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- Review -

Advances of Genome Research in Livestock Animals

Ki Duk Song and Byung Wook Cho[1]*

Laboratory of Mamm Genes and Development, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda MD20892, U.S.A.
[1]*Department of Animal Science, Pusan National University, Kyung Nam, Miryang 627-706, Korea*

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Genome research in economic animals has progressed rapidly in recent years, transforming from primitive genome maps to quantitative/qualitative trait maps that are indispensable to gene discovery. These advances have been benefited from the result of animal genome sequencing projects and functional genomics that are being extensively applied in livestock animal research following the development of large expressed sequences tags (ESTs). Genome sequencing efforts will provide information to QTL study by larger scale single nucleotide polymorphisms (SNPs) association study. Comparative genomics which is applying the information from human genome research as well as rodents model has contributed to important discoveries in economic animal genome research. These efforts will speed up much denser QTL maps development for phenotypic traits which are not easy to measure and to be identified by quantitative genetics [20] and lead to development of convincing markers associated with economically important trait, which will be eventually applied to livestock industry. In addition to practical application, animal genome research will enrich the understanding of human physiology in terms of genome biology.

Key words : Livestock, genome research, QTL

Advances in cattle genome research

Genome map

Genome research in cattle had its origins in somatic cell genetics [77,78]. The first "genome maps" for cattle were synteny groups, genes on the same chromosome, defined by protein gene products segregating in hybrid somatic cell lines. These synteny groups were assigned to specific chromosomes by integrating somatic cell genetics with in situ hybridization [16,17,18] and were greatly expanded with the advent of molecular markers, initially defined by probed Southern blots and later by PCR-based markers. An international consortium organized at the 1988 meeting of the International Society for Animal Genetics (ISAG) assembled a set of families for linkage mapping, and the development of microsatellite markers in the early 1990s resulted in an international linkage map [6]. These maps were quickly expanded [6,34] into tools that have proved effective for mapping loci underlying both monogenic and quantitative traits. 2277 microsatellite markers developed by the Shirakawa Institute of Animal Genetics (SIAG) and the United States Meat Animal Research Center (MARC) were incorporated to generate second generation bovine linkage map, reducing the average interval between markers from 3.0 cM to 1.4 cM [31]. Recent addition of 918 SNPs markers from 799 from EST and 119 from BAC subclone sequence resulted in the current SIAG-MARC bovine linkage maps represented by 4779 markers with a mean (maximum) of 1.2 cM (9.1 cM) between markers [64].

Using bovine linkage map based on polymorphic markers and SNP, trait loci associated with economically important traits of the bovine have been identified. Weikard et al. [73] reported that they identified the bovine peroxysome proliferator-activated receptor-gamma coactivator-1alpha gene (PPARGC1A) as a possible positional and functional candidate gene for a previously described QTL for milk fat yield on BTA6 because of its chromosomal position and its key role in energy, fat, and glucose metabolism. A significant association between an SNP in intron 9 of the PPARGC1A gene and milk fat yield was observed in a major dairy cattle population, indicating that the PPARGC1A gene could be involved in genetic variation underlying the QTL for milk fat synthesis on BTA6. As to milk production, a SNP in upstream of osteopontin gene (OPN 3907) was identified by sequence analysis of 12.3kb region around this gene in chromosome 6, which is fine mapped by linkage analysis with 38 microsatellite

*Corresponding author
Tel : +82-55-350-5515, Fax : +82-55-350-5519
E-mail : bwcho@pusan.ac.kr

markers in a pedigree of 3,417 Holstein bulls [59]. Another SNP of osteopontin gene associated with milk production in Holstein cow (intron 4 [C/T]) was identified by an analysis of 362 bulls obtained from Cooperative Dairy DNA Repository and from 214 cows from the University of Wisconsin herd [39].

