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A Review

Organization and Comparative Analysis of the Genome of Ruminants and Canids – A Review

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Abstract

In the present day context, study of the genomic organization of any species of interest makes it easy to undertake studies on the comparative analyses of the genome. Chromosomal painting, cytogenetic and physical mapping along with transcriptomic analysis have greatly helped in evolutionary studies as well. This is further enhanced by the full genome sequencing. The present review deals with the genomic organization, sequencing and comparative studies involving different ruminant and canine species with a view to increase the depth of the knowledge of the readers regarding the understanding of their evolutionary process.

Keywords: Analysis, animals, comparative, domesticated, genome, poultry.

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Introduction

Knowledge of the genome organization of a species of interest is required for detailed genetic analyses, including the identification of genes causing hereditary diseases and comparative genomic studies. Genome organization has been traditionally inferred by taking two approaches *viz.,* cytogenetic mapping and genetic-linkage or physical mapping. Comparisons of G-banded chromosome patterns have been first used to infer homologies of whole chromosomes or sub regions between species and so also across mammalian orders (Yunis *et al.,* 1980; Nash and O'Brien, 1982; Dutrillaux and Couturier, 1983). Subsequently, gene mapping using somatic cell hybrids has lead to the confirmation that large tracts of mammalian genomes are remarkably conserved (Lalley *et al.,* 1978; O'Brien and Nash, 1982; O'Brien *et al.,* 1997a). This suggests that transferring information from species having gene-rich maps like human and mouse to the gene-poor developing maps of domestic animals may be feasible (O'Brien *et al.,* 1997b; O'Brien, 1991; O'Brien *et al.,* 1993). The pattern of genome conservation in mammals is bimodal and the pattern of gene rearrangement is slow which is evident from genome of mammals like cat, min, ferret, dolphin and human (O'Brien *et al.,* 1999; Cavagna *et al.,* 2000). On the contrary, in case of mouse and rat genome, the rate of gene rearrangement is high when compared to mammalian species (Stanyon *et al.,* 1999) or avian outgroup species like chicken (Burt *et al.,* 1999). This is evident from the fact that when several orthologous mRNA and protein sequence pairs from rats, mice and human have been studied, it has been found that the mammalian genes are evolving at a slow rate which ranges from 17-30 per cent (Makalowski and Boguski, 1998). Again, the concept of reciprocal genetic exchange through recombination is strengthened by the evidence for a GC-biased gene conversion process in mammals, and its consequences for genomic landscapes, molecular evolution and mammalian functional genomics (Duret and Galtier, 2009) as the GC (correlated with genomic features like repeat element distribution and methylation pattern) content turns out to vary continuously, and somewhat erratically, along chromosomes (Galtier *et al.,* 2001; Jabbari and Bernadi, 1998) and most remarkably, gene density (Mouchiroud *et al.,* 1991; Duret *et al.,* 1995). Using genome wide studies of EST and microarray data from human and mouse, the distribution of various subsets of alternatively spliced exons have been analyzed based on their inclusion level and evolutionary history versus increasing intron length. Alternative exons may be included in either a major or minor fraction of all transcripts, otherwise known as major-form and minor-form exons, respectively (Roy *et al.,* 2008). Again, another interesting fact involving the evolution of mammalian genome is the study of mobile elements that make up large portions of most mammalian genomes. The recent wealth of genomic sequencing data has been a particular boon to understanding the distribution and evolution of mobile elements which has been studied vividly in mouse (Waterston *et al.,* 2002). They are important from the point of view that they create genetic instability, not only through insertional mutation but also by contributing recombination substrates, both during and long after their insertion (Deninger *et al.,* 2003). Moreover, apart from GC-biasness, the gene conversion or recombinational repair can also be affected by mobile elements (Roy-Engel *et al.,* 2002). Among the mobile element, the role of retrotransposons in genome evolution is quiet noteworthy. There are numerous pairs of retrotransposons containing long clusters of G-to-A mutations that cannot be attributed to random mutagenesis. As DNA editing simultaneously generates a large number of mutations, each affected element begins its evolutionary trajectory from a unique starting point, thereby increasing the probability of developing a novel function. This fact suggests a potential mechanism for retrotransposon domestication in mammalian genome evolution (Carmi *et al.,* 2011). For understanding the mechanism of control of transcription, present algorithms are aimed at TSS prediction have proven unsatisfactory (Bajic *et al.,* 2004). Although many TSSs from mouse can be inferred from the 5' ends of full-length cDNAs and 5' ESTs, the depth of coverage is limited. So, in order to increase the depth of coverage, systematic 5'-end analysis of the mouse and human transcriptome using the cap analysis of gene expression (CAGE) approach has been carried out that redefines basic promoter features and helps in understanding the diversity, evolutionary conservation and dynamic regulation of mammalian promoters on a genome-wide scale (Carninci *et al.,* 2007).

