Published in final edited form as:
Science. 2009 April 24; 324(5926): 522–528. doi:10.1126/science.1169588.

The Genome Sequence of Taurine Cattle: A window to ruminant biology and evolution

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Abstract

To understand the biology and evolution of ruminants, the cattle genome was sequenced to ~7× coverage. The cattle genome contains a minimum of 22,000 genes, with a core set of 14,345 orthologs shared among seven mammalian species of which 1,217 are absent or undetected in non-eutherian (marsupial or monotreme) genomes. Cattle-specific evolutionary breakpoint regions in chromosomes have a higher density of segmental duplications, enrichment of repetitive elements, and species-specific variations in genes associated with lactation and immune responsiveness. Genes involved in metabolism are generally highly conserved, although five metabolic genes are deleted or extensively diverged from their human orthologs. The cattle genome sequence thus provides an enabling resource for understanding mammalian evolution and accelerating livestock genetic improvement for milk and meat production.

Domesticated cattle (*Bos taurus* and *Bos taurus indicus*) provide a significant source of nutrition and livelihood to nearly 6.6 billion humans. Cattle belong to a phylogenetically distant clade compared to humans and rodents, the Cetartiodactyl order of eutherian mammals, which first appeared ~60 million years ago (1). Cattle represent the Ruminantia, which occupy diverse terrestrial environments with their ability to efficiently convert low quality forage into energy-dense fat, muscle and milk. These biological processes have been exploited by humans since domestication, which began in the Near East some 8,000-10,000 years ago (2). Since then, over 800 cattle breeds have been established representing an important world heritage and an enabling scientific resource for understanding the genetics of complex traits.

The cattle genome was assembled with methods similar to the rat and sea urchin genomes (3, 4). The most recent assemblies, Btau3.1 and Btau4.0, combined bacterial artificial chromosome (BAC) and whole genome shotgun (WGS) sequences. Btau3.1 was used for gene-specific analyses. Btau4.0, which includes finished sequence data and used different mapping methods to place the sequence on chromosomes, was used for all global analyses other than gene prediction. The contig N50 (50% of the genome is in contigs of this size or greater) is 48.7kb for both assemblies; the scaffold N50 for Btau4.0 is 1.9 Mb. In the Btau4.0 assembly, 90% of the total genome sequence was placed on the 29 autosomes and X chromosome and validated (3). Of 1.04 million expressed sequence tag (EST) sequences, 95.0% were contained in the assembled contigs. With an equivalent gene distribution in the remaining 5% of the genome, the estimated genome size is 2.87 Gbp. Comparison to 73 finished BACs and single nucleotide polymorphism (SNP) linkage data (5,6) confirmed this assembly quality with greater than 92%

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genomic coverage and fewer than 0.8% of SNP were incorrectly positioned at the resolution of these maps (3,4).

We used the cattle genome to catalog protein-coding genes, microRNA genes and ruminant-specific interspersed repeats and manually annotated over 4000 genes. The consensus protein-coding gene set for Btau3.1 (OGSv1), from six predicted gene sets (4), consists of 26,835 genes with a validation rate of 82% (4). On this basis we estimate that the cattle genome contains at least 22,000 protein-coding genes. We identified 496 microRNA genes of which 135 were putative novel microRNAs (4). About half of the cattle miRNA occur in 60 genomic microRNA clusters, containing 2 to 7 microRNA genes separated by less than 10 kbp (Fig. S2). The overall GC content of the cattle genome is 41.7%, with an observed-to-expected CpG ratio of 0.234, similar to other mammals.

The cattle genome has transposable element classes similar to other mammals as well as large numbers of ruminant-specific repeats (Table S4) that comprise 27% of its genome. The consensus sequence of BovB, a non-LTR LINE retrotransposon, lacked a functional open reading frame (ORF), suggesting it was inactive (7). However, BovB repeats with intact ORF were identified in the genome and their phylogeny (Fig. S4) indicates that some are still actively expanding and evolving. Mapping chromosomal segments of high and low density ancient repeats, L2/MIR (a LINE/SINE pair) and BovB, and more recent repeats, BovB/Art2A (BovB derived SINE pair), revealed that the genome consists of ancient regions enriched for L2/MIR and recent regions enriched for BovB/Art2A (Fig. S7). Exclusion of BovB/Art2A from contiguous blocks of ancient repeats suggests that evolution of the ruminant/cattle genome experienced invasions of new repeats into regions lacking ancient repeats. Alternatively, older repeats may have been destroyed by insertion of ruminant/cattle-specific repeats. AGC trinucleotide repeats, the most common simple sequence repeat (SSR) in artiodactyls (which include cattle, pigs and sheep), are 90 and 142 fold over-represented in cattle compared to human and dog, respectively (Fig. S10). 39% of the AGC repeats in the cattle genome were associated with Bov-A2 SINE elements.

