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Mapping quantitative trait loci and identification of genes that control fatness in poultry

David W. Burt[1]* and Paul M. Hocking[2]
[1]Department of Genomics and Bioinformatics and
[2]Department of Genetics and Biometry, Roslin Institute (Edinburgh), Roslin, Midlothian EH25 9PS, UK

Chicken genomics has benefited from the rapid technological advances in the genomics of model organisms and man. A number of resources and approaches are now well established, in the chicken, including genetic markers and maps (both genetic and physical), quantitative trait loci mapping, comparative mapping, expressed sequence tag and bacterial artificial chromosome resources, and physical mapping. In addition, the next phase of gene discover, functional genomics, is underway. Progress in mapping quantitative trait loci for growth and fatness traits will be discussed, as an application of these new technologies and approaches in the study of avian physiology and genetics.

Résumé

La génomique de la volaille a bénéficié des avancements technologiques rapides acquis en génomique humaine et sur les organismes modèles. Certains outils et certains approches sont maintenant bien établis chez le poulet, y compris les cartes et marqueurs (génétiques comme physiques), mapping loci pour caractères quantitatifs, mapping comparative, ressources EST et BAC, et mapping physique. De plus, la phase suivante de la découverte génétique, la génomique fonctionnelle, est en cours. Les progrès dans le mapping de loci pour caractères quantitatifs de croissance et d'adiposité seront discutés pour illustrer ces nouvelles technologies et ces nouvelles approches dans l'étude de la génétique et de la physiologie avicole.

Quantitative trait loci: Genomics: Fatness: Functional Genomics: Chicken

During the past 15 years there have been rapid advances in genomics, with the key driving force being the human genome project (Lander & Weinberg, 2000). Research on livestock genetics has benefited from these developments, with the creation of detailed genetic marker maps and mapping of trait-genes (Andersson, 2001). Chicken genomics is finding applications in both animal breeding and medicine. In animal breeding, genomics is being used to identify the genes that control traits as diverse as growth, fatness, fertility, osteoporosis and even behavioural traits, such as feather pecking and cannibalism. In animal health, genomics is being used to understand the genetics and molecular biology of disease resistance and response to vaccines. Besides these applications in agriculture, the chicken is like any other vertebrates and is being used as a model organism. Traditionally, the chicken has been used to understand developmental processes, but is also being used as a genetic model of human disease, e.g. blindness in mutant models and quantitative traits such as obesity and osteoporosis in selected lines.

Lean and fat animals are at the two ends of a continuous distribution of fatness (Pomp, 1997). It is a complex trait affected by a host of genetic and environmental factors, such as, lipid metabolism, nutrition partitioning, growth hormone axis, appetite, behaviour, diet, etc. The genetic basis of fatness is of interest in both animal breeding and human health. In the present paper progress in mapping quantitative trait loci (QTL) for growth and fatness in the chicken, and how these results may be used in animal breeding and to understand obesity in man, will be reviewed.

Abbreviations: QTL, quantitative trait loci
***Corresponding author:** Dr David Burt fax +44 131 440 0434, email Dave.Burt@bbsrc.ac.uk

The principles of genome mapping and gene discovery

In a few cases the M genes that control genetic variation between animals have a large enough effect to be individually recognisable, such as the sex-linked *dwarf* gene in the chicken. Usually this is not the case for traits such as growth and fatness, which are traits controlled by many genes. The trait-genes that control these quantitative traits are located at QTL. The chicken genome contains 30 000–40 000 genes distributed over thirty-nine pairs of chromosomes. QTL mapping is the first stage in the discovery process of identifying the trait-genes at these loci. QTL can be located in the genome through associations between performance and the inheritance of genetic markers in a suitable pedigree (Mackay, 2001). The key to this process is a map of genetic markers evenly spaced throughout the genome.

Recent advances in chicken genomics

Genomics is the science of whole genome studies applied to biological systems (Lander & Weinberg, 2000). Chicken genomics has developed along two parallel paths, the development of tools for genome analysis and the application of these tools for QTL mapping and trait-gene identification (Schmid *et al.* 2000). The strategy to identify trait-genes is: (1) to map the location of the QTL using marker maps and large pedigreed populations; (2) predict candidate genes from high-resolution comparative gene maps at these QTL; (3) to establish a causal link between the genetic trait and the candidate genes from functional evidence. The tools for QTL mapping include: integrated genetic and physical maps; tools for whole-genome analysis ('genome scans'); QTL mapping populations; comparative gene mapping; whole-genome gene expression.