Structural Organization of the Genome of Large Ruminants

Bovine Genome

The genome of the cattle has been sequenced to about seven fold coverage in order to understand the biology and evolution of ruminants. The genome as such contains a minimum of 22,000 genes, with a core set of 14,345 orthologs shared among seven mammalian species of which 1217 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 a resource for understanding mammalian evolution. The genome also bears transposable element classes like those of other mammals in addition to large number of ruminant-specific repeats. One of the long interspersed nuclear element (LINE) in the cattle genome is Bov-B which lacks a functional open reading frame (ORF) that suggests its inactivity. Moreover, Bov-b repeats with intact ORF have been identified in the genome and their phylogeny indicates that some are still actively expanding and evolving. Mapping of the chromosomal segments of high and low density ancient repeat content L2/ MIR, which is a LINE/SINE pair and Bov-B, along with most recent repeats like Bov-B/ART2A (*i,e.* Bov-B-derived SINE pair) reveals that the genome consists of ancient regions enriched for L2/MIR and recent regions enriched for Bov-B/ART2A. Exclusion of Bov-B/ART2A from contiguous blocks of ancient repeats suggest that evolution of the ruminant genome or more specifically cattle genome experiences invasions of new repeats into regions lacking ancient repeats (Elsik *et al.,* 2009). The protein size heterogeneity is governed by the alternative splicing of transcripts and this in turn is controlled by the presence of internal deletions in cDNA clones for bovine tau (Himmler, 1989).

Copy Number Variation (CNV) in Bovine Genome

To assess the bovine CNV landscape, the genomic DNA of various bovine samples from dairy cattle breeds, mainly belonging to the Holsteins and Red Danish have been analyzed (Fadista *et al.,* 2010). Assessment of copy number variation between samples has been done using a set of Nimblegen HD2 CGH arrays. This array mainly tile across the genome with approximately 6.3 million unique oligo probes with a mean probe spacing of 420 base pairs, using the latest genome assembly, known as the BT4. It has been found that the substantial number of CNVs in the cattle genome are smaller than 1.5 kilo base in size and there exists a relation between the segmental duplication (SD) and CNVs in the cattle genome. SDs are important elements in the formation of CNVs via non-allelic homologous recombination (NAHR) throughout the mammalian lineage (Lupski and Stankiewicz, 2005; Shaw and Lupski, 2004; Hastings *et al.,* 2009).

Linkage Map of the Bovine Genome

As per as the linkage map of the bovine genome is concerned, there are over 200 DNA polymorphisms in cattle which have been genotyped that have been genotyped in cattle families which comprise of more than 250 individuals in full sibling pedigrees. There are also several loci that are linked that are linked to one other locus. There exists less than 50 cM difference in the male and female genetic maps The conserved loci in such map show many differences which are consistent with the patterns of karyotypic evolution found in the rodents, primates and artiodactyls (Barendse *et al.,* 1994). As far as the linkage disequilibrium map is concerned, cattle and human share a high similarity in linkage disequilibrium (LD) and haplotype block structure between dairy breeds that make them non-differentiable and more than 30,000 uniformly distributed SNPs are necessary to construct a complete genome linkage disequilibrium map in *Bos taurus* breeds and 58,000 SNPs are necessary to characterize the haplotype block structure across the complete cattle genome (Villa-Angulo *et al.,* 2009).