A comparative analysis examined the rate of protein evolution and the conservation of gene repertoires among orthologs in the genomes of dog, human, mouse and rat (representing placental mammals), opossum (marsupial), and platypus (monotreme). Orthology was resolved for >75% of cattle and >80% of human genes (Fig. 1A). There were 14,345 orthologous groups with representatives in human, cattle or dog, mouse or rat, and opossum or platypus, which represent 16,749 cattle and 16,177 human genes, respectively of which 12,592 are single copy orthologs. We also identified 1,217 placental mammal-specific orthologous groups with genes present in human, cattle or dog, mouse or rat, but not in opossum or platypus. About 1,000 orthologs shared between rodents and laurasiatherians (cattle and dog), many of which encode G-protein coupled receptors, appear to have been lost or may be mis-annotated in the human genome (Fig. 1B). Gene repertoire conservation among these mammals correlates with conservation at the amino-acid sequence level (Fig. 1C). The elevated rate of evolution in rodents relative to other mammals (10) was supported by the higher amino acid sequence identity between human and dog or cattle proteins relative to that between human and rodent proteins. However, maximum-likelihood analysis of amino acid substitutions in single-copy orthologs supports the accepted sister lineage relationship of primates and rodents (1) (Fig. 1D).

Alternative splicing is a major mechanism for transcript diversification (8), yet the extent of its evolutionary conservation and functional impact remain unclear. We used the cattle genome to analyze the conservation of the most common form of alternative splicing, exon skipping, defined as a triplet of exons in which the middle exon is absent in some transcripts, in a set of 1,930 exon-skipping events across human, mouse, dog and cattle (4). We examined 277 cases,

with different conservation patterns between human and mouse, in 16 different cattle tissues with RT-PCR (4). These splicing events were divided into a shared set (163 in both human and mouse) and a non-shared set (114 in human but not in mouse). Of the 277, we detected exon skipping for 188 cases in cattle (Table S5) suggesting that the majority of genes with exon-skipping in human were present and regulated in cattle, and that if an event is shared between human and mouse, it was more likely to be found in cattle. It was estimated that at most 40% of exon skipping is conserved among mammals and our data agrees with the upper bound from previous analyses with human and rodents [e.g. (9)].

We constructed a cattle-human Oxford Grid (Fig. S12) (4) to conduct synteny-based chromosomal comparisons which reinforced that human genome organization is more similar to cattle than to rodents because most cattle chromosomes primarily correspond to part of one human chromosome; albeit with multiple rearrangements [e.g. (10)]. In contrast, the cattle-mouse Oxford Grid shows poorer chromosomal correspondence. Lineage-specific evolutionary breakpoints were identified for cattle, artiodactyls, and ferungulates (a group encompassing artiodactyls and carnivores, represented by cattle, pig and dog), and are shown with cattle (Fig. S11) and human sequence coordinates (Fig. 2) (4). Primate, dog, rodent, mouse, and rat lineage-specific breakpoint positions were similarly identified. A total of 124 evolutionary breakpoint regions (EBRs) were identified in the cattle lineage, of which 100 were cattle/ruminant specific and 24 were artiodactyl-specific (e.g. Fig. 2). Nine additional EBRs represent presumptive ferungulate-specific rearrangements. *Bos taurus* chromosome 16 (BTA16) is populated with four ferungulate specific EBRs, suggesting that this region was rearranged before the Artiodactyla and Carnivora divergence (Fig. 2). Such conserved regions demonstrate many inversions that occurred prior to the divergence of the carnivores and artiodactyls have probably been retained in the ancestral form within the human genome. In contrast to the cattle genome, a pig physical map identified only 77 lineage-specific EBRs. Interchromosomal rearrangements and inversions characterize most of the lineage-specific rearrangements observed in the cattle, dog, and pig genomes.