Integrated genetic and physical map

The chicken has been the target for a large number of genetic studies, and currently there is a linkage map of over 2000 genetic loci, covering most of the genome of 1200×10^6bp and 4000 centiMorgans (Schmid *et al.* 2000). Over 1000 microsatellite markers and approximately 400 human gene orthologues have been mapped; this information is crucial for genome scans and comparative mapping. The chicken karyotype comprises thirty-nine pairs of chromosomes, which are divided into eight pairs of cytologically-distinct macrochromosomes along with the Z and W sex chromosomes and thirty pairs of small cytologically-indistinguishable 'microchromosomes'. Integrated genetic and physical maps of all macrochromosomes have been produced (Smith *et al.* 2000). Since they cannot be distinguished individually, the microchromosomes are ordered arbitrarily by decreasing size and only an estimate of the chromosome number can be given. Bacterial artificial chromosome and phage artificial chromosome clones (Zoorob *et al.* 1996; Crooijmans *et al.* 2000) were used as tags for identification of microchromosomes in two-colour fluorescent *in situ* hybridisation experiments (Fillon *et al.* 1998; Schmid *et al.* 2000) from which twenty-two individual chromosome pairs were identified. A nomenclature based on the estimated size of each labelled microchromosome pair has been proposed (Schmid *et al.* 2000). The genetic marker-containing clones led to the integration of genetic and cytogenetic maps for sixteen linkage groups (Fillon *et al.* 1998). The chicken genome project is the product of an ongoing collaboration of over thirty laboratories throughout the world, which started at the 1992 International Society of Animal Genetics meeting in Interlaken, Switzerland. All data on markers and maps is available through the *Arkdb* genome databases (http://www.thearkdb.org/) and associated WWW site links (Law & Archibald, 2000).

Mapping quantitative trait loci

The first key steps in mapping the genes that control any trait, be it a simple Mendelian or a complex quantitative trait, is to provide a robust definition of the trait and then to identify population resources showing genetic differences. If the trait cannot be measured reliably, then the ability to map any QTL will be reduced and of course, if there is no genetic component or genetic resources, then there is no hope of genetic progress. In mice, inbred lines differing in a large number of traits have been developed during the last century. These inbred lines have been used to map and identify genes controlling simple and complex traits, including growth and fatness (Pomp, 1997). In the chicken there are a number of outbred lines and selected lines that differ in a large number of traits (Schmid *et al.* 2000). Unlike the mouse with a limited number of inbred lines, the genetic variation available for genetic mapping in these chicken populations is huge. This variation is illustrated in the range of chicken strains, such as the fast-growing broilers, high-yielding egg layers to aggressive cock-fighting birds of Asia. A multi-strain comparison is a very useful starting point to establish trait definitions, detect genetic variation and identify extreme populations for further genetic study. A wide range of quantitative traits is currently under investigation at the Roslin Institute and elsewhere. These investigations exploit both commercial strains selected for growth (broilers) and egg production (layers), as well as experimental lines divergently selected for specific traits (fat *v.* lean, high and low susceptibility to osteoporosis, etc).

The key to QTL mapping is a map of highly polymorphic genetic markers evenly spaced throughout the genome; in particular, the use of microsatellite markers has been very successful (Georges & Andersson, 1996). Assays based on polymerase chain reaction can be used to identify different allele sizes by gel electrophoresis. Developments in robotics and thermostable enzymes, together with the use of ninety-six-lane capillary electrophoresis have increased the throughput and reliability of microsatellite assays. With a ninety-six-lane sequencer, a single technician can now type approximately 800 DNA samples for approximately ten markers per d or approximately 8000 genotypes per d, making rapid genetic association studies practical.

The generation of large numbers of genotypes from populations of 400–600 animals, required for QTL mapping, has also been matched by developments in database management. Resource databases (http://www.resspecies.org/; Law & Archibald, 2000) have been crucial in the management and

analysis of these large datasets. A resource database for the chicken, resCHICK has been designed to record simple and complex pedigrees, trait data and the genotypes of all animals in the experimental populations. The resCHICK database has been used to manage the analysis of ten crosses of over 5000 animals, and is currently being used to analyse some populations of 3000–5000 animals. Once the data has been entered and checked, a number of export routines are used in conjunction with analytical tools for genetic and QTL mapping. *Crimap* (Lander & Green, 1987) is used to calculate multipoint genetic maps and *QTLexpress* (Seaton *et al.* 2002) is used for most QTL analyses. *QTLexpress* provides a number of tools for QTL analysis, including interval mapping of QTL (Haley *et al.* 1994), and permutation and bootstrapping analysis (Visscher *et al.* 1996) to provide CI for mapped QTL. Least-squares linear models of trait values at QTL provide estimates of additive and dominance effects, and contributions towards the total phenotypic variance (Knott *et al.* 1998).

