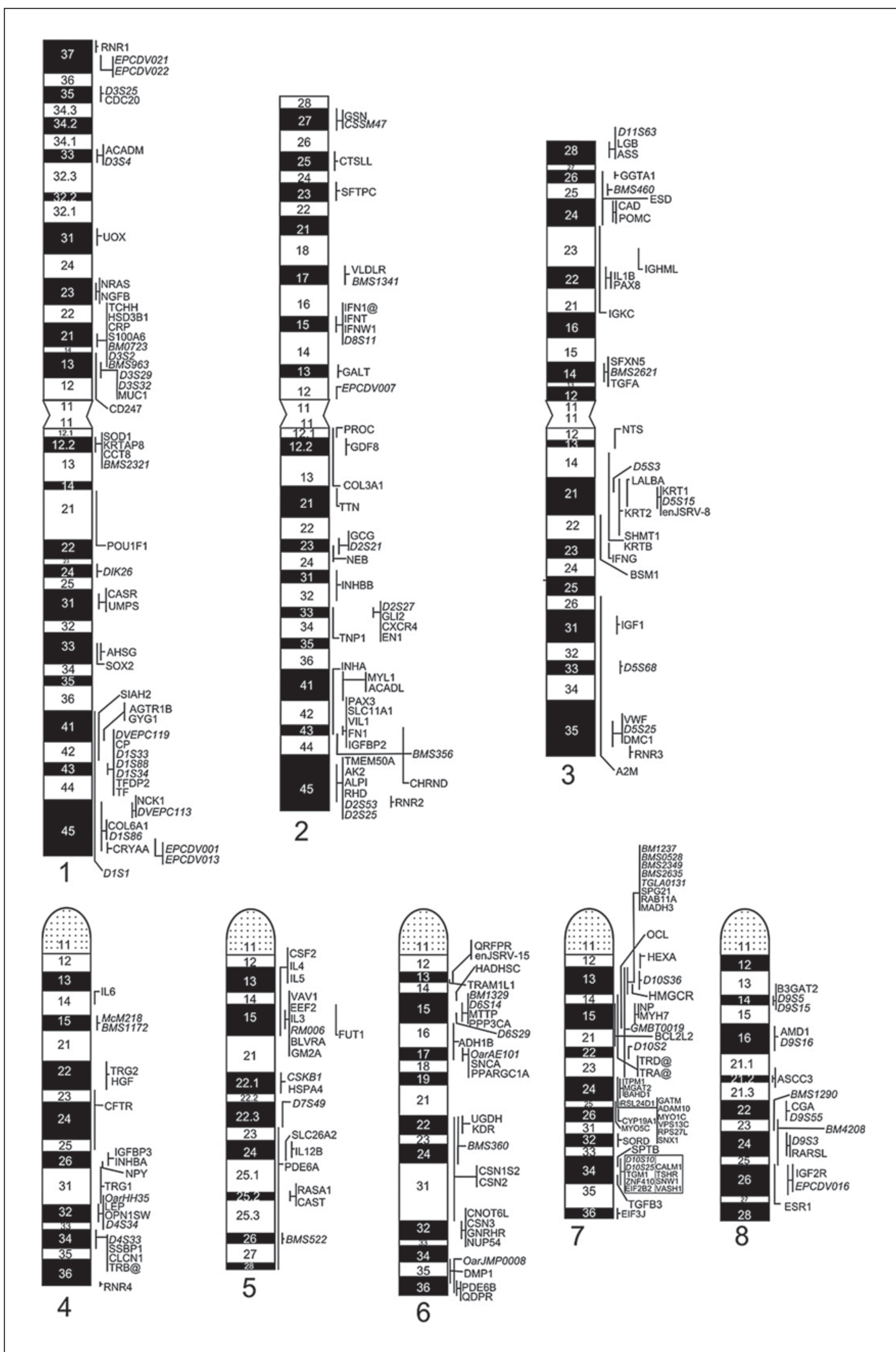

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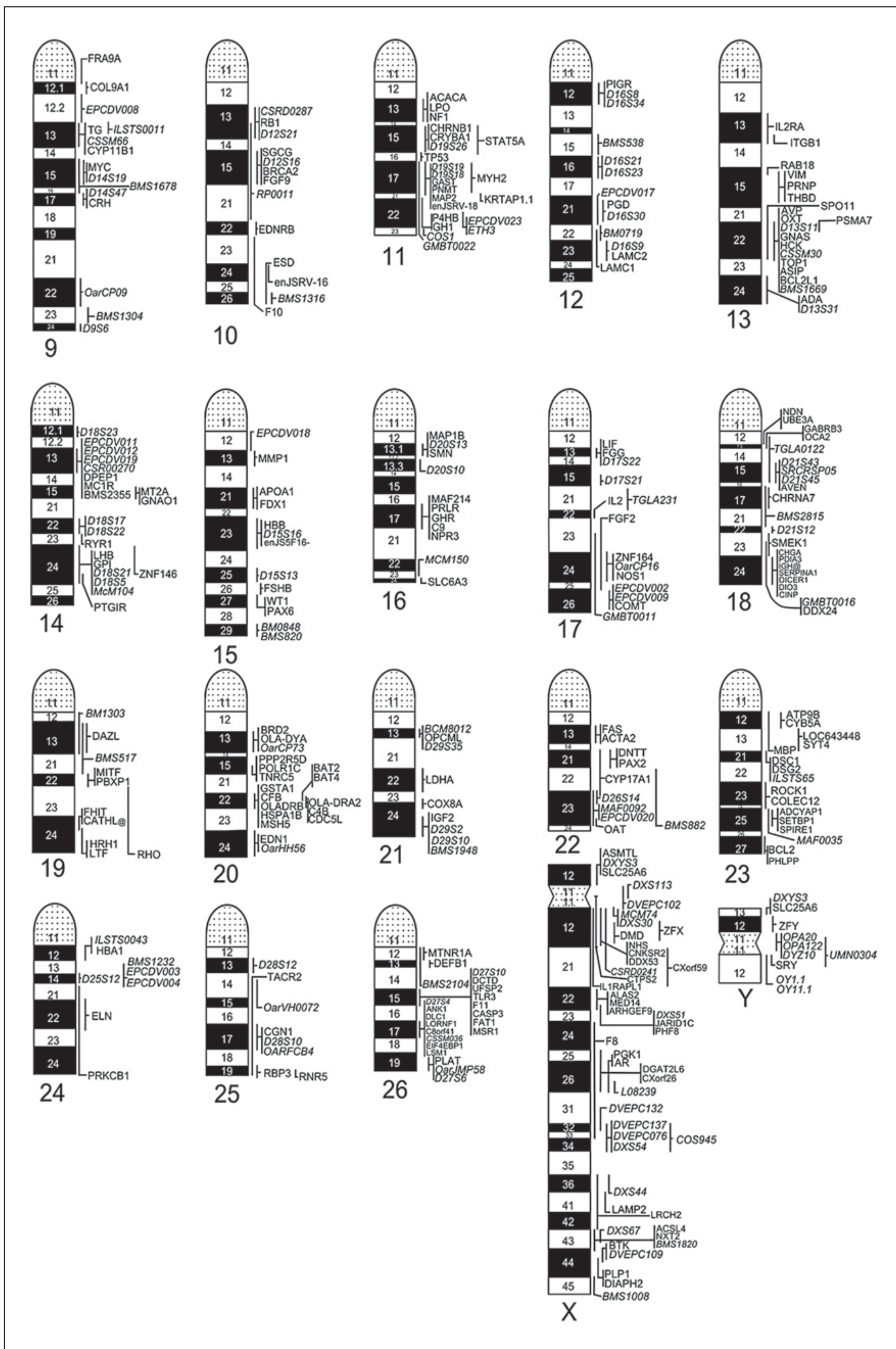

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Table 1. A list of 113 loci (83 type I, 30 type II) added to the comprehensive cytogenetic sheep map of Di Meo et al. [2007], arranged by year of publication