An examination of repeat families and individual transposable elements within cattle-, artiodactyl- and ferungulate-specific EBRs showed a significantly higher density of LINE-L1 elements and the ruminant-specific LINE-RTE repeat family (11) in cattle-specific EBRs relative to the remainder of the cattle genome (Table S6). In contrast, the SINE-BovA repeat family and the more ancient tRNAGlu–derived SINE repeats (12) were present in lower density in cattle-specific EBRs, similar to other LINEs and SINEs (Table S7). The differences in repeat densities were generally consistent in cattle-, artiodactyl- and ferungulate-specific EBRs, with the exception of the tRNAGlu–derived and LTR-ERVL repeats, which are at higher densities in artiodactyl EBRs compared to the rest of the genome.

The tRNAGlu (CHRS) repeats originated in the common ancestor of Suina (pigs and peccaries), Ruminantia and Cetacea (whales) (12), suggesting that tRNAGlu –derived SINEs were involved in ancestral artiodactyl chromosome rearrangements. Furthermore, the lower density of the more ancient repeat families in cattle-specific EBRs suggests that either more recently arising repeat elements were inserted into regions lacking ancient repeats or that older repeats were destroyed by this insertion (Table S7). The differing density of repeat elements in EBRs were also found in regions of homologous synteny suggesting that repeats may promote evolutionary rearrangements (see below). Differences in repeat density in cattle-specific EBRs are thus unlikely to be caused by the accumulation of repeats in EBRs after such rearrangements occur. We identified a cattle-specific EBR associated with a bidirectional promoter (Figs. S14 and S15), that may affect control of the expression of the *CYB5R4* gene which has been implicated in human diabetes and therefore may be important in the regulation of energy flow in cattle (4).

1,020 segmental duplications (SDs) corresponding to 3.1% (94.4 Mbp) of the cattle genome were identified (4). Duplications assigned to a chromosome showed a bipartite distribution with respect to length and percent identity (Fig. S16) and interchromosomal duplications were shorter (median length 2.5 kbp) and more divergent (<94% identity), relative to intrachromosomal duplications (median length 20 kbp, ~97% identity), and tended to be locally clustered (Fig. S17). Twenty-one of these duplications were >300 kbp and located in regions enriched for tandem duplications (e.g. BTA18, Fig. S18). This pattern is reminiscent of the duplication pattern of the dog, rat and mouse but different from that of primate/great-ape genomes (13,14). On average cattle SDs >10 kbp represent 11.7% of base pairs in 10 kbp intervals located within cattle-specific EBRs and 23.0% of base pairs located within the artiodactyl-specific EBRs. By contrast, in the remainder of the genome sequence assigned to chromosomes the fraction of SDs was 1.7% ($p < 1 \times 10^{-12}$). These data indicate that SDs play a role in promoting chromosome rearrangements by non-allelic homologous recombination [e.g. (15)] and suggest that either a significant fraction of the SDs observed in cattle occurred before the Ruminant-Suina split, and/or that the sites for accumulation of SDs are non-randomly distributed in artiodactyl genomes.

SDs involving genic regions may give rise to new functional paralogs. Seventy six percent (778/1,020) of the cattle SDs correspond to complete or partial gene duplications with high sequence identity (median 98.7%). This suggests that many of these gene duplications are specific to either the artiodactyla or the *Bos* lineage and tend to encode proteins that often interface with the external environment, particularly immune proteins and sensory/olfactory receptors. Several of these gene duplications are also duplicated in other mammalian lineages (e.g. cytochrome P450, sulfotransferase, ribonuclease A, defensins and pregnancy-associated glycoproteins). Paralogs located in segmental duplications present exclusively in cattle may have functional implications for the unique physiology, environment and diet of cattle.

An over-representation of genes involved in reproduction in cattle SDs (Tables S8 and S9) is associated with several gene families expressed in the ruminant placenta. These families encode the intercellular signaling proteins pregnancy associated glycoproteins (on BTA29), trophoblast Kunitz domain proteins (on BTA13) and interferon tau (*IFNT*) (on BTA8). A gene family encoding prolactin-related proteins (on BTA23) was only identified in the assembly-dependent analysis of SDs. These genes regulate ruminant-specific aspects of fetal growth, maternal adaptations to pregnancy and the coordination of parturition (16, 17). While Type I IFN genes are primarily involved in host defense (18), *IFNT* prevents regression of the corpus luteum during early pregnancy resulting in a uterine environment receptive to early conceptus development (19).