Mapping quantitative trait loci for growth and fatness traits

At the Roslin Institute a number of QTL mapping experiments are underway, including a major study on the genetic analysis of broiler traits in a cross between a broiler sire-line and an egg-laying (White Leghorn) line (Ikeobi *et al.* 2002; Sewalem *et al.* 2002). These lines are the result of > 50 years of intense selection. The broiler lines were selected for rapid growth rate and increased meat yield, and differ from layers in growth by > 15 phenotypic SD. The layers were selected for increased egg production, higher and more persistent than broiler lines. The cross was between two males and two females from both lines in the base (F_0) population. The F_1 progeny consisted of eight males and thirty-two females. F_2 offspring (> 500) were reared to slaughter at a live weight of 2 kg at 9 weeks of age. A large number of typical broiler traits were recorded on all the F_2 offspring, including, body weights (3, 6 and 9 weeks), abdominal-fat weight, skin-fat weight, carcass weight, muscle yield, etc. DNA was extracted from blood samples and genotypes for 102 informative microsatellites determined, from an initial set of 249 microsatellites screened. These markers covered twenty-seven linkage groups and approximately 3400 centiMorgans or approximately 85 % of the genome. Permutation analysis was used to determine significance thresholds based on the definitions of Lander & Kruglyak (1995). These thresholds were suggestive (F > 5), and $P > 0{\cdot}05$ (F> 8) and $P > 0{\cdot}01$(F > 10) genome-wide significance levels. Interval mapping was used to map QTL for growth (Sewalem *et al.* 2002) and fatness traits (Ikeobi *et al.* 2002).

In Table 1 at least eleven QTL affecting body weight on chromosomes 1, 2, 3, 4, 7, 8, 13, 27 and Z were detected. The CI suggest that there were a least three QTL on chromosome 1. In general, genetic effects were additive and the broiler alleles increased body weight at all QTL. The effects for these QTL accounted for 0·2–1·0 phenotypic SD in body weight. The sum of the effects, albeit over estimated, account for up to 75% of the line difference in body weight at 6 weeks of age. There was no family × QTL interaction, suggesting that QTL for body weight were not segregating in the parental lines. Significant QTL for abdominal fatness (abdominal-fat weight adjusted for carcass weight) were found on chromosomes 1 ($P > 0{\cdot}05$), 5 ($P > 0{\cdot}01$), 7 ($P > 0{\cdot}01$) and 28 ($P > 0{\cdot}05$; Table 2). QTL for skin and subcutaneous fatness (skin-fat weight adjusted for carcass weight) were found on chromosomes 3 and 28. Finally, QTL for fat distribution (abdominal-fat weight adjusted for skin-fat weight) were found on chromosomes 5, 7 and 15. The magnitudes of the QTL effects were similar to the body-weight QTL, 0·2–0·7 phenotypic SD or 3–5 % of the residual phenotypic variation. In contrast to the QTL for body weight where only positive alleles were found in the broiler lines, both positive and negative alleles for fatness were found in both lines. Interactions with family or gender were not significant. This finding would also suggest that QTL for fatness were not segregating in the parental lines, and that both positive and negative QTL were fixed in the two parental populations. The lack of any sex interaction with QTL was surprising given that abdominal fatness, corrected for carcass weight, was greater in females than

Table 1. Significant additive and dominance effects of quantitative trait loci (QTL) for body weight in the chicken (based on Sewale *et al.* 2002)

Chromosome	CI (cM)†	3 weeks‡	6 weeks‡	9 weeks‡
1	113, 180	+0.2* (–0.3)	+0.4‡	
1	374, 419			+0.3‡ (+0.4)
1	438, 486	+0.4*	+0.6‡	
2	230, 313		+0.3**	+0.3**
3	0, 122	+0.2* (+0.6)		+0.4‡
4	108, 193		+0.8**	+1.0‡
7	40, 106	+0.7**	+0.6‡	
8	40, 92		+0.6‡	+0.8‡
13	0, 38	+0.5**	+0.4**	+0.4‡
27	0			+0.4‡
Z	98, 127	+0.3**		

CM, centi Morgans; +, –, broiler allele increases or decrease body weight.
*$P > 0.05$, **$P > 0.01$, genome-wide significance (Lander & Kruglyak, 1995).
†CI for QTL, positions relative to the reference genetic linkage map (Schmid *et al.* 2000).
‡Additive effects (dominance effects in parentheses), expressed as phenotypic SD.