Physical mapping and whole genome sequencing

The next significant advance in cattle genome research was the development of radiation hybrid (RH) maps [56,78] and the use of these maps for high-resolution comparative mapping [5,33]. A consortium to generate a bacterial artificial chromosome (BAC) map of the bovine genome has generated a 294,651 whole clone HindIII fingerprint map that is currently being refined by BAC end sequencing and is scheduled for completion in 2008. Highly developed linkage and RH maps and the progress of the BAC consortium were instrumental in the success of a White Paper proposal to the NHGRI for whole-genome sequencing in cattle (http://www.genome.gov/Pages/Research/Sequencing/SeqProposals/BovineSEQ.pdf).

A single partially inbred Hereford female was selected to contribute 6× whole-genome shotgun (WGS) reads and another 1.5× will come from individual animals of the Holstein, Angus, Jersey, Limousin, Brahman, and Norwegian Red breeds for SNP detection. In addition, an 1× BAC skim sequence will aid assembly. Sixfold WGS has been achieved and breed skims for SNP detection are under way.

Functional genomics

Although an early effort of EST development in cattle generated 82 ESTs from cattle ovary [43], rapid expansion of data entry followed yielding 47,787 ESTs [52], 62,580 sequences from four pooled libraries composing with various tissues and organs with highest likelihood to have impact on production parameters of animal health, growth, reproductive efficiency, and carcass merits [63,64] and 36,310 ESTs from 10 different libraries by 3′-end sequencing [66]. dbEST statistics shows that total 1,318,208 of ESTs have been deposited to this database. Recent release of UniGene Build #84 (as of 23 April, 2007) reveals that total 1,172,713 sequences with 21,603 mRNA sequences and 1,318,208 ESTs are clustered to 41,891 UniGene sets (http://www.ncbi.nlm.nih.gov/UniGene/UGOrg.cgi?TAXID=9913).

Advances in swine genome research

Genome map

The history of pig genomics does not parallel that of cattle in that the linkage map was the first whole-genome map produced. The early efforts by the European PiGMaP initiative [4] and USDA-MARC [54], generated two linkage maps which were constructed with around 1,200 polymorphic DNA markers, mostly microsatellite markers and limited number of genes. In the European PigMaP initiative, genetic map was constructed with cross between European wild boar and domestic breed (Large white) [4] and USDA pig linkage map utilized the resource populations composed of crosses between Chinese breeds and domestic breeds [54] to maximize the resolution power of the map. Over the years, with the massive development of molecular markers, porcine genome map rapidly expanded to have over 4,000 loci with more than 1,588 genes as well as 2,493 markers [10].

In order to identify the QTLs important for pig industry, genome scan strategy using polymorphic DNA marker has been applied in crossing European Wild Boar or Chinese Meishan breed with a domestic breeds. Since the first identification of QTL for fat deposition on chromosome 4, total 1,675 QTLs from 110 publications are curated into the database and those QTLs represent 281 different traits [58; 2007;http://www.animalgenome.org/QTLdb/)].

Kim et al. [35] identified a missense mutation (Asp298Asn) in a region highly conserved among melanocortin receptor (MCR) genes associated with backfat and growth rate in a number of lines as well as feed intake overall. Furthermore, association of this mutation with feed intake, fatness and growth was confirmed in the population of Large White populations [27] as well as Mangalitsa x Piétrain cross [45].

Physical mapping and whole genome sequencing

Shift from the whole genome linkage maps to whole genome radiation hybrid (RH) maps allowed for many more genes to be mapped and anchored using expressed genes and or microsatellites [24,36,55,79] developed 12,000 rd (IMNpRH2) RH panels covering whole porcine genome facilitating the comparative mapping with other species and these panels will assist the integration of linkage map with RH maps. As resources for physical mapping in specific chromosome with high resolution, BAC libraries of porcine

genome have been available with 35X coverage of porcine genome [2,15]. International efforts for whole porcine genome sequencing led to establishment of the Swine Genome Sequencing Consortium (SGSC) [60].