Locus symbol	Locus name	Localization OAR	Reference
BMS963	DNA segment D3S73	1p21	Tabet-Aoul et al., 2000
BMS2321	DNA segment D1S91	1q12	
BMS1341	DNA segment D8S42	2p17	
BMS356	DNA segment D2S71	2q44	
BMS460	DNA segment D11S87	3p25	
BMS1172	DNA segment D0S044	4q15	
BMS522	DNA segment D7S47	5q26	
BMS360	DNA segment D6S48	6q22–q24	
BMS1290	DNA segment D9S47	8q22–q23	
BMS1678	DNA segment D14S38	9q15–q16	
BMS1304	DNA segment D14S44	9q23	
BMS1316	DNA segment D12S50	10q26	
ETH3	DNA segment D19S2	11q22	
BMS538	DNA segment D16S45	12q15	
BMS1669	DNA segment D13S40	13q22	
BMS2355	DNA segment D18S35	14q13	
BMS820	DNA segment D15S42	15q29	
MCM150	DNA segment L39829	16q22–q23	
TGLA231	DNA segment D17S19	17q21	
BMS2815	DNA segment D21S49	18q17–q21	
BMS517	DNA segment D22S34	19q13–q21	
BMS1948	DNA segment D29S38	21q24	
BMS882	DNA segment D26S31	22q22–q23	
ILSTS65	DNA segment L37269	23q21	
BMS1232	DNA segment D25S32	24q13–q14	
OARFCB4	DNA segment OARFCB4	25q17	
BMS2104	DNA segment D27S28	26q12–q14	
BMS1008	DNA segment D0S025	Xq45	
SPG21	spastic paraplegia 21 (autosomal recessive, Mast syndrome)	7q13	Cosseddu et al., 2002
RAB11A	RAB11A, member RAS oncogene family	7q13	
SMAD3	SMAD family member 3	7q13	
BAHD1	bromo adjacent homology domain containing 1	7q24	
GATM	glycine amidinotransferase (L-arginine:glycine amidinotransferase)	7q24–q25	
MYO5C	myosin VC	7q25–q26	
RSL24D1	ribosomal L24 domain containing 1	7q25	
ADAM10	ADAM metallopeptidase domain 10	7q24–q25	
MYO1C	myosin IC	7q24–q25	
VPS13C	vacuolar protein sorting 13 homolog C *(S. cerevisiae)*	7q24–q25	
RPS27L	ribosomal protein S27-like	7q24–q25	
SNX1	sorting nexin 1	7q24–q25	
ZNF410	zinc finger protein 410	7q34	
EIF2B2	eukaryotic translation initiation factor 2B, subunit 2 beta, 39 kDa	7q34	
VASH1	vasohibin 1	7q34	
SNW1	SNW domain containing 1	7q34	
TSHR	thyroid-stimulating hormone receptor	7q34	
CALM1	calmodulin 1 (phosphorylase kinase, delta)	7q34	
EIF3J	eukaryotic translation initiation factor 3, subunit J	7q36	
NDN	necdin homolog (mouse)	18q12	
UBE3A	ubiquitin protein ligase E3A	18q12	
GABRB3	gamma-aminobutyric acid (GABA) A receptor, beta 3	18q12–q13	
OCA2	oculocutaneous albinism II	18q12–q13	
AVEN	apoptosis, caspase activation inhibitor	18q15	
SMEK1	SMEK homolog 1, suppressor of mek1 *(Dictyostelium)*	18q23	
DDX24	DEAD (Asp-Glu-Ala-Asp) box polypeptide 24	18q23–q24	
DICER1	dicer 1, ribonuclease type III	18q24	
DIO3	deiodinase, iodothyronine, type III	18q24	
CINP	cyclin-dependent kinase 2-interacting protein	18q24	

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Table 1 (continued)

