The Sheep Gene Map
Thomas E. Broad, Diana F. Hill, Jillian F. Maddox, Grant W. Montgomery, and Frank W. Nicholas

INTRODUCTION

Since their domestication around 7000 to 9000 BC, sheep have significantly influenced the economic, social, and cultural fabric of human society. The volume entitled “The Genetics of Sheep,” edited by Piper and Ruvinsky (1997), contains comprehensive reviews of several aspects outlined in the following brief discussion of the sheep gene map. Only summary details of these aspects are included below.

Taxonomy

The genus *Ovis* (Figure 1) comprises several wild and domesticated species (Maijala 1997). This taxonomical usage is controversial since all of these so-called “species” can interbreed (Franklin 1997). However, based on chromosome number, 4 cytogenetic groupings of at least 8 species of sheep are recognized at the time of this writing:

2n=52 *Ovis nivicola* (snow sheep or Siberian bighorn)
2n=54 *Ovis aries* (domestic sheep)

*Ovis canadensis* (bighorn)
*Ovis dalli* (thinhorn or Dall’s sheep)
*Ovis musimon* (European mouflon)
*Ovis orientalis* (Asiatic mouflon, Urial)

2n=56 *Ovis ammon* (Arkhar-Argali, giant wild sheep)
*Ovis ammon severtzovi* (Severtsov wild sheep)
(Lyapunova and others 1997)

2n=58 *Ovis vignei* (Oriental steppe sheep)

The name *Ovis aries*, which has been given to the domestic sheep apparently to distinguish it from the wild sheep, is thought to be derived from *Ovis orientalis* (the Asiatic mouflon, which may also be the ancestor of the European mouflon [Maijala 1997]). Of the wild sheep, the thinnhorn, bighorn, and snow sheep have never been domesticated (Maijala 1997). Most if not all of the gene mapping work has been, and continues to be, done on various breeds of the domestic sheep, *Ovis aries*. For details of these breeds, see Maijala (1997).

The genus *Ovis* is one of the 10 genera usually included in the subfamily Caprinae. A variety of evidence suggests that *Ovis* diverged contemporaneously from the goats (*Capra*) and chamois (*Rupicapra*) approximately 5 million yr ago (Franklin 1997).

The subfamily Caprinae is one of the 9 subfamilies that comprise the family Bovidae, which includes the subfamily Bovinae and comprises the bison, buffalo, and wild and domestic cattle. The Caprinae are believed to have diverged from the Bovinae and other bovid species approximately 17 to 25 million yr ago (Franklin 1997). Robertsonian translocations appear to be common in many of the bovid lineages and result in the differences in chromosome number between them. Thus, 3 centric fusion events account for the differences in chromosome number of sheep compared with goats.
and cattle (2n=60). Apart from a few other minor chromosomal rearrangements, there is a very high level of banding similarity between the chromosomes of sheep, goats, and cattle. This similarity has enabled the nomenclature of the karyotypes of these species to be correlated (Popescu and others 1996), a development that together with their close evolutionary relatedness, has been particularly important for the mapping of the genomes of all 3 genera.

The family Bovidae (cattle, sheep, and goats) is a member of the suborder Ruminantia. The deer also comprise a large grouping (family Cervidae) of this suborder. These groupings also have important implications for the mapping of the sheep genome, as discussed below. (The true ruminants, with 3-chambered stomachs, are classified into the Pecoran infraorder.) The suborders Ruminantia (deer, cattle, goats, and sheep), Tylopoda (camelids), and Suiformes (pigs, peccaries, and hippopotamuses) are members of the order Artiodactyla (Franklin 1997). Thus, a relatively close evolutionary relationship can be seen to exist between sheep, goats, cattle, deer, and pigs.

Genetic Nomenclature

Following the recommendations of the International Society for Animal Genetics, mapped loci on sheep and other farmed animal genomes are named using human nomenclature guidelines. These human guidelines are designed to facilitate the identification of orthologues in sheep, reflecting the extensive past and current use made of heterologous (particularly human) gene probes and nucleotide sequence data in the mapping of these genomes. The names and symbols of human genes can be obtained on the World Wide Web (Web) from the Genome Database (http://gdwww.gdb.org/gdb/gdbtop.html) and the Human Genome Organization (HUGO) Genome Database Nomenclature Committee (http://www.gene.ucl.ac.uk/nomenclature/). Condensed guidelines containing rules for homologies with other species have recently been published by White and others (1997).