Signatures of positive selection (obtained by measurement of their rates of synonymous and nonsynonymous substitutions) identified 71 genes (4) including ten immune related genes (i.e. *IFNAR2*, *IFNG*, *CD34*, *TREM1*, *TREML1*, *FCER1A*, *IL23R*, *IL24*, *IL15* and *LEAP2*). As previously mentioned, immune genes are over-represented in SDs (see Table 1 and Fig S20). Examples of genes varying in cattle relative to mouse include a cluster of β-defensin genes, which encode antimicrobial peptides, the anti-microbial cathelicidin genes [which show increased sequence diversity of the mature cathelicidin peptides (20)], changes in the numbers of interferon genes (21) and the number and organization of genes involved in adaptive immune responses in cattle compared to human and mouse (4). This extensive duplication and divergence of genes involved innate immunity may be because of the substantial load of microorganisms present in the rumen of cattle which increases the risk of opportunistic infections at mucosal surfaces and positive selection for the traits that enabled stronger and more diversified innate immune responses at these locations. Another possibility is that immunity may have been under selection due to the herd structure which can promote rapid disease transmission. Also, immune function-related duplicated genes have gained non-

immune functions e.g. *IFNT* (see above), and the C-class lysozyme genes, which are involved in microbial degradation in the rumen, a fermentative foregut (see below).

There has been substantial reorganization of gene families encoding proteins present in milk. One such rearrangement affecting milk composition involves the histatherin (*HSTN*) gene within the casein gene cluster on BTA6 (Fig. S21). In the cattle genome *HSTN* is juxtaposed to a regulatory element (*BCE*) important (22) for β-casein (*CSN2*) expression, and as a probable consequence *HSTN* is regulated like the casein genes during the lactation cycle. This rearrangement that led to the juxtaposition of *HSTN* next to the *BCE* is also the probable cause of deletion of one of the two copies of α-S2-like casein genes (*CSN1S2A*) present in other mammalian genomes (23). The biological implications of this change in casein gene copy number are not yet clear.

Additionally, the cattle serum amyloid A (*SAA*) gene cluster arose from both a laurasiatherian SD and a cattle-specific EBR, resulting in two mammary gland-expressed *SAA3*- like genes, *SAA3.1* and *SAA3.2* on BTA29, and an *SAA3*-like gene on BTA15 (Fig. S21). SAA3.2 has been shown to inhibit microbial growth (24) Two additional milk protein genes were associated with SDs: cathelicidin (*CATHL1*) and beta-2 microglobulin (*B2M*) - part of the neonatal Fc receptor (FcRn) that transfers IgG immunoglobulin across epithelial cells of many tissues including the gut and mammary gland (25,26). IgG is the predominant immunoglobulin in cow's milk compared to IgA in human milk (27), and unlike humans, which acquire passive immunity from the mother via placental transfer of immunoglobulins during pregnancy, calves acquire passive immunity via ingestion of IgG in milk (27). *B2M* is also redistributed in epithelial cells upon calving and it protects IgG from degradation (25). A genetic variant of *B2M* has negative effects on passive immune transfer (28), The additional copy of the gene encoding *B2M* may potentially be associated with the abundance of IgG in cows' milk and an increased capacity for uptake in the neonatal gut. Considering that the passive transfer of immunity to the calf is one of the important functions of milk, it is striking that lactation-related genes affected by genomic rearrangements encode immune-related proteins in milk.