Locus symbol	Locus name	Localization OAR	Reference
BCL2L2	BCL2-like 2	7q15–q21	Lyahyai et al., 2005
BCL2L1	BCL2-like 1	13q22	
BCL2	B-cell CLL/lymphoma 2	23q27	
DCTD	dCMP deaminase	26q15	Perucatti et al., 2007
UFSP2	UFM1-specific peptidase 2	26q15	
CASP3	caspase 3, apoptosis-related cysteine peptidase	26q15	
TLR3	Toll-like receptor 3	26q15	
MSR1	macrophage scavenger receptor 1	26q15	
FAT1	FAT tumor suppressor homolog 1 *(Drosophila)*	26q15	
LONRF1	LON peptidase N-terminal domain and ring finger 1	26q17	
DLC1	deleted in liver cancer 1	26q17	
C8orf41	chromosome 8 open reading frame 41	26q17	
CSSM036	DNA segment U03827	26q17	
LSM1	LSM1 homolog, U6 small nuclear RNA associated *(S. cerevisiae)*	26q17	
EIF4EBP1	eukaryotic translation initiation factor 4E binding protein 1	26q17	
ATP9B	ATPase, class II, type 9B	23q12	Tetens et al., 2007
LOC643448	hypothetical protein LOC643448	23q13	
SYT4	synaptotagmin IV	23q13	
ROCK1	Rho-associated, coiled-coil containing protein kinase 1	23q23–q24	
COLEC12	collectin sub-family member 12	23q23–q24	
SPIRE1	spire homolog 1 *(Drosophila)*	23q25	
SETBP1	SET-binding protein 1	23q25	
PHLPP	PH domain and leucine-rich repeat protein phosphatase	23q27	
enJSRV-8	endogenous retroviruses	3q21	Chessa et al., 2009
enJSRV-15	endogenous retroviruses	6q13	
enJSRV-16	endogenous retroviruses	10q24	
enJSRV-18	endogenous retroviruses	11q17	
enJS5F-16	endogenous retroviruses	15q23	
QRFPR	pyroglutamylated RFamide peptide receptor	6q13	Perucatti et al., 2009
TRAM1L1	translocation-associated membrane protein 1-like 1	6q13dist	
PPP3CA	protein phosphatase 3 (formerly 2B), catalytic subunit, alpha isoform	6q15	
SNCA	synuclein, alpha (non-A4 component of amyloid precursor)	6q17	
PPARGC1A	peroxisome proliferator-activated receptor gamma, coactivator 1α	6q17	
UGDH	UDP-glucose dehydrogenase	6q22prox	
KDR	kinase insert domain receptor (a type III receptor tyrosine kinase)	6q22	
CNOT6L	CCR4-NOT transcription complex, subunit 6-like	6q32prox	
NUP54	nucleoporin 54 kDa	6q32	
DMP1	dentin matrix acidic phosphoprotein 1	6q34dist–q36prox	
QDPR	quinoid dihydropteridine reductase	6q36	
ASMTL	acetylserotonin O-methyltransferase-like	Xp12	Goldammer et al., 2009
CTPS2	CTP synthase II	Xq11–q12	
NHS	Nance-Horan syndrome (congenital cataracts and dental anomalies)	Xq12	
CNKSR2	connector enhancer of kinase suppressor of Ras 2	Xq12	
DDX53	DEAD (Asp-Glu-Ala-Asp) box polypeptide 53	Xq12	
IL1RAPL1	interleukin 1 receptor accessory protein-like 1	Xq12–q21	
CXorf59	chromosome X open reading frame 59	Xq21	
MED14	mediator complex subunit 14	Xq22	
ARHGEF9	Cdc42 guanine nucleotide exchange factor (GEF) 9	Xq22	
JARID1C	lysine (K)-specific demethylase 5C	Xq23	
PHF8	PHD finger protein 8	Xq23	
DGAT2L6	diacylglycerol O-acyltransferase 2-like 6	Xq25–q26	
CXorf26	chromosome X open reading frame 26	Xq25–q26	
LRCH2	leucine-rich repeats calponin homology (CH) domain containing 2	Xq36–q42	
ACSL4	acyl-CoA synthetase long-chain family member 4	Xq43	
NXT2	nuclear transport factor 2-like export factor 2	Xq43	
BMS1820	DNA segment D0S108	Xq43	