Buffalo Genome Sequencing and Its Significance

Due to the agricultural significance, Mediterranean buffalo are usually selected as the animals to be sequenced and there is a need to supplement the reference sequence with low density coverage from reduced representation libraries. This helps in identifying SNPs for the development of

genotyping panel. Moreover, the sequencing of the wild type buffaloes apart from the domestic water buffaloes ultimately helps in evolutionary analysis of genome structure to define those features that are associated with domestication and selection for production traits. Moreover, the comparison of the buffalo genome sequence with that of the other ruminant and non-ruminant species ultimately helps in genomic evolution and divergence between mono-gastric and ruminant species. Such analysis ultimately helps in identifying genomic functions associated with the development of rumen, which ultimately contributes to a more informed selection of ruminant production traits like identification of the genes involved in variation in the rumen environment and hence the colonisation of micro-flora that are necessary for the digestive process. The wider comparison within and among classes of animals ultimately helps in contributing to the annotation of the genome and the understanding of conserved regions, specialised variation in the genome structure and important regulatory elements. For sequencing of the buffalo genome, Illumina sequencing technology, either on a GAIIX or HiSeq 2000 basis with a target of at least 60X coverage is needed. Mate pair libraries can be produced with short insert length of around 200-1 Mb that can be used to construct sequence contigs (Report of Williams, 2010). Moreover, large insert libraries are needed to be constructed to support the assembly of contigs into scaffolds. A radiation hybrid map also exists for the water buffalo which can be used to verify the initial assembly and further order and orientate contigs wherever necessary. Fluorescent in situ hybridization reveals altogether 309 loci which cover all chromosome and chromosome regions of the river buffalo genome (Iannuzzi L and Di Meo, 2009). Whole genome sequencing of the buffalo genome reveals a total of 66,935 nucleotide sequences that have been submitted in the GenBank database and 64,212 whole genome shotgun sequences, while the rest includes 974 mitochondrial genomic sequences and 1,748 nuclear gene sequences. By the use of Illumina GAIIx technology, approximately 40 Gb of sequences for water buffalo can be sequenced. Genomic sequencing in water buffalo also involves satellite, minisatellite and microsatellite sequencing. There are two types of satellites in water buffalo which has been revealed by sequencing analysis by digestion with restriction endonucleases BamHI and StuI viz., one with 1400 bp tandem repeat unit and the other with 700 bp tandem repeat unit (Tanaka *et al.*, 1999). Furthermore, the hybridization signals with the satellite I DNA on the acrocentric autosomes and X chromosome were much stronger than those on the biarmed autosomes and Y chromosome. However, the hybridization signals with buffalo satellite II DNA was almost the same over all the chromosomes, including the Y chromosome (Pathak *et al.*, 2006).

Cytogenetic studies show that river buffalo have 25 chromosome pairs while swamp buffalo have 24 pairs. These subspecies differ by one chromosome, a fusion between river buffalo (BBU) chromosome 4 and 9, which is comparable to swamp buffalo chromosome 1 and all chromosomes and chromosome arms are preserved between these two subspecies. Crosses between the two subspecies are fertile but hybrids possess 49 chromosomes, which is thought to lead to lower reproductive values in subsequent matings. River buffalo have 5 biarmed chromosome pairs and all others, including the sex chromosomes are acrocentric. Several studies have shown that river buffalo and domestic cattle, both members of the Bovidae family, are closely related. Indeed, both share chromosome banding and gene order homology, and have been cytogenetically characterized (Amaral, 2008).

Special Reference of Mitochondrial and Nuclear Genome Sequencing of Water Buffalo

Similar to other mammals, each mitochondrial mtDNA molecule in water buffalo harbors genetic material that encodes 37 genes, out of which 13 are for proteins and 22 for transfer RNA (tRNA) and one each for the small and large subunits of ribosomal RNA (rRNA). Among 13 coding mitochondrial genes in water buffalo, the length of the coding sequences of four genes - *COX1*, *ND4L*, *ND4* and *ND6* are identical to those in *Bison bison*. The overlapping size varies from 1 bp to 40 bp. Certainly some genes are also distanced from each other, but the distance gap ranges only from 1 bp to 4 bp in length. In addition to these complete mitochondrial genome sequences of water buffalo, the D-loop and CYTB regions have also been investigated and the D-loop is having 784 entries and CYTB region has 162 entries in the GenBank database. There are 277 functional genes in the nucleus out of which 29 have been well investigated. Some of the sequences of genes are

related to growth and milk production, such as lectin like receptor-1, leptin, growth hormone receptor, lactalbumin alpha, casein beta, growth hormone 1, insulin like growth factor 1, casein kappa and myostatin. The buffalo nuclear genes are also useful for studying the disease resistance properties in this species and the noteworthy ones are lactoferrin, CD14 molecule and toll like receptor 4 coding genes (Michelizzi *et al.*, 2010).