In order to have whole genome sequences of porcine, several BAC resources- two BAC libraries from J. de Jong at Children's Hospital Oakland Reseach Institute, one library made at the Roslin Institute [2], a library generated at INRA [54] and a library from NLRI are being used for whole genome sequencing (http://www.sanger.ac.uk/Projects/S_scrofa/mapping.shtml). Meanwhile, the "Sino-Danish Pig Genome Project" has published pig genome sequence with <1× coverage generated by shot-gun sequencing of 5 different domestic breeds of domestic pig [74]. The results showed that the average trimmed length of the ~3.84 million sequences was 543 base pairs, yielding a total of 2.1 billion base pairs, equivalent to 0.66X coverage of redundancy of the 3.15 billion base pair pig genome. Recent release of genome sequences by Sanger Institute shows around 508,715,359 base reads and the preliminary assemblies for chromosomes 4, 7, 14 and 17 of the pig genome.

Functional genomics

Soon after Tuggle and Schimtz [69] described the muscle EST data in pig, ESTs were developed with small intestine [76] and ovary [68]. Currently, over 646,434 ESTs has been being deposited to NCBI-dbEST (NCBI-dbEST June 1, 2007). The NCBI UniGene build #29 for pig shows total 550,384 sequences over 100 libraries. These sequences come from thirteen categories of tissues, ranging from a low of 3 libraries found for the adipose, brain, and conceptus categories to 31 libraries in the genito-urinary category. In NCBI Build #29 (as of July 12, 2007), the mRNAs (5,357), high-throughput cDNAs (11,312) and ESTs (487,234) are clustered into 38,782 UniGene sets. On the other hand, in the Porcine Gene Index (SsGI Release 12.0; June 20; http://compbio.dfci.harvard.edu/tgi/cgi-bin/tgi/gimain.pl?gudb=pig) revealed total 6,854 expressed transcripts from 257 cDNA libraries with 575,730 ESTs. And total 64,746 tentative clusters (TCs) and 88,117 singleton ESTs and ETs were estimated [71]. Additional information on these databases and others is discussed in the section on bioinformatics. and large cDNA sequencing and EST projects are advancing rapidly.

Advances in chicken genome research

Genome map

Although the first genetic map in chicken was published more than 70 years ago [30], it was not before the expansion of genetic maps by the development of large numbers of DNA markers from the middle of 1990s. First generation of genetics maps in chicken came from three different resource populations. The first genetic map with the Compton reference populations derived from two lines of White Leghorn chickens, which differ in susceptibility to a number of diseases. This map was based on the restriction fragment of polymorphism (RFLP) markers [8]. The second map was published by Levin et al. [41,42]. This map was based on the East Lansing (EL) reference population and consisted of three sorts of polymorphic DNA markers, RFLPs, random amplified polymorphic DNA (RAPD) markers, and chicken repeat element 1 (CRI) markers. Since then, these two maps have been expanded by considerable number of microsatellite markers [11,13,19] as well as amplified-length-fragment-polymorphism's (AFLP) markers [37]. At the late of 1990s, the third map [21,25] was developed by segregation analysis of 430 microsatellite markers within a cross between two extreme broiler lines. The population used to construct the linkage map consists of 10 families with a total of 458 F2 individuals. The consensus map contains 2,012 loci with 51 linkage groups and spanning 4,000 centimorgans (cM) [23]. With the application of ESTs to detect SNPs, density of genetics map of chicken has been increased to be enough to perform the QTL analysis for economically important traits. The first report of QTL analysis using polymorphic DNA markers to identify the QTLs associated with Marek's disease (MD) resistance [71] and growth and feed efficiency [72]. For QTL analysis of MD resistance, using interval mapping and permutation tests, two significant (*chromosome 2* and *8*) and two suggestive QTL (*chromosome 4* and *7*) affecting several components of MD susceptibility were identified on four chromosomal subregions [71] and subsequent study added 14 MD QTL associated with one or more MD trait with 127 genetic markers cover ≈ 68% of the genome; seven at the significant level and seven at the suggestive level. Individually each QTL accounts for 2-10% of the variation [81]. Later, this approach proved to be applicable in the resource population composed of commercial