For all other loci, or those for which no human equivalent was available at the time of preparation, the naming of sheep loci followed the recommendations of the Committee on Genetic Nomenclature of Selected Animal Genera (COGNOSAG1). Recommendations of COGNOSAG are published in reports of the COGNOSAG Ad Hoc Committee (1995), Lauvergne and others (1996), and Dolling (1997). In these guidelines, the nomenclature for the keratins—especially the wool keratins and associated proteins—are from Powell and Rogers (1994).

1Abbreviations used in this paper: CAB, Center for Animal Biotechnology; COGNOSAG, Committee on Genetic Nomenclature of Selected Animal Genera; CSIRO, Commonwealth Scientific and Industrial Research Organization; FAO, Food and Agriculture Organization; FISH, fluorescence in situ hybridization; IMF, International Mapping Flock; NCL, neuronal ceroid lipofuscinosis; USDA, US Department of Agriculture; Web, World Wide Web.

REASONS FOR MAPPING THIS SPECIES

As is the case for most species, gene mapping of the sheep is being performed mainly for the following purposes:

1. to enhance the quality and diversity of sheep and their products by positive or negative marker-assisted selection;
2. to improve animal health and welfare by marker-assisted selection to eliminate diseases and to protect the environment by reducing the need for widespread use of agrochemicals;
3. to investigate aspects of speciation and evolution;
4. to establish models for elucidating the etiology and treatment of human genetic disease; and
5. to protect genetic diversity and rare breeds and species.

CURRENT MAP STATUS

Maps and associated sheep genome mapping data in the public domain are compiled and available on the Web in SheepBase (http://zaphod.invermay.cri.nz/). As of December 3, 1997, 627 loci, of which 245 are known genes, have been mapped in sheep. These loci are graphically displayed in 2 linkage maps and 1 cytogenetic map, depending on the method of their mapping. The linkage maps are (1) SM1, which is a static framework linkage map of Crawford and others (1995) constructed using the International Mapping Flock (IMF1) pedigrees; and (2) SMC, a dynamic consensus sheep linkage map, calculated using SM1 as a framework, containing newly published loci. Included in SMC is a map of the X chromosome based on the publication of Galloway and others (1996). The cytogenetic map contains mainly physically mapped loci. Loci that have been assigned only to a syntenic group are listed in the Locus Manager of SheepBase.

The framework linkage map of Crawford and others (1995) has been updated by a second-generation linkage map based on the IMF and US Department of Agriculture (USDA1) Meat Animal Research Center (Clay Center, Nebraska) pedigrees (De Gortari and others 1998). This map has 519 markers, including 504 microsats of which 74% have also been mapped in cattle, and a total autosomal length of 3063 cM. Work is under way to install it in SheepBase where it will be displayed together with the first-generation framework map of Crawford and others (1995).

A third-generation autosomal linkage map with an estimated length of 3492 cM is presently under construction at the time of this writing (Dr. Jill Maddox, Centre for Animal Biotechnology (CAB1), University of Melbourne, personal communication, 1998). Based on and extending the first- and second-generation maps (see above), the CAB map is 3270 cM long. A list of markers that are included in the third-generation map and CAB map is presently accessible on the Web at http://rubens.its.unimelb.edu.au/~jillm/JILL.HTM. Comparative data on the relative lengths of each...
of the autosomes in the CAB second- and third-generation maps and the numbers of markers mapped on each autosome are also available at this site. The third-generation map gives an average coverage of 4.2 cM between markers on the sheep genome except for regions missing from ends of chromosomes as deduced from comparisons among cattle and sheep maps (Table 1) and regions of the sheep map with gaps greater than 20 cM as deduced from comparisons among cattle and sheep maps (Table 2).

**APPROACHES USED TO DEVELOP THE MAP**

Physical (cytogenetic) and genetic (linkage) mapping procedures constitute the main mapping approaches for sheep. Both have been reviewed (Broad and others 1997; Montgomery and Crawford 1997).

**Physical Mapping**

Several attempts have been made since 1976 to produce a globally accepted standard karyotype for the sheep (Ansari and others 1994). Agreement was reached in Texas in 1995 for a standard sheep karyotype that was correlated with the cattle standard on the basis of similar banding patterns and gene loci (Broad and others 1997). The G-/Q- and R-banded idiograms of Ansari and others (1996), derived from sequentially Q- to G-banded and Q- to R-banded metaphase spreads, are fully consistent with the 1995 (Texas) standard sheep karyotype. These karyotypes were constructed by conventional cytogenetic procedures from sheep with 3 different Robertsonian chromosomes that served as morphological markers. Nucleolar organizer chromosomes were used as cytological markers.

At the lowest level of resolution, loci may be mapped to individual chromosomes by analysis of somatic cell hybrids. A cytogenetically characterized panel of 30 sheep-hamster cell hybrids representing the complete sheep genome has been produced for this purpose (Burkin and others 1997a). Alternatively, mapping to synteny groups (which have now been assigned to specific ovine chromosomes) can be performed using the panel of hamster-sheep cell hybrids developed by Saidi-Mehtar, Hors Cayla, and colleagues (Imam-Ghali and others 1991). The production of individually flow-sorted sheep chromosomes (Burkin and others 1997b) complements these cell hybrids as an additional resource for assigning loci to sheep chromosomes.

At a higher level of resolution, loci may be assigned to subchromosomal regions by in situ hybridization using iso-topically or fluorescently labeled probes (reviewed in Broad and others 1997). Whereas the level of resolution achievable by fluorescence in situ hybridization (FISH) on metaphase or prometaphase chromosomes is generally recognized to be about 1% of the length of the genome, considerably higher resolution (to between 200 and 300 kb) can be obtained using fiber FISH (Mann and others 1997).

Beyond this chromosomal level of resolution, physical mapping is performed by molecular techniques using a sheep yeast artificial chromosome library with an average insert size of approximately 650 kb (Broom and Hill 1994), and a sheep bacterial artificial chromosome library with an average insert length of 100 kb (C. Bottema, University of Adelaide, Waite Campus, South Australia, personal communication, 1998). Cosmid and plasmid libraries of the sheep genome have been constructed in commercial laboratories such as Clontech and various research institutions (including AgResearch in New Zealand; CAB, Commonwealth Scientific and Industrial Research Organization (CSIRO), and Howard Florey in Australia; and Basel Institute for Immunology in Switzerland). Specific libraries may be available on request from particular laboratories.

**Linkage Mapping**

Laboratories in New Zealand, Australia, and the United States have collaborated to develop the sheep linkage map using a common set of reference pedigrees. The first linkage map was published in 1995 using the AgResearch International Mapping Flock (IMF, Crawford and others 1995). The map contained 232 markers covering 2070 cM with an average distance of 14.4 cM between markers (Crawford and others 1995). This map represented approximately 75% coverage of the sheep autosomes.

The IMF flock, on which this first map was based, comprises 9 3-generation full-sib pedigrees with 222 informa-
tive meioses. DNA from these families has been distributed to 14 laboratories worldwide. Subsequently, additional families were developed by the USDA at Clay Center, Nebraska (De Gortari and others 1998). These families consist of 247 backcross progeny from mating 4 F1 Romanov-cross rams to Romanov ewes. The combined set of reference pedigrees was used for the second-generation linkage map (De Gortari and others 1998). This map containing 519 markers increases the coverage of the map by approximately 1000 cM and consolidates all of the linkage groups into 1 per chromosome. A third set of sheep mapping pedigrees has been developed by CSIRO and comprises 15 3-generation full-sib families of 182 progeny produced by mating 2 Romney rams carrying the t1 and t2 Robertsonian translocations with 9 fine-wool Merino ewes carrying the Booroola fecundity gene. The largest of these families has 29 offspring. Combined with the other flocks, this is the basis of the third-generation map (see above) of 3492 cM comprising 829 markers.

An important feature of the sheep linkage map has been the extensive use of cattle microsatellite markers, which greatly facilitates the comparison of the ovine and bovine maps. Approximately 50% of bovine microsatellite primer pairs amplify informative markers in sheep (De Gortari and others 1997); 402 (80%) of the linked microsatellites in the second-generation sheep map are bovine primer pairs, and 553 (67%) in the third-generation map are bovine in origin. The ovine and bovine maps show extensive conservation of marker order even within linkage groups, with some exceptions. One such exception is sheep chromosome 9 whose proximal region appears to have been translocated from the subtelomeric end of cattle chromosome 9 to fuse with cattle chromosome 14, which has conserved linkage with the remainder of sheep chromosome 9 (Crawford and others 1995). An equivalent translocation event is observed in goats (Vaiman and others 1996).

In addition to the reference families used for the framework maps, several groups are mapping in resource families (see below) as part of searches to identify quantitative trait loci or for positional cloning projects. A map of sheep chromosome 6 was developed using the IMF pedigrees together with families segregating for the Booroola fecundity gene (Lord and others 1996). A map of the sheep X chromosome with 14 markers and 7 genes was reported by Galloway and others (1996). A detailed map of the distal region of sheep chromosome 18, which harbors the Callipyge gene, has been reported by Cockett and others (1996).

Although the large majority of markers are microsatellites, other categories of markers are single-strand conformation polymorphisms, restriction fragment length polymorphisms, minisatellites, and protein polymorphisms (Montgomery and Crawford 1997). Random-amplified polymorphisms have been developed and mapped by Cushwa and others (1996); and more recently, amplified fragment length polymorphism markers have also been mapped in sheep (J. Lumsden, AgResearch Molecular Biology Unit, Dunedin, New Zealand, personal communication, 1998).

### AVAILABLE FLOCKS FOR MAPPING

#### Reference Flocks

Three flocks have been generated specifically for mapping (see above also): (1) IMF, comprising 9 pedigrees each of 3 generations (Crawford and others 1995); (2) the CSIRO mapping flock of 15 3-generation full-sib families (Dr. Beryl van Hest, CSIRO Prospect, NSW, Australia, personal communication, 1998); and (3) the USDA Meat Animal Research Center Clay Center flock (De Gortari and others 1998). DNA from these flocks is available on request for mapping purposes. The widespread use of these flocks (particularly the IMF early on) by the sheep genome mapping community has been instrumental in coordinating the global development of a single major map for the species.

#### Resource Flocks

The wealth of material generated in both single and quantitative trait loci selection lines for genetic studies may also be of value in genetic studies in other species. Because of the potential comparative benefit of this material, we briefly list and describe this material below. However, it should be noted that this compilation is not comprehensive.

#### Disease-resistant Flocks

**Parasite resistance.** Eight independent lines of sheep have been selected in New Zealand and Australia for resistance and susceptibility to internal parasites (see Morris 1998). In New Zealand, gene mapping studies have focused primarily on divergent fecal egg count lines of Romney sheep that have now diverged by a population standard deviation of 2.6. Rams produced by reciprocal crosses between these lines have been outcrossed to unselected Coopworth ewes, and the progeny that exhibit variation in their resistance to parasites (from susceptible to tolerant/resistant) are being genotyped using a full genomic scan (Crawford and others 1997a). Work is under way to genotype a Haemonchus selection flock between Dr. Jill Maddox of Melbourne University, Melbourne, Australia, and Dr. Jim Miller of Louisiana State University, Baton Rouge, Louisiana.

**Facial eczema.** Facial eczema is a mycotoxicosis caused by the ingestion of the hepatotoxin sporedesmin produced by the fungus *Pithomyces chartarum*, which lives on rye grass litter in pasture. Since 1975, resistant and susceptible lines of Romney sheep have been bred while being monitored by the serum concentrations of the hepatic enzyme gamma glutamyl transpeptidase after oral administration of the toxin. The lines have now diverged by 2.3 standard deviations (Morris and others 1995b). The selection lines were crossed in 1992, and 4 F1 rams were outcrossed to unselected Romney ewes. The resulting progeny are being genotyped using both a candidate
gene and genomic scan approach (Crawford and others 1997b).

**Rye grass staggers.** The toxin lolitrem B of an endophytic fungus in rye grass produces rye grass staggers. A genetic correlation of 0.3 has been found between this condition and facial eczema, suggesting possible common pathways of detoxification. Based on natural challenge, selection lines in Romney sheep established since 1993 show a divergence of 0.8 phenotypic standard deviations (Morris and others 1995a). Genotypic analysis is presently limited to the investigation of candidate genes from the facial eczema study.

**Footrot.** Morris (1998) lists heritability estimates in Australian Merino and New Zealand Romney sheep for susceptibility to footrot, a disease produced by the bacterium *Dichelobacter nodosus*. Selection lines were established in Australian Merinos in 1993 (Raadsma and others 1996). Candidate genes are being tested in half-sib families that have been scored for clinical and antibody response to infection and vaccination.

**Medical Models**

**Cystic fibrosis.** A DNA variant has been found of the ovine cystic fibrosis transmembrane conductance regulator (CFTR) gene that was previously reported as a putative mutation causing cystic fibrosis in humans (Tebbutt and others 1996). Using multiple ovulation-embryo transfer techniques, a ram lamb carrying this mutation in the homozygous state has been produced and will be used to generate progeny for subsequent clinical and genetic investigation. The advantages of an ovine model for cystic fibrosis have been discussed by Harris (1997).

**Batten disease/neuronal ceroid lipofