Current Status of Comparative Mapping in Livestock

J. H. Lee*, C. Moran[1] and C. S. Park

Division of Animal Science and Resources, Research Center for Transgenic Cloned Pigs
Chungnam National University, Daejeon 305-764, Korea

ABSTRACT : Comparative maps, representing chromosomal locations of homologous genes in different species, are useful sources of information for identifying candidate disease genes and genes determining complex traits. They facilitate gene mapping and linkage prediction in other species, and provide information on genome organization and evolution. Here, the current gene mapping and comparative mapping status of the major livestock species are presented. Two techniques were widely used in comparative mapping: FISH (Fluorescence *In Situ* Hybridization) and PCR-based mapping using somatic cell hybrid (SCH) or radiation hybrid (RH) panels. New techniques, using, for example, ESTs (Expressed Sequence Tags) or CASTS (Comparatively Anchored Sequence Tagged Sites), also have been developed as useful tools for analyzing comparative genome organization in livestock species, further enabling accurate transfer of valuable information from one species to another. *(Asian-Aust. J. Anim. Sci. 2003. Vol 16, No. 10 : 1411-1420)*

INTRODUCTION

Progress in cytogenetics and genomics in livestock species gains great benefit from the human genome project providing we can recognize conserved genomic blocks between different species including the major domestic animal species. The conservation of genomic organization in different mammals has long been postulated, ever since Haldane's review of color-determining genes in several species (Haldane, 1927). More recently, Ohno (1967) recognized the conservation of X chromosomes among eutherians. Graves and Watson (1991) showed that even marsupials, and monotremes share a highly conserved region of the X chromosome, represented in human chromosome Xq. Even though mammalian divergences began approximately 70 million years ago, vertebrate species presumably share most of their genes, even among distantly related classes like birds and some fish species (Andersson et al., 1996). Comparative genome mapping sets out systematically to recognize conserved synteny (defined as the presence of genes on a single chromosomal segment) between species. For example chicken chromosome 13 exhibits conserved synteny with human chromosome 5 (HSA5) (Buitenhuis et al., 2002) and zebrafish (*Danio rerio*) linkage group 9 is closely homologous to the long arm of HSA2 (Postlethwait et al., 1998). On the assumption, justified by comparative maps, that relatively large chromosomal segments are conserved among species of mammals, it is possible to deduce the

* Corresponding Author: J. H. Lee. Tel: +82-42-821-5779, Fax: +82-42-825-9754, E-mail: junheon@cnu.ac.kr
[1] Centre for Advanced Technologies in Animal Genetics and Reproduction, Faculty of Veterinary Science, University of Sydney, NSW 2006, Australia.

position of a gene in one species by knowledge of its position in another (Eppig and Nadeau, 1995; Gillois, 1991). Because of this, comparative mapping has emerged as a research area with important practical implications (Andersson et al., 1996; Wakefield and Graves, 1996).

Comparing two well-mapped species, human and mouse, there are at least 181 different conserved syntenies (DeBry and Seldin, 1996). This high number of conserved syntenies between the two species has mainly come from rapid evolution in the rodents (Andersson et al., 1996). The large number of breakpoints and internal rearrangements between human and mouse makes comparative mapping between these species more difficult compared with contrasts between humans and the major mapped mammalian livestock species (eg. pig, cattle, sheep).

In the present review, first a brief overview of the current status of gene mapping in livestock species is presented with accessible Internet addresses, followed by a review of large-scale and small-scale comparisons between species. Finally, the application of comparative maps and future prospects are briefly discussed.

CURRENT STATUS OF GENETIC MAPS

The new era of gene mapping of livestock species started in the past ten years and is still growing dramatically. Two quite different mapping methods, namely linkage mapping and physical mapping, must be distinguished. A linkage map is based on the recombination frequency (r) between genes or markers detectable among the offspring of parents with distinguishable alleles at two or more loci. On the other hand, a physical map does not require variants or recombination, but assigns loci to chromosomal positions either by *in situ* hybridization or by using somatic cell hybrid panels. The most widely used markers in linkage

Table 1. Internet URL addresses for comparative or livestock species-specific mapping databases

Species	URL addresses	Database names and institutes
Pig, cattle, sheep	http://www.marc.usda.gov/genome/genome.html	USDA Meat Animal Research Center, Clay Center, Nebraska, USA
Cattle, goat, horse, buffalo, rainbow trout, comparative mapping	http://locus.jouy.inra.fr/	Institut National de la Researche Agronomique, Jouy-en-Josas, Laboratorie de genetique biochemique, France
Pig	http://ws4.nias-k.affrc.go.jp/agp/index.html	Agriculture, Forestry and Fisheries Research Council, Japan
Pig, chicken, horse, cat, turkey, sheep, cattle, tilapia, deer, salmon	http://www.thearkdb.org/	Livestock Animal Genome Database, Roslin Institute, Scotland, UK
Cattle, comparative mapping	http://www.cgd.csiro.au/	Cattle Genome Database, CSIRO, Australia
Cattle, comparative mapping	http://bos.cvm.tamu.edu/bovgbase.html	Bovine Genome Database, Texas A & M University, USA
Sheep	http://rubens.its.unimelb.edu.au/~JILLM/jill.htm	Centre for Animal Biotechnology (CAB), University of Melbourne, Australia
Comparative mapping	http://www2.bioch.ox.ac.uk/~jhe/	MedVet, University of Oxford, UK
Vertebrate animal species	http://www.angis.org.au/Databases/BIRX/omia/	OMIA (Online Mendelian Inheritance in Animals), University of Sydney, Australia
Mouse, comparative mapping	http://www.informatics.jax.org/	MGI (Mouse Genome Informatics), The Jackson Laboratory, Bar Harbor, USA

maps are anonymous DNA sequences, usually microsatellite markers (also called Type II markers), which are tandem repeat sequences widely spread throughout the genome. For example, there are over 2,500 mapped loci in pigs, but only a quarter of them are functional genes (also called Type I markers). Even though microsatellites have the great advantage of high level of polymorphisms, their use in comparisons between different species is minimal because microsatellites only very rarely are involved in encoding proteins and thus are not strongly conserved or easily recognized between widely different species. Therefore, this article mainly deals with the mapping of functional genes rather than using non-functional DNA markers. It provides a brief summary of the current mapping status in the major livestock species, mainly dealing with conserved type I markers and mapping tools. Further details are available from the addresses listed in Table 1.

Two major methods are currently used for physically finding map locations. The use of somatic cell hybrid (SCH) or radiation hybrid (RH) panels is one of them. When cells from two species are fused, chromosomes from one of the donor species are progressively and randomly lost. A set of cell hybrid clones with different chromosome combinations constitutes a somatic cell hybrid panel. The chromosomal location of a gene can be deduced by conventional PCR analysis of the panel. In a radiation hybrid, the chromosomes from the species of interest are irradiated. As a result, small fragments, rather than entire chromosomes, are randomly lost or retained. Consequently the mapping resolution is much higher, being determined by the size of the fragments. Since higher doses of radiation

generate smaller chromosomal fragments, the resolution increases with radiation dose. The second physical mapping method is FISH which involves the use of specifically labelled DNA fragments, called probes, for hybridization on metaphase spreads of chromosomes. This technique has greatly improved with the progress of chemical reagents to detect positive signals, but its sensitivity is still limited by the size of the probe.

Pigs

Pigs are one of the best-mapped animal species. They not only have a smaller number of chromosomes compared with cattle, sheep and chicken, but also are physiologically similar to humans and thus their biomedical relevance has further encouraged genetic studies. About 800 type I loci are mapped in pig suitable for making comparison between species (Pigbase: http://www.thearkdb.org/browser?species =pig). Pig-rodent somatic-cell-hybrid panels are widely used to physically map genes at low resolution in pigs (Yerle et al., 1996). The PiGMaP (Archibald et al., 1995) and USDA (Rohrer et al., 1996) reference populations have also enabled linkage mapping. Very recently, new reference populations were made in pigs, even in Asian countries, for identifying chromosomal regions that have effect on quantitative traits (Su et al., 2002, Lee et al., 2003). Recently a 7,000-rad radiation hybrid panel has been made publicly available for mapping in pigs. The great advantage of this radiation hybrid panel is that the resolution of the radiation hybrid map is 18 times higher than that obtained by linkage analysis with a theoretical resolution of 145 kb (Yerle et al., 1998; Hawken et al., 1999). Very recently, a 12,000-rad radiation hybrid panel has been constructed with two to three times higher resolution than the 7,000-rad

radiation hybrid panel enabling construction of an even higher resolution map (Yerle et al., 2002).

Cattle

About 700 type I loci have been mapped in cattle (http://www.thearkdb.org/browser?species=cow) mostly using somatic cell hybrid panels and FISH. For linkage mapping, three different reference populations are currently used, namely the International Bovine Reference Family Panel (IBRP) (Barendse et al., 1997), the Meat Animal Research Center (MARC) reference population (Kappes et al., 1997), and the Illinois reference/resource families (IRRF) (Ma et al., 1996).

A cattle 5,000-rad radiation hybrid panel was the first developed in livestock species (Womack et al., 1997). When the BTA19 radiation hybrid map was compared with human chromosome 17 cytogenetic and radiation hybrid maps, rearrangements of linear order were revealed for homologous genes on these two chromosomes that were not apparent using lower resolution methods of mapping. Thus radiation hybrids, with their higher resolution compared to other mapping tools, are potentially powerful resources for recognizing orders in comparative maps (Yang et al., 1998). Recently, a whole-genome comparative map between human and cattle was constructed using radiation hybrid mapping of ESTs and unmapped cattle genes and a bioinformatics approach called COMPASS (comparative mapping by annotation and sequence similarity) for targeting homologous regions. As a result, 768 genes and 319 microsatellites were located on the bovine radiation hybrid map and revealed over 105 conserved chromosomal segments between the human and bovine genomes (Band et al., 2000; Rebeiz and Lewin, 2000). Recently, a higher resolution 12,000-rad radiation hybrid panel was made available for public use for fine mapping complex disease genes and elucidating mammalian chromosome phylogeny (Rexroad et al., 2000).

Sheep

The first linkage map of sheep was published in 1995 (Crawford et al., 1995) using the AgResearch International Mapping Flock (IMF) and contained 246 markers of which 33 were functional genes. Subsequently the number of mapped loci has dramatically increased. Later, a second-generation linkage map was published, comprising 512 loci with an average spacing of 6 cM (de Gortari et al., 1998). Most recently, the third generation linkage map was established with 1,093 markers representing 1,062 unique loci (941 anonymous loci, 121 genes) and spanning 3,500 cM (sex-averaged) for the autosomes and 132 cM (female) on the X chromosome. There is an average spacing of 3.4 cM between autosomal loci and 8.3 cM between highly polymorphic autosomal loci (Maddox et al., 2001). The total number of physically mapped type I loci is more than

300 at the time of writing (SheepBase: http://www.thearkdb.org/browser?species=sheep). Two somatic cell hybrid panels have been widely used for physical mapping in sheep (Saidi-Mehtar et al., 1979; Burkin et al., 1991). Very recently, funding has been provided for making a sheep radiation hybrid panel (Personal Communication: Prof. N. E. Cockett, Utha State Univ., USA).

Chicken

Genome studies of birds have mostly concentrated on the domestic chicken (*Gallus gallus*) because of its economic importance. Even though the first linkage map of the chicken was published in 1936 (Hutt, 1936), progress has been slow. Physical mapping in chickens has been restricted to the large macrochromosomes because of the impossibility of distinguishing between the numerous microchromosomes. Recent international collaboration to map the chicken genome has used three different mapping reference populations (East Lansing in the United States, Compton in the United Kingdom and Wageningen in the Netherlands) and approximately 600 functional genes and over 1,500 microsatellite or AFLP (amplified fragment length polymorphism) markers have been mapped (Chickmap: http://www.ri.bbsrc.ac.kr/chickmap/). Very recently, a Japanese group has developed a new resource population, called the Kobe University (KU) resource family, primarily for identifying the chromosomal region of the muscular dystrophy gene in chicken (Lee at al., 2002). Also, a lot of effort has been put into comparing orthologous genes between human and chicken for studying genome evolution (Crooijmans et al., 2001; Smith et al., 2002).

INTERNET LIVESTOCK COMPARATIVE MAPPING RESOURCES

Progress in information technology has provided access to genomic information in databases on the Internet. There are several public databases for comparative mapping (Table 1). The most comprehensive is the mammalian homology database, located at the Mouse Genome Informatics (MGI) site. This database is updated regularly and enables searches for homologous genes between two or more mammalian species with variable search options including gene names, chromosome numbers and even GenBank accession numbers. Databases have been developed in Scotland, Japan, and the United States with a focus on specific species. An excellent comparative mapping home page for the pig is hosted by INRA in France and provides graphic comparisons between human and pig maps based on bi-directional chromosomal painting and somatic cell hybrid mapping. Since the whole human genome sequence is now in the public domain, and genome sequencing is commencing for domestic animals,
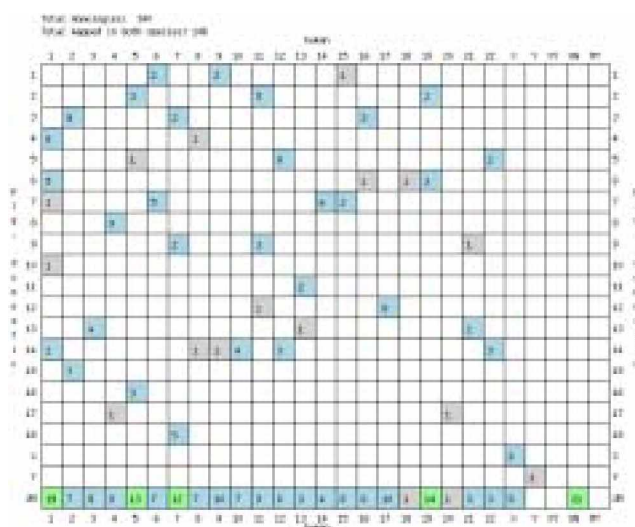
Figure 1. Example of the initial stage of comparative mapping between human and pig using an Oxford grid (Edwards, 1991). Each cell in this Oxford grid represents a comparison of a human and a pig chromosome. The number of homologies appears inside each cell. This grid recognizes 46 conserved syntenies between human and pig.

comparative mapping in the future will rapidly change to comparative alignment of human and livestock genome sequences.

LARGE-SCALE CHROMOSOME-WIDE COMPARISONS

Oxford grid

An early attempt at comparing the positions of orthologous genes between two species was the Oxford grid (Edwards, 1991). An example can be viewed at the Mouse Genome Informatics (MGI) database. Even though the comparisons are presented in the context of the chromosome numbers in the two species, they quickly home in on the conserved chromosomal segments between two species. An example of an Oxford grid between human and pig is shown in Figure 1. MedVet, a database hosted by the Department of Biochemistry, University of Oxford, UK (Table 1), systematically presents Oxford grids for many species for which data are available.