broiler chicken lines, suggesting that loci affecting MD resistance can be mapped in commercial layer lines [44]. As for growth and feed efficiency, four significant QTLs were initially identified; The most significant QTL was located on Chromosome 1 at 235 cM and had a 4% genome-wise significance for feed intake between 23 and 48 day. Furthermore, this QTL exceeded suggestive linkage for growth between 23 and 48 day and BW at 48 day. A second QTL was located on linkage group WAU26 at 16 cM and showed suggestive linkage for feed intake between 23 and 48 day. On chromosome 4, at 147 cM a third QTL, which had an effect on both feed intake traits, was found. Finally, a fourth QTL, which affected feed intake adjusted for BW, was located on chromosome 2 at 41 cM [72]. With the expansion of polymorphic markers as well as anchored markers, many of economically important traits, such as growth, egg quality and production and disease resistance have been extensively studied to identify the QTLs associated with these traits. According to the chicken QTL database, currently most of all, QTLs associated with growth trait are well studied (368 QTLs are reported), and traits important for layer including egg quality and production followed (141 QTLs) http://www.animalgenome.org/cgi-bin/QTLdb/GG/summary?summ=type&qtl=698&pub=50&trait=115**).** The current Release of the chickenQTLdb contains 657 QTLs from 45 publications. Those QTLs represent 112 different traits (http://www.animalgenome.org/QTLdb/chicken.html).

Physical mapping and whole genome sequencing

Toward the physical map generation using radiation hybrids, the first whole chicken genome radiation hybrid panel (ChickRH6) was developed [50]. Chromosome 14 were constructed using microsatellite markers ESTs and localization with chicken genome sequences [40,50].

To construct the contig map of the chicken genome, two BAC libraries were developed and used [13,38]. Crooijmans et al. [13] constructed BAC library using genomic DNA from a female White Leghorn chicken. The library was prepared by partial digestion of genomic DNA with Hind III restriction enzyme and total 49,920 clones obtained covering 5.5-fold of whole chicken genome. The second BAC library by Lee et al. [38] was constructed with a female of the Jungle Fowl line UDC001 as its DNA source using three restriction enzymes, Hind III, BamHI and EcoRI. Each library contained 39,400 BAC clones of for a total over 115,000 BACs. In addition to these BAC resources, de Jong at CHORI constructed a chicken BAC library CHORI-261) using same female genomic DNA from Jungle Fowl line UDC001 as above. CHORI-261 has 73,700 BAC clones with 12-fold coverage of the genome [9] (http://bacpac.chori.org/chicken261.html).

The National Institute of Human Genome Research-funded whole genome sequencing of the chicken genome began in 2003 at Washington University Genome Sequencing Center (WUGSC) after publication of White Paper by this Institute as an initiative for whole genome sequencing of economically important animals. Sequences was determined with 6-7 fold coverage of the halploid genome, mostly with whole genome shotgun (WSG) reads, supplemented with direct sequencing of selected chicken BAC inserts [9]. For this purpose, two BAC libraries made with a female of Jungle Fowl line UDC001 as its genomic DNA source were used. Fingerprinting of clones of these libraries yielded 136,000 BAC end sequences [9].

First draft of whole genome sequences were published in 2004 and the sequence assembly generated from a 6.6-fold coverage of whole genome shotgun reads, a combination of plasmid, BAC, fosmid and BAC end read pairs (International Chicken Genome Sequencing Consortium, 2004). Recent release of Chicken genome Build 2.1 shows that whole genome size would be 1.05095×10^9 bases and df the 1.05 Gb genome, approximately 95% of the sequence has been anchored to chromosomes, which include autosomes 1-28 and 32, two additional linkage groups, and sex chromosomes W and Z. All unknown gap sizes have been set to 100 bp. The N50 ultracontig size is 15.5 Mb (n=19); the longest ultracontig is 80.3Mb on chicken chromosome 3. The N50 supercontig size is 11.1 Mb (n=26); the longest supercontig is 52 Mb on chr2. The N50 contig size is 45 kb (n=5863); the longest contig is 625 kb (http://genome.wustl.edu/pub/organism/Other_Vertebrates/Gallus_gallus/assembly/Gallus_gallus-2.1/).