Genome Sequencing of Small Ruminants

The virtual sheep genome is the sequence of the bovine genome reorganised into the structure of the sheep genome based on syntenic blocks which has been defined using sheep BACs. In the real sheep genome, the bovine sequence in the virtual sheep genome is replaced with actual sheep sequence, where no sheep sequence is available.

The real sheep genome sequence assembly covers approximately 43 per cent of the actual total genome sequence and as only information mappable by sequence alignment is displayed many sheep markers, BAC-end sequences are not mappable and are not displayed. In contrast, the virtual sheep genome contains markers, BAC-end sequences etc. mapped using comparative approaches and therefore is much more comprehensive in its coverage. Virtual sheep genome is used for maximum information about a region and real sheep genome assembly are usually used for real sheep sequence. As both are based on the same comparative framework the orders of features should be the same and are heavily biased towards synteny with the cattle genome. The sheep genome has been virtually mapped with the aid of data from cows, dogs, and humans which has been accepted internationally. A virtual map has been created taking into consideration 98 per cent of the sheep genome by comparing small, known portions to the well-mapped genomes of related mammals. The map can help breeders to quickly identify animals with good wool quality, parasite resistance or other favourable qualities. It has been found that most of the genes of sheep are similar to that of cattle and certain carnivores like dog, but the only difference is in the order of their arrangement. Around 1,170 sections of sheep genome are similar to that of human, dog and cattle genome which has been done by the mapping of the BAC-end sequences. Efforts have also been made to break up the sheep genome by using restriction enzymes which cut DNA at specific places, which has generated about 200,000 DNA fragments of various lengths which are then inserted into bacteria to create the BAC-end sequences which have been mentioned earlier for their use in mapping the genome of sheep (Lester, 2006). Skim sequencing of the sheep genome assembly has been done which has given rise to the evidence that 82 per cent of the ovine genome constitutes non repetitive fraction. This assembly also identifies 277,000 high quality single nucleotide polymorphisms and additional reduced representational sequencing using Illumina's genome analyzer. Such study has been conducted involving various sheep breeds. Further, 76,000 high quality SNPs have been generated out of which 59,94 have been selected for inclusion on a 50K+Illumina Infinium iSelect (tm) SNP BeadChip, giving an average spacing of 46 kb across the whole genome (http://www.sheephapmap.org).

For goat genome sequencing, whole genome shotgun sequencing technology is usually selected based on different categories of paired-end sequencing libraries with various insert sizes of 180-20,000 base pairs. In total, approximately 200 Gb of useable sequences are used to assemble the short reads using SOAPdenovo. About 13,958 orthologue genes specific for Capra hircus have been identified comparing with cattle and other nor-ruminant mammals (Zhang *et al.*, 2011). Assembly of the goat genome is now underway in the Beijing Genome Institute (BGI), where it has been found that the average depth of sequencing is around 60X and optical mapping has been used to increase the scaffold size. Collection of samples for resequencing from around the world is now underway and once completed may provide information on domestication events (http://www.toulouse.infra.fr).

Genomic Organization and Mapping of the Genome of Dog and Comparative Study with that of Other Wild Canids

The dog genome organization has been extensively studied in the last two decades. The most important achievements are the well-developed marker genome maps, including over 3200 marker loci and a survey of the DNA genome sequence. This knowledge, along with the most advanced map of the human genome, turned out to be very useful in comparative genomic studies (Switonski *et al.*, 2004). The diploid chromosome

number of the dog is 78 and all the autosomes are acrocentric, while the sex chromosomes are biarmed. The X chromosome is submetacentric and the Y chromosome is metacentric. A partial standard karyotype, including 21 biggest autosomes and the sex chromosomes has been established by using the G-banding technique (Switonski *et al.,* 1996). A comprehensive map, also called an integrated map is established by gathering data obtained by different mapping approaches viz., the analysis of radiation- hybrid panels, and linkage studies. Mapping of 600 markers by the radiation hybrid approach and combined with data on linkage mapping of 341 markers has been done (Werner *et al.,* 1999; Mellersh *et al.,* 2000). Finally, the integrated map has been found to be composed of 724 markers.