Cattle metabolic pathways demonstrated a strong degree of conservation among the comprehensive set of genes involved in core mammalian metabolism (4) and permitted an examination of unique genetic events that may be related to ruminant-specific metabolic adaptations. However, among 1,032 genes examined from the human metabolic pathways, five were deleted or extensively diverged in cattle: *PLA2G4C* (phospholipase A2, group IVC), *FAAH2* (fatty acid amide hydrolase 2), *IDI2* (isopentenyl-diphosphate delta isomerase 2), *GSTT2* (glutathione S-transferase theta 2) and *TYMP* (thymidine phosphorylase), which may be adaptations that impact on fatty acid metabolism, the mevalonate pathway (synthesis of dolichols, vitamins, steroid hormones and cholesterol), detoxification, pyrimidine metabolism, respectively. Phylogenetic analysis shows that *PLA2G4C* was deleted ~87-97 Mya in the Laurasiatherian lineages (Fig. S22). Strikingly, ~20% of the sequences from two abomasum (last chamber of the cattle stomach) EST libraries (a total of 2,392 sequences) correspond to three C-type lysozyme genes. Lysozyme primarily functions in animals as an antibacterial protein suggesting they probably function in the abomasum (similar to the monogastric stomach) to degrade the cell walls of bacteria entering from the foregut (29). The cattle genome contains 10 C-type lysozyme genes (Table S14, Fig. S23) and EST evidence (Fig. S23) shows that six of the seven remaining C-type lysozyme genes are expressed primarily in the rumen and/or intestine suggesting additional roles for the encoded proteins in ruminant digestion.

In summary, the biological systems most impacted by changes in the number and organization of genes in the cattle lineage include reproduction, immunity, lactation, and digestion. We highlighted the evolutionary activity associated with chromosomal breakpoint regions and their propensity for promoting gene birth and rearrangement. These changes in the cattle lineage

probably reflect metabolic and immune adaptations due to microbial fermentation in the rumen, the herd environment and its influence on disease transmission, and the reproductive strategy of cattle. The cattle genome and associated resources will facilitate the identification of novel functions and regulatory systems of general importance in mammals and may provide an enabling tool for genetic improvement within the beef and dairy industries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The master accession for this WGS sequencing project is AAFC03000000. The individual WGS sequences are AAFC03000001-AAFC03131728, and the scaffold records are CM000177-CM000206 (chromosomes) and DS490632-DS495890 (unplaced scaffolds).

Funded by: the National Human Genome Research Institute (NHGRI U54 HG003273); the U.S. Department of Agriculture's Agricultural Research Service (USDA ARS Agreement No. 59-0790-3-196) and Cooperative State Research, Education, and Extension Service National Research Initiative (Grant No. 2004-35216-14163); the state of Texas; Genome Canada through Genome British Columbia; The Alberta Science and Research Authority; The Commonwealth Scientific and Industrial Research Organization of Australia (CSIRO); Agritech Investments Ltd., Dairy Insight, Inc. and AgResearch Ltd., all of New Zealand; the Research Council of Norway; the Kleberg Foundation; and the National, Texas and South Dakota Beef Check-off Funds.