Table 2. Significant additive and dominance effects of quantitative trait loci (QTL) for fatness in the chicken (based on Ikeobi *et al.* 2002)

Chromosome	CI (cM)†	AF‡	SF‡	FD‡
1	100, 182	–0.2*		
3	129, 184		+0.4*	
5	0, 57	+0.3** (+0.3)		+0.3*
7	0, 63	+0.7**		+0.7**
15	0, 36			+0.2* (+0.4)
28	0, 39	–0.3* (+0.4)	–0.3*	

CM, centi Morgans; AF, abdominal fat weight adjusted for carcass weight (abdominal fatness); SF; skin fat weight adjusted for carcass weight (skin fatness); FD, abdominal fat weight adjusted for skin fat weight (fat distribution); +, – broiler allele increase or decreases fatness.
*$P > 0.05$, **$P > 0.01$; genome-wide significance (Lander & Kruglyak, 1995).
†CI for QTL, positions relative to reference genetic linkage map (Schmid *et al.* 2000).
‡Additive effects (dominance effects in parentheses), expressed as phenotypic SD

Table 3. Mammalian orthologues and candidate genes of chicken quantitative trait loci (QTL)

Chromosome	CI (cM)	Trait	Human	Mouse	Orthologous QTL	Candidate genes
1	100, 182	AF	6, 8, 12, 22	6, 7, 10, 13, 14, 15	Many	
3	129, 184	SF	4, 6, 16	5, 10, 17	Obq4	
					Bw6g	
					Qlw4	
5	0, 57	AF, FD	11p15.5-q13	2, 7, 19	BBS1	IGF2
					Qfa1	ABCC8
					Obq3	TUB
					Tub	
7	0, 63	AF, FD	2q31-q37	1	BBS5	
					Obq2	
					Obq3	
15	0, 36	AF, FD	22q11.2	5, 10, 16		
28	0, 39	AF, SF	19p13.3-p12	10	*Qlw9*	LDLR
					FH	INSR

CM, centi Morgans; AF, abdominal fat weight adjusted for carcass weight (abdominal fatness); SF, skin fat weight adjusted for carcass weight (skin fatness); FD, abdominal fat weight adjusted for skin fat weight (fat distubution).
*CI for QTL, positions relative to reference genetic linkage map (Schmid *et al.* 2002)

in males (0·042 *v.* 0·034, SED 0·001). The differences in fatness were not large in this experiment and may have been too small to detect a gender interaction.

QTL mapping of diverse crosses has taught us a number of lessons. First, they prove that QTL of moderate to large effects for traits of economic importance can be detected. Multiple QTL for the same trait can be found on a single chromosome, and QTL can have pleiotropic effects. Apparently, a few QTL can account for most of the additive genetic variance. Estimates of QTL effects may be over-estimated; however, it is clear that the distribution of QTL effects in a population is not that of a large number of QTL of small effect.

Comparative mapping and candidate-gene identification

Once a QTL has been defined, the next step is to predict candidate-genes for the genetic trait. Examination of the chicken genome may identify candidate-genes, which have been mapped to the region of interest with a function appropriate to the trait under investigation. Given that < 400 genes have been mapped in the chicken (Schmid *et al.* 2000) makes this approach unlikely, until a dense gene map is available. Comparative gene mapping is a possible solution, where the maps of chicken and man are compared using genes that have been mapped in the chicken as anchor loci. From these comparisons the gene content of chicken QTL can be predicted. Extensive conservation of genome organisation is found between chicken and man (Burt *et al.* 1999; Schmid *et al.* 2000), and this factor allows us to estimate the number of conserved segments between these species (Burt *et al.* 1999; Waddington *et al.* 2000). The number of conserved segments between chicken and man may only be approximately 150, of which 100 have already been defined (Schmid *et al.* 2000). Recently, high-resolution comparative maps between chicken and specific human chromosomes (Crooijmans *et al.* 2001; Buitenhuis *et al.* 2002; Jennen *et al.* 2002; Smith *et al.* 2002) have increased this estimate by 30% to about 200. This estimate is about the same at that found between mouse and man; however, the chicken diverged from a common ancestor with mammals 310×10^6 years ago. Thus, the rate of change within the avian lineage is less than one-third of that found in the mouse lineage. The mouse rate is at least 10-fold greater than that found in the human lineage. A practical consequence of this conservation is the relative ease of comparing human and chicken genomes, and predicting the gene content of specific chicken QTL. This procedure is illustrated in Table 3 where the orthologous regions of the fatness QTL described in Table 2 can be defined in both the mouse and human genomes. In some cases candidate genes and candidate disease loci ('Orthologous QTL'; Mackay, 2001) can be predicted.