Functional genomics

Total 599,330 ESTs are deposited to dbEST by NCBI (June 15 2007) and current release of UniGene build #33 for the chicken shows that total 558,874 sequences are in 31,777 clusters (http://www.ncbi.nlm.nih.gov/UniGene/UGOrg.cgi?TAXID=9031). These sequences include 31,382 mRNAs and 414,349 5′ EST reads as well as 22,553 3′ EST reads. First report of chicken EST development came from

activated chicken splenic T cell library generating first EST datbase with 5251 clones by the University of Delaware [66] and an EST database bursal of Fabricius with more than 7,000 clones by the GSF-Berlin [1].

The EST collection which was performed by Boardman et al. [7] showed that total 339,314 ESTs have been sequenced from 64 cDNA libraries generated from 21 different embryonic and adult tissues. These were clustered and assembled into 85,486 contiguous sequences (contigs). We find that a minimum of 38% of the contigs have orthologs in other organisms and define an upper limit of 13,000 new chicken genes. Furthermore, recent study by Hubbard et al. [28] demonstrated an analysis of the chicken transcriptome based on the full insert sequences for 19,626 cDNAs, combined with 485,337 EST sequences. Analysis of the ncRNAs reveals a set that is highly conserved in chickens and mammals, including sequences for 14 pri-miRNAs encoding 23 different miRNAs. As efforts of identification of tissue or organ specific transcriptosome, several tissue specific ESTs were developed from chicken reproductive organs such as testis [58,61], brain [58] and parasite activated intestinal intraepithelial lymphocytes (iIELs) [46].

Future direction of livestock animal genome research

The advances in animal genome research have led to the identification of genes and markers associated with quantitative traits or economically important traits in livestock animals. The annotation of livestock genome sequences offers crucial source of information that can be used to identify candidate genes responsible for complex traits that are not ease to be measured, and quantitative trait loci effects. The information getting from genome research of animals has assisted to broadening and deepening the understanding of biological processes.

As an emerging field, proteomics will provide new opportunities regarding gene expression study, since it will allow to analyze many genes and their products at the same time with conjunction with functional genomics. These systemic approaches will be very useful to understand the mechanisms which regulates gene expression at transcriptional level and are working to control the phenotype of traits through protein networks. In addition to proteomics, miRNA studies will open new chances to understand gene expression regulation even though this research has just begun in livestock. Nonetheless, miRNA study will reveal the differential layer of mechanisms which are important to regulate characteristics of traits on the top of functional genomics and proteomics. Therefore, it is imperative to integrate many of these information emerging from genome studies, functional genomics, proteomics and miRNA studies to understand biological processes which control the phenotypic variations in livestock animals. Finally, development of this knowledge will benefit scientists, industry and breeders considering that the efficiency and accuracy of the traditional pig selection schemes will be improved by the implementation of molecular data into breeding programs.

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초록 : 경제동물 유전체학 연구의 최근 연구 동향

송기덕 · 조병욱[1]*
(미국 국립보건원, [1]부산대학교 생명자원과학대학 생명자원과학부)

경제 동물의 유전체 연구는 최근에 급속하게 발전하여 초기의 유전체 지도로 부터 유전자의 발견에 필수적인 양적/질적 형질 유전자를 확인 동정가능한 수준의 지도가 개발되었다. 이러한 발전은 경제동물의 전체 게놈 염기서열 결정과 대량 ESTs의 개발에 의해 가능해졌다. 특히 염시서열 결정은 경제형질과 연관된 대규모의 SNPs 개발에 의한 QTL 연구에 유용한 정보를 제공할 것으로 사료된다. 비교 유전체 연구를 통해 인간 및 설치류 모델동물에서 나온 유전체 정보를 이용하여 경제 동물의 유전체 연구에 있어 중요한 발견을 이루었다. 이러한 노력은 좀더 밀도 높은 QTL지도의 작성을 가능하게 하여 쉽게 측정하기 어려운 경제형질과 연관된 유전자의 확인 및 동정을 가능하게 하고 궁극적으로 산업체에서 이용 가능한 표지인자의 개발을 가능하게 할 것으로 사료된다. 이와 더불어, 경제동물 유전체 연구 성과는 인간의 생리현상의 유전체 측면의 이해를 더욱 증진시킬 것이다.