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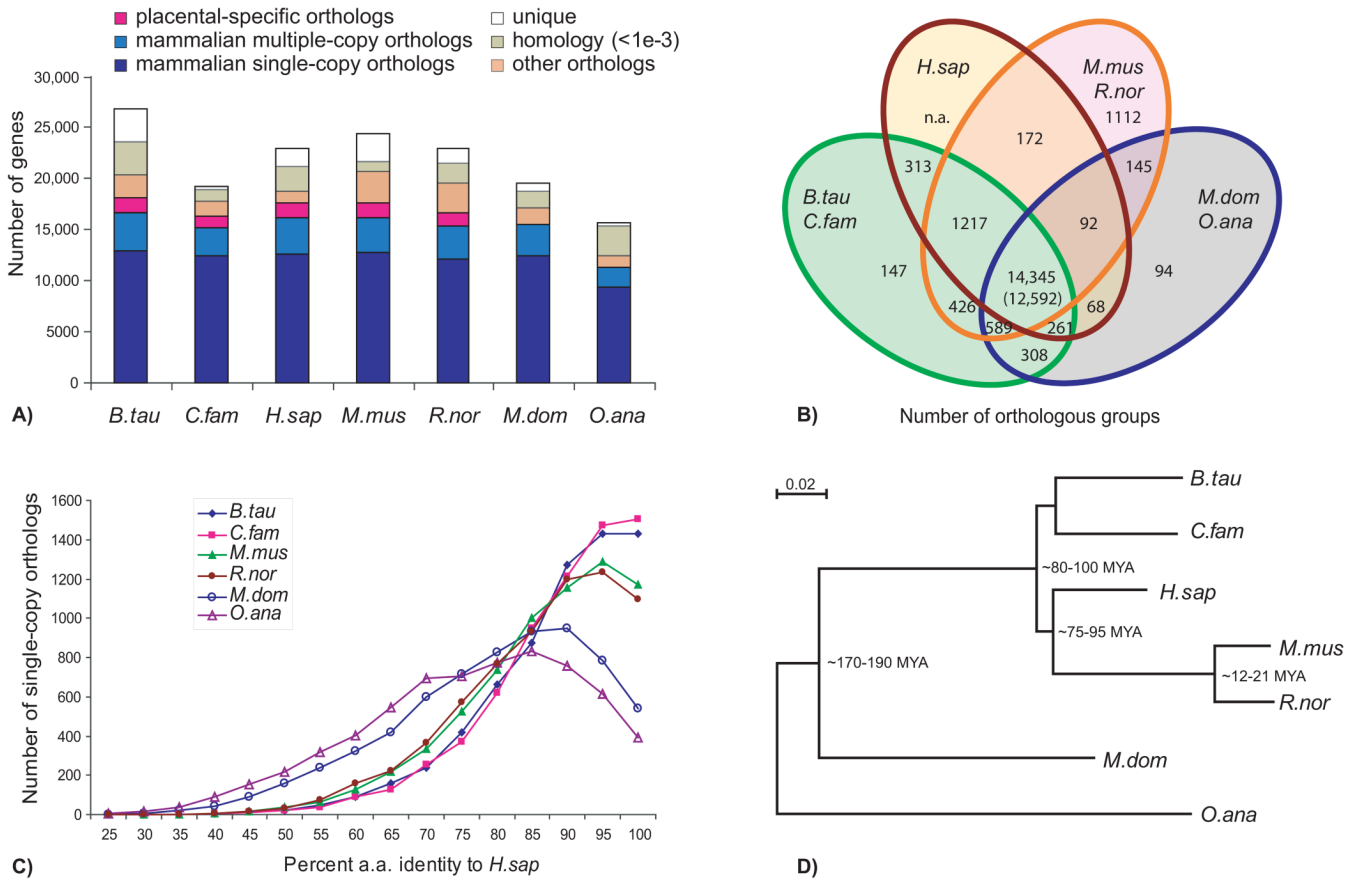

Fig. 1.

Protein orthology comparison among genomes of cattle, dog, human, mouse and rat (Bos taurus, Canis familiaris, Homo sapiens, Mus musculus, Rattus norvegicus, representing placental mammals), opossum (Monodelphis domestica; marsupial), and platypus (Ornithorhynchus anatinus; monotreme). (A) The majority of mammalian genes are orthologous, with over half preserved as single-copies (dark blue); a few thousand have species-specific duplications (blue); another few thousand have been lost in specific lineages (orange). We also show those lacking confident orthology assignment (green), and those that are apparently lineage specific [unique (white)]. Placental-specific orthologs are shown in pink. Single- or multiple-copy genes were defined on the basis of representatives in human, bovine or dog, mouse or rat, and opossum or platypus. (B) Venn diagram showing shared orthologous groups (duplicated genes were counted as one) between laurasiatherians (cattle and dog), human, rodents (mouse and rat), and non-placental mammals (opossum and platypus) on the basis of the presence of a representative gene in at least one of the grouped species (as in A). (C) Distribution of ortholog protein identities between human and the other species for a subset of strictly conserved single-copy orthologs. (D) A maximum likelihood phylogenetic tree using all single-copy orthologs supports the accepted phylogeny and quantifies the relative rates of molecular evolution expressed as the branch lengths.