Comparative chromosomal painting (Zoo-FISH)

A fragment of DNA of interest can be radioactively or fluorescently labelled and allowed to hybridize to metaphase chromosome spreads. The development of fluorescent *in situ* hybridization (FISH) has almost replaced the use of radiolabelled probes. The sensitivity of detection by FISH is dependent upon the probe size and type of tag used in labeling the probe (Gillois, 1991). The great advantage of FISH compared with radioactive *in situ*

hybridization (RISH) is that not only is it safer, but also multicolor analysis is amenable to detection of different loci on the same metaphase spreads using differently colored dyes (Trask, 1991a; Trask, 1991b). Chromosome painting is a form of FISH using chromosome specific libraries as probes. It was first used to elucidate karyotype rearrangements in primate evolution (Jauch et al., 1992) using human chromosome specific libraries. It is called Zoo-FISH (Zoo indicates between species) when it is used to detect conserved chromosomal segments between species and provides a rapid low resolution comparative map between species (Scherthan et al., 1994).

Until recently, most Zoo-FISH studies used human chromosome-specific libraries mainly because of their easy availability. Zoo-FISH using human chromosome specific painting probes (CSPPs) has been applied in various economically important livestock species such as cattle (Hayes, 1995; Solonas-Toldo et al., 1995; Chowdhary et al., 1996), pig (Rettenberger et al., 1995; Fronicke et al., 1996; Goureau et al., 1996; Milan et al., 1996; Chaudhary et al., 1998), and sheep (Chowdhary et al., 1996; Iannuzzi et al., 1999). These studies have shown that there are three different types of synteny conservation. Firstly, whole chromosomes may be conserved with only one chromosome in the target species lighting up when probed with a single chromosome from the query species. Secondly, large chromosomal blocks may be conserved, with sections of two or three chromosomes showing hybridization in the target species. Thirdly, only relatively small neighboring segment combinations may be conserved and signal may be seen from several chromosomes (Chowdhary et al., 1998). There are now good Zoo-FISH comparisons, often bi-directional, between human and major domestic animal species (pig, cattle and sheep). Over the past few years, data on comparative chromosome painting has expanded dramatically, even among domestic animal species (for review, see Chowdhary and Raudsepp, 2001).

The comparative status of chromosomes of humans and three livestock species identified by Oxford grid analysis and Zoo-FISH is summarized in Table 2. The data indicate that most of the homologous chromosomal relationships identified by Zoo-FISH were also detected by Oxford grid analysis. However some of the chromosomal relationships identified by Oxford grid were not detected by Zoo-FISH. This confirms the limitation of Zoo-FISH for detecting intrachromosomal rearrangements or small homologous segments as discussed by Chowdhary and Raudsepp (2001).

SMALL-SCALE: SEQUENCE-BASED COMPARISONS

Across-species PCR amplification

A large amount of sequence from many species is lodged in DNA databases and software for retrieving and

Table 2. Comparative status of human and major livestock species (cattle, pig, sheep) chromosomes as identified by Oxford grid and Zoo-FISH*

Human chrom.	Cattle		Pig		Sheep	
	Oxford grid	Zoo-FISH	Oxford grid	Zoo-FISH	Oxford grid	Zoo-FISH
1	2, 3, 6, 16, 28	2, 3, 6	4, 6, 7, 10, 14	4, 6, 9, 10	1, 2, 12	1, 2, 12
2	2, 11	2, 11	3, 15	3, 15	2, 3	2, 3
3	1, 22	1, 22	13	13	1, 19	1, 19
4	4, 6, 17, 27	6, 17, 24	8, 17	8	6, 17, 26	6, 17
5	1, 7, 10, 20	7, 20	2, 5, 16	2, 16	5, 7, 16	5, 16
6	9, 23	9, 23	1, 7	1, 7	8	8, 20
7	4, 8, 25	4, 29	3, 9, 18	9, 18	4, 24	4, 24
8	8, 14, 27	8, 14, 27	4, 14	4, 14, 15	2, 9	9, 26
9	8, 11	8	1, 14	1, 10	2, 3	2, 3
10	13, 26, 28	13, 26, 28	14	10, 14	13, 22, 25	13, 22, 25
11	15, 25, 29	15, 25	2, 9, 12	2, 9	15, 21	15, 21
12	5, 17	5	5, 14	5, 14	3	3, 17
13	11, 12	12	11, 13	11	3, 10	10
14	3, 10, 21	10, 21	7	1, 7	7	7, 18
15	10, 21	10, 21	1, 7	1, 7	7, 18	7, 18
16	18, 25, 29	18, 29	3	3, 6	24	14, 24
17	7, 19	19	12	12	11	11
18	5, 24	24	2, 6	1, 6	23	23
19	7, 18	7, 18	2, 6	2, 6	5, 14	5, 14
20	13	13	17	17	10, 13	13
21	1	1	9, 13	13	1	1
22	5, 17	5, 17	5, 14	5, 14	-	17, 23