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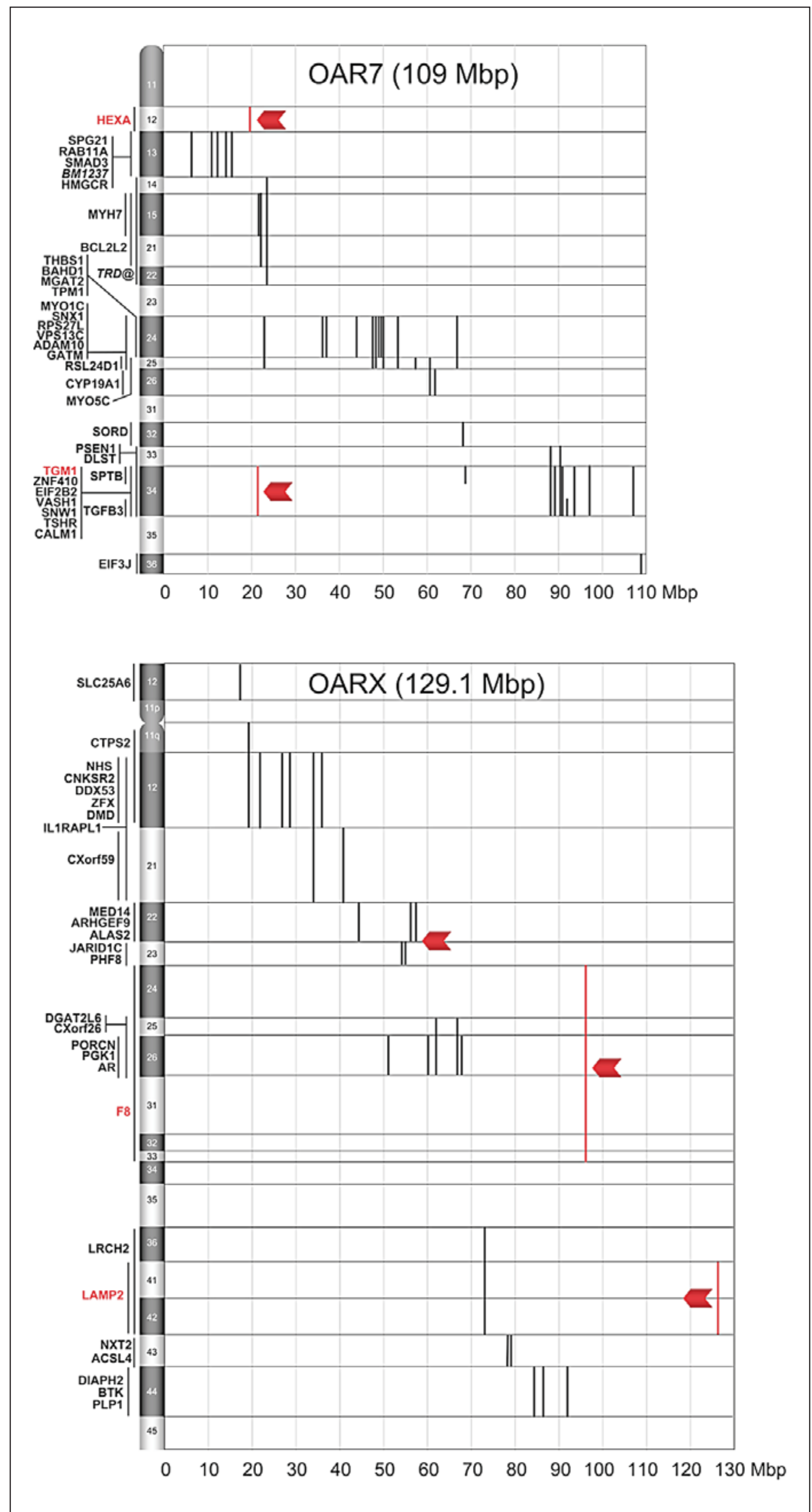

Fig. 5. Correspondence between cytogenetic location (R-bands) and position on the ovine sheep genome assembly (v1.0) for OAR7 and OARX. Only markers with assignments on both maps have been included (OAR7: 35 out of 44 cytogenetic loci; OARX: 27 out of 45 cytogenetic loci). Red arrows and loci in red indicate clear mismatches between the 2 maps.

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Table 2. Comprehensive data set of ovine genome analysis