On the one hand, the study of genomic organization in dog has promoted the development of marker genome maps of other species of the family Canidae that include red fox, arctic fox and Chinese raccoon dog as well as studies on the evolution of their karyotype. But the most important approach is the comparative analysis of human and canine hereditary diseases. At present, causative gene mutations are known for 30 canine hereditary diseases. A majority of them have human counterparts with similar clinical and molecular features. Advancement has been made in the studies on identification of genes having a major impact on some multifactorial diseases like hip dysplasia, epilepsy and cancers (multifocal renal cystadenocarcinoma and nodular dermatofibrosis. The above-mentioned examples prove a very important model role of the dog in studies of human genetic diseases. The identification of gene mutations responsible for hereditary diseases has a substantial impact on breeding strategy in the dog.

Comparative Chromosome Mapping Studies of Domestic and Wild Canids

The comparative chromosome painting (Zoo-FISH) is a well-known method to visualize homologies between genomes of different species. This technique facilitates the identification of the conserved chromosome segments in the compared karyotypes and has been applied to compare the dog genome with those of the red fox (Yang *et al.,* 1999), arctic fox (Graphodatsky *et al.,* 2000), cat (Yang *et al.,* 2000), Japanese raccoon dog (Graphodatsky *et al.,* 2001), and Chinese raccoon dog (Nie *et al.,* 2003) and a number of conserved chromosome segments have been identified viz., 68 in the cat, 43 in the red fox, 42 in the arctic fox and 41 in the raccoon dog. The close relationship of the fox and dog enables canine genomic tools to be utilized in developing a fox meiotic map and mapping behavioral traits in the fox (Kukekova *et al.,* 2004).

The advanced canine linkage-radiation integrated map brings new insight into the evolutionary conservation of chromosome segments in the dog and human genomes. The comparison of chromosome locations of 229 RH mapped genes, whose location in the human genome is known, has revealed the presence of 65 conserved segments (Breen *et al.,* 2001). Moreover, 85 dog/human conserved fragments have been detected, including 3270 RH markers (Guyon *et al.,* 2003). Moreover, studies with the use of locus-specific probes are required to detect intrachromosomal mutations like inversions, duplications or deletions. Such an approach has been applied for the dog, arctic fox and Chinese raccoon dog genomes. A comparative analysis of FISH-mapped markers has facilitated the identification of inversion events that has taken place in the course of karyotype evolution of canids (Rogalska-Niznik *et al.,* 2003).

In order to determine the possible differences between mtDNAs in carnivores, two rRNA and 13 protein-coding genes from the cat, dog and seal have been compared. The combined molecular differences in two rRNA genes as well as in the inferred amino acid sequences of the mitochondrial 13 protein-coding genes suggest that there is a closer relationship between the dog and the seal than there is between either of these species and the cat. Based on the molecular differences of the mtDNA, the evolutionary divergence between the cat, dog and the seal has been dated to approximately 50 +- 4 million years ago. The degree of difference between carnivore mt DNAs has varied according to the individual protein-coding gene applied, showing that the evolutionary relationships of distantly related species should be presented in an extended study based on ample sequence data like complete mt DNA molecules (Kim *et al.,* 1998).

Conclusion

Comparative genome analysis in mammals has revealed complex differences in the pattern of

change in different species of ruminants and canids. With the advent of development and refinement of comparative maps, combining chromosomal painting, mapping and sequencing approaches, it is possible to estimate lineage-specific rates of chromosomal change and to make more accurate reconstruction of ancestral genomes. With such efforts, undoubtedly, a large amount of fascinating insight and function can finally be gained concerning the organization and distribution of genes within chromosomes of such animals and will make us understand the forces driving genomic evolution.

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