* Oxford grid results are from Mouse Genome Informatics (MGI). Zoo-FISH information is from Frönicke et al., 1996; pig, Chowdhary et al., 1996; cattle, Burkin et al., 1997; sheep.

analyzing these sequences provides the opportunity to compare the sequences between species and recognize regions of sequence conservation. These conserved sequences can be used to amplify orthologous genes in different species by designing consensus or degenerate PCR primers (Sarkar et al., 1990; Mai et al., 1994). Comprehensive attempts to make cross-species primers have been reported by Venta et al. (1996) for Universal Mammalian Sequences-Tagged Sites (UM-STSs), Lyons et al. (1997) for Comparative Anchor Tagged Sequences (CATS), and Jiang et al. (1998) for Traced Orthologous Amplified Sequence Tags (TOASTs). CATS primers were partly successful. For example, Lee et al. (2001) evaluated 53 CATS primers in pigs with 23 PCR products confirmed by sequencing. Only 12 of these could be physically mapped using the French somatic cell hybrid panel. The main problem for using these cross-species primers was the low level of polymorphism, meaning that they could not be linkage mapped, and frequently indistinguishable rodent and porcine products, meaning that they could not be physically mapped using the somatic hybrid panel. Most of these primers were designed in exon sequences to enable identification of orthologous genes between species and included rodent sequences for primer alignment (Lee et al., 2001). In August 1998, a preliminary report on comparative mapping using CATS was presented at the 26th International Society for Animal Genetics Conference in

Auckland, New Zealand. Results from several pig mapping groups showed that although over 131 CATS primer sets had been tried at that stage, only 35 CATS PCR products had been confirmed by sequencing, and only 22 were subsequently mapped. Although the efficiency of CATS was not particularly high, they indicated that consensus primers had some useful contributions to comparative gene mapping. TOASTs on the other hand have had a better success rate in physical mapping than CATS mainly because their primer sequences have little homology with rodent sequences. Lahbib-Mansais et al. (2000) reported that 58 porcine markers from 76 TOASTs (76% success rate) were mapped in somatic cell hybrid panel and/or INRA/University of Minnesota porcine Radiation Hybrid Panel (IMpRH).

ESTs

Large-scale sequencing of cDNAs (complementary DNAs) from numerous tissues is currently being carried out in animals. Already about 4 million human Expressed Sequences Tags (ESTs), partial sequences of cDNAs, are available (Benson et al., 2002). Although the genes from which many ESTs are derived are unknown, in part because 3'UTRs from which ESTs are often derived are poorly conserved between species or because the gene is uncharacterized in any species, ESTs are a valuable resource for gene mapping. Enormous numbers of ESTs from various tissues have been generated in livestock