OAR Chr	Zoo-FISH [Iannuzzi et al., 1999] HSA Chr	Recent Cyto Map loci No.	Average loci number per band [399 band level]	Bands with no cyto loci [399 band level]	Chr length (OGA v1.0, May 2009) Mbp	Average cyto locus distance in OGA v1.0 Mbp	RH Map (USUo 5,000 panel, May 2009) loci No.	Microsatellite/SNP Map sex averaged (Maddox v5)		SNP50 (predicted) SNP No.	QTL (data base plus new QTL) QTL No.
								loci No.	cM		
1	1, 3, 21	49	1.2	22	299.8	6.1	297	251	340.0	6,016	2
2	1, 2, 9	42	1.2	13	263.2	6.3	141	240	333.0	5,553	4
3	2, 9, 12, 22	33	1.1	8	242.9	7.4	130	227	313.4	5,071	8
4	4	19	1.1	4	128.1	6.7	64	95	167.7	2,723	0
5	5, 19	19	1.1	11	117.2	6.2	68	91	168.2	2,385	3
6	7	26	1.4	8	129.1	5.0	181	103	154.6	2,624	3
7	14, 15	44	2.6	6	109.0	2.5	73	98	147.9	2,280	0
8	8	15	0.9	7	98.0	6.5	148	61	131.5	2,084	2
9	6	15	1.1	8	100.8	6,7	102	73	138.0	2,168	0
10	13	13	1.2	2	94.2	7.3	78	58	118.3	1,871	2
11	17	22	2.2	3	67.1	3.0	45	81	117.7	1,202	2
12	1	13	1.1	5	86.5	6.7	58	64	120.5	1,738	1
13	10, 20	20	2.2	4	89.1	4.4	57	78	135.2	1,718	2
14	16, 19	20	1.7	7	69.3	3.4	51	77	126.8	1,193	5
15	8	13	1.0	5	90.1	6.9	61	91	130.7	1,716	1
16	5	11	0.8	7	77.2	7.0	54	55	100.2	1,596	0
17	4, 12, 22	14	1.3	3	78.6	5.6	98	80	130.4	1,439	0
18	14, 15	22	2.0	2	72.5	3.3	46	88	130.8	1,434	4
19	3	10	1.4	2	65.0	6.5	42	64	84.7	1,257	0
20	6	18	2.0	5	55.9	3.1	123	63	104.9	1,166	6
21	11	9	1.3	4	55.5	6.2	35	56	78.4	912	0
22	10	10	1.2	4	55.9	5.6	42	33	104.6	1,107	0
23	18	16	1.6	3	66.8	4.2	110	79	93.3	1,140	2
24	8	8	1.0	1	45.3	5.7	49	60	81.6	750	2
25	10	8	0.9	2	48.3	6.0	37	63	84.0	1,016	8
26	7, 16	22	2.4	3	50.1	2.3	30	42	81.8	933	0
X	X	45	2.1	2	129.1	2.9	130[a]	147	93.7	1,502	1
Y	Y	10	2.0	0	–	–	0	–	–	1	0
Total		566		151	2,784.6		2,350[a]	2,518	3,811.9	54,595[b]	58[c]
Average			1.4			5.1					

OAR Chr = Ovine chromosome number; OGA = ovine genome assembly. QTL database, http://sphinx.vet.unimelb.edu.au/cgi-bin/QTLdb/OA/viewmap.

[a] Data in Wu et al., 2008b together with data in Goldammer et al., 2009a.

[b] Additional 382 unpositioned SNPs. New QTL (not in QTL database): OAR1 – milk fat content [Calvo et al., 2006]; OAR2 – muscle depth [Hadjipavlou et al., 2008]; carcass [Johnson et al., 2005]; OAR3 – facial eczema [Phua et al., 2009]; OAR6, OAR18 – scrapie incubation time [Moreno et al., 2008].

[c] A QTL for host resistance to internal parasite *Haemonchus contortus* [Marshall et al., 2009] is not included.

tween the 2 maps (fig. 5). Given the precision of the ovine FISH mapping process, including a step whereby probes are sequenced to confirm gene content, it is likely that most of the FISH positions are correct (e.g. *HEXA* and *TGM1* loci on OAR7) and that the sequence assembly positions, largely derived from chromosome orders for species other than sheep, are incorrect. The FISH mapping method offers a way for positioning more loci to the sheep cytogenetic map and contributes to a sheep sequence assembly process of higher quality. In summary, the generation of many more cytogenetic loci is important to complete the accurate assignment between ovine DNA sequence and metaphase chromosome band morphology.

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The relatively low density of cytogenetically mapped loci as compared to other mapped chromosome features is shown in table 2, as well as the gross correspondence between sheep and human chromosomes. Zoo-FISH has been used to identify several rearrangements between ovine and human chromosomes. The description of the regions flanking the breakpoints at the cytogenetic level in sheep is in most cases very imprecise. The same conclusion can also be made when comparing the number of loci with chromosome bands, as on average only 1.42 DNA probes per band have been assigned to date. The ISCNDB 2000 publication [Di Berardino et al., 2001] describes 399 distinct single chromosome bands for the sheep genome. Only 62% of the bands (248 bands) have one or more loci that have been cytogenetically mapped to them (fig. 4). No physical anchors are available for definition or differentiation of the remaining 151 bands. Comparing the number of DNA sequences obtainable from radiation hybrid or genetic maps with the cytogenetic map indicates again that the link between these maps to the metaphase chromosome morphology is only of appropriate density for a small number of genome regions. Consequently, the current cytogenetic map provides several useful physical anchors for sheep genome analysis or comparative studies, but it is inadequate for the completion of the sheep genome assembly or for studies that depend on a high resolution of loci.

Conclusions and Future Aspects

Major efforts based on close collaboration of the laboratories have contributed to the development of the cytogenetic sheep map. However, an increase in the number of mapped loci per chromosome is needed. In addition to the targeted assignment of trait-associated candidate genes or informative markers, which link a QTL region to a chromosome segment, future cytogenetic mapping in sheep should focus on the chromosomal assignment of selected DNA probes which anchor the different types of maps to banded metaphase chromosomes. Targeted comparative mapping is suggested based on chromosome morphology and DNA sequence information between human and sheep and will be necessary to assign genes to ovine chromosome bands that currently have no locus assignments. Likewise, the ovine DNA probes that are used should be selected according to their use in comparative mapping approaches, such as cytogenetically mapped loci in other domestic *Bovidae* such as cattle, goat or river buffalo. Building these bridges between the different maps and chromosome morphology has already been reported for OAR23 [Tetens et al., 2007], OAR10 [Drögemüller et al., 2008], OAR6 [Perucatti et al., 2009] and OARX [Goldammer et al., 2009a, b]. Other map comparisons are being performed for other sheep chromosomes to demonstrate the evolutionary rearrangements in other Bovidae and human.

Procedures for the identification of chromosomal polymorphisms such as whole-comparative genomic hybridization (W-CGH) or DNA breakage detection FISH (DBD-FISH) have also proven useful in phylogenetic studies between domestic sheep and the mouflon, a direct ancestor [Dávila-Rodríguez et al., 2009]. Expanding such studies to other *Ovis* species should improve information about the genetic diversity and evolution of the genus *Ovis* and complement other phylogenetics studies such as the recent study that used retroviral insertion to delineate different sheep lineages and mitochondrial lineages studies [e.g. Tapio et al., 2006; Meadows et al., 2007; Chessa et al., 2009]. For Hominidae, studies have shown that the process of chromosome evolution is the result of numerous small segment duplications and deletions [Locke et al., 2003; Fortna et al., 2004], and this is likely to be the case also for Caprinae and other ruminants. The human studies used array-based methods, with the first being an array-comparative genomic hybridization (A-CGH) approach that used a human BAC array and showed about 60 small segment mutations. The second approach was a higher-resolution approach that looked at differences in gene copy number in Hominidae by using a cDNA-array that included almost the complete gene coding genome. Generation of analogous genome-wide DNA arrays based on the well-characterized ovine CHORI-243 BAC library or cDNA libraries from sheep, would be powerful tools for analysis of chromosome evolution in sheep. Moreover, such tools would also be useful for comparative analysis in other closely related Ruminantia and for clinical cytogenetics. In addition to their use for investigating the evolution of sheep, such information would contribute to the completion of the sheep genome DNA sequence and could likewise be linked with information about quantitative traits. In this way, ovine cytogenomic data would be a valuable contribution to the study of sheep phenotypes that are optimally adapted to a specific environment, as well as modern breeding and production conditions.

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Acknowledgements

The authors thank Domenico Incarnato, CNR-ISPAAM of Naples for construction of the sheep cytogenetic map on an R-banded standard ideogram, as well as the listed organizations for funding sheep genome analysis: German Research Foundation – DFG-Grant GO-896/6-3; USDA National Research Initiative Grants no. 2005-591-0649-01; National Research Council of Rome, Italy, DG.RSTL.083.001 and DG.RSTL.083.002; LR5 of Campania Region, Italy; co-authors funding bodies e.g. sheepGENOMICS (a joint initiative of Meat and Livestock Australia (MLA) and Australian Wool Innovation (AWI).

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