Causal role of candidate genes

Once candidate genes have been defined, the next problem is to establish a causal relationship between these genes and the traits under study. This problem is complex and has only been solved in a few cases in plants and *Drosophila* (Mackay, 2001). The first problem is that the QTL mapping studies described so far are at low resolution. Usually an F_2 experimental design can only locate a QTL of moderate effect within a CI of 20, 40 centiMorgans ($6, 12 \times 10^6$). In the chicken this interval may contain 200–400 genes. Clearly, the choice of candidate genes needs to be reduced further. This reduction is possible in species such as chickens and mice using genetic recombination to dissect the QTL into smaller intervals. There are a number of approaches available (Mackay, 2001), including the use of linkage disequilibrium, backcross introgression, interval specific congenics and advanced intercross lines. At the Roslin Institute fine mapping of chicken QTL is based on the advanced intercross lines approach. Through repeated inter-crosses, starting with a standard F_2, it is possible to 'stretch' the recombination map at the QTL. Thus, at F_6–F_8 it is possible to map QTL within a CI of 5 centiMorgans (Darvasi, 1998). The Roslin Institute advanced intercross

line population will be available in 2003, after which suitable populations will be expanded (500 offspring) for genotyping, trait recording and fine mapping of specific QTL. Currently, the number of useful genetic markers in the public domain, such as microsatellite markers, is limited to about 1/10 centiMorgans (Schmid *et al.* 2000), and the frequency of microsatellite markers in the chicken genome is also low, at about $1/150 \times 10^3$bp. Once bacterial artificial chromosome clones and sequences are available, searching for new genetic markers such as single nucleotide polymorphisms is relatively straightforward; in the chicken single nucleotide polymorphisms occur at an average frequency of 1/50–100 bp. These markers can then be used in large population studies to test for association between candidate-genes and traits. Further evidence for a causal role of a gene in a genetic trait can be sought from gene expression patterns from selected lines. This process requires new tools: normalised cDNA libraries; expressed sequence tag databases of partially-sequenced clones; cDNA microarrays (Brown & Botstein, 1999) for high-throughput whole-genome gene expression studies. Expressed sequence tags are simply a partial sequence of the transcribed portion of these genes (Gerhold & Caskey, 1996). During the last year, collaboration between UK Universities (Nottingham, Dundee and University of Manchester Institute of Science and Technology) and Research Institutes (Roslin and Compton) with Incyte Genomics (Palo Alto, CA, USA) has resulted in a collection of approximately 350 000 chicken expressed sequence tags. Over twenty-three normalised cDNA libraries from a wide range of adult and embryo tissues were constructed and sequenced from the 5' ends. Currently, these expressed sequence tags have been clustered into approximately 60 000 unique gene clusters and will be submitted to the European Molecular Biology Laboratory database in February 2002. These cDNA clones will be used to create cDNA microarrays for high-throughput gene expression analyses. In addition, the cDNA clones and microarrays will be made available to any interested groups from the *ARK-Genomics* facility (contact Richard.Tablot@bbsrc.ac.uk or access the WWW site at http://www.ark-genomics.org/).

Testing candidate-genes will be difficult for quantitative traits when compared with genetic diseases, since the effect is likely to be subtle. Evidence in favour of a candidate-gene is likely to be an accumulation of evidence, such as: (a) sequence homologies and literature searches; (b) sequence variants; (c) population-wide association studies; (d) changes in gene expression patterns; (e) models of protein structure and function. This new era of functional genomics (Lander & Weinberg, 2000) requires access to large resources (arrayed cDNA and bacterial artificial chromosome libraries, expressed sequence tag databases, etc.) and high-throughput technologies (sequencing, microarrays, etc.). *ARK-Genomics* (http://www.ark-genomics.org/), the 'UK Centre for Functional Genomics in Farm Animals', is an initiative funded by the Biotechnology and Biological Sciences Research Council (UK) that aims to fill this gap (Burt *et al.* 2002). The aim of this project is to build strong links between genomics, physiology, immunology and developmental biology to identify genes controlling traits of interest in agriculture and human health.

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