species (Smith et al., 2001b; Takasuga et al., 2001; Band et al., 2002; Fahrenkrug et al., 2002; Pascual et al., 2002; Rink et al., 2002; Smith et al., 2002; Sonstegard et al., 2002). These EST sequence databases provide a species-specific sequence resource enabling physical mapping in livestock species and frequently provide an entry point into the human genome sequence for EST annotation and high-resolution comparative mapping. Many ESTs in pigs and cattle have been mapped (Ma et al., 1998; Grosse et al., 2000; Maak et al., 2001; Ponsuksili et al., 2001; Smith et al., 2001a; Muramatsu et al., 2002; Schlapfer et al., 2002). Rebeiz and Lewin (2000) have recently applied a systematic *in silico* approach they have entitled Comparative Mapping by Annotation and Sequence Similarity (COMPASS) and demonstrated it to be an effective method for predicting the chromosome location of ESTs. They predicted the cattle chromosome locations of 21,311 cattle ESTs for which human orthologs could be recognized and for which high resolution human mapping data were available from the GB4 radiation hybrid mapping resource (Rebeiz and Lewin, 2000).

BAC contigs and comparative sequencing

To facilitate multi-species comparative genome sequence analysis, sequence-ready bacterial artificial chromosome (BAC) contig maps from targeted genomic regions are being developed (Thomas et al., 2002). An indication of their utility is provided by comparisons with model species like mouse. DeSilva et al. (2002) identified nine previously unidentified genes, which may cause the Williams syndrome in humans, by comparing 3.3 Mb of mouse genomic sequences with the relevant genomic region in human. Sequence-ready whole-genome BAC contigs are under development in chicken, cattle, and pig (Bosdet et al., 2003; Larkin et al., 2003; Marron et al., 2003; Ren et al., 2003). High-throughput BAC-end sequences are being generated in animal species to enable alignment into contigs. For example in cattle, more than ten thousand BAC-end sequences have been integrated into a BAC contig to produce a comparatively-anchored whole-genome physical map. The significant BLAST (Basic Local Alignment Search Tool, Altschul et al., 1990) hits of the BAC-end sequences against human genome sequences are newly termed comparatively anchored sequence tagged sites (CASTS). The creation of the whole genome BAC contig in cattle and recognition of CASTS provide a template for the comparative sequencing with other species (Larkin et al., 2002). This interspecies sequence comparison is particularly powerful for inferring genome function and is based on the simple premise that conserved sequences are likely to be important.

APPLICATIONS OF COMPARATIVE MAPPING

The main advantage of comparative mapping is that information from a sequence, resource and map-rich species can be transferred to a sequence-poor species. Establishing gene homologies enables identification of candidate disease genes by exchanging information between species (Eppig, 1996; Nicholas and Harper, 1996). There are already precedents for mutations in orthologous genes in mouse, human and even in livestock species, being associated with the same disease. Malignant hyperthermia in pigs and humans is a good example (MacLennan et al., 1990).

Comparative maps are also useful for identifying genes contributing to variation in complex traits. One can search for positional candidate genes within specific chromosomal regions of a well-studied species for a quantitative trait locus (QTL) or economically important traits locus (ETL) mapped in a less well-studied species. This positional candidate gene approach can hasten the identification of the genes underlying economically important traits (Womack and Kata, 1995).

Genome organization and evolution can be ascertained by use of comparative maps. For example, the rate of chromosome rearrangements during mammalian evolution can be estimated. DeBry and Seldin (1996) defined at least 181 regions of conserved synteny between human and mouse. The comparison between synteny conservation and disruption can be used for making phylogenetic trees, based on chromosomal rearrangements among mammalian species lineages (Ehrlich et al., 1997).

CLOSING REMARKS

The current status and applications of comparative mapping have been reviewed in this article. Interest in comparative mapping has been growing during the past decade mainly because of broad benefits of identifying genes underlying disease states and QTL. A subsidiary benefit has been a better understanding of genome organization and evolution between species. The new era of the comparative mapping is being powered by RH mapping, high-throughput DNA sequencing and bioinformatics. Well-documented comparative maps and ultimately comparative genome sequences in animals will provide new insights into speciation as well as facilitating the transfer valuable information from one species to another.

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