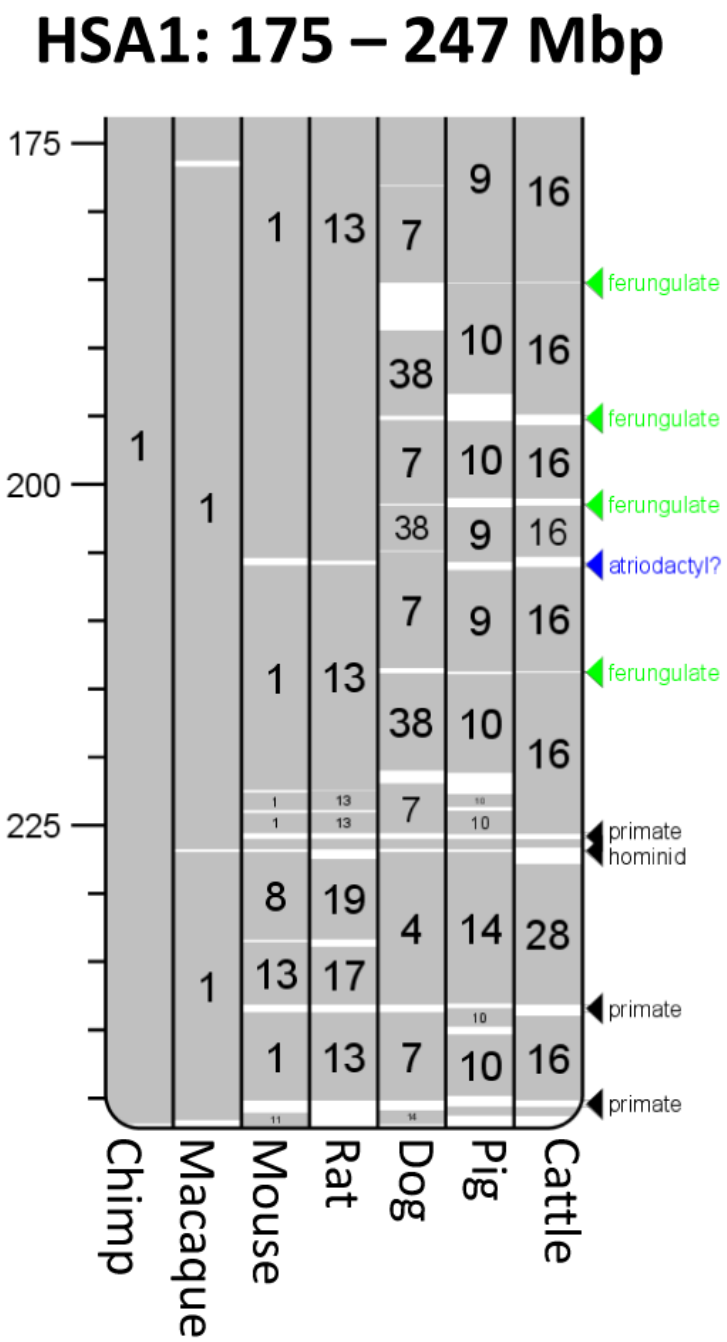

Fig. 2.

Examples of evolutionary breakpoint regions (EBRs). Ferungulate- artiodactyl- and primate-specific EBRs on HSA1 at 175-247 Mbp (other lineage-specific EBRs not shown). Homologous synteny blocks constructed for the macaque, chimp, cattle, dog, mouse, rat and pig genomes were used for pair-wise comparisons (4). White areas correspond to EBRs. Arrows to the right of the chromosome ideogram indicate positions of representative cattle-specific, artiodactyl-specific (specific to the chromosomes of pigs and cattle), ferungulate-specific (cattle, dog and pig), primate-specific (human, macaque, chimp), and hominoid-specific (human and chimp) rearrangements. Opossum is shown as an outgroup to the eutherian clade, which allows classification of ferungulate-specific EBRs.

Table 1

Changes in the number of genes in innate immune gene families

Gene Family	Bovine	Human	Murine
Cathelicidin	10	1	1
RNase	21	13	25
BPI-like	13	9	11
BPI/LBP	3	2	2
β-Defensin[1]	~106	39	52
Interferon subfamilies[2]			
IFNK	1	1	1
IFNE	1	1	1
IFNB	6	1	1
IFNA	13	13	14
IFNW	24	1	0
IFNT	3	0	0
IFNX[4]	3	0	0
IFNL	0	3	2
IFNZ	0	0	2
C-type Lysozyme	10	1	3
ULBP[3]	30	3	1

[1] Many of the β-defensin genes are present in unassigned scaffolds, i.e. they are not yet part of the current assembly. The exact number of genes is uncertain.

[2] Pseudogenes predicted on the basis of frame-shift mutations or stop codons within the first 100 amino acids of the coding sequence have been excluded from the table.

[3] (17)

[4] The IFNX genes represent a newly discovered subfamily of IFN and are so named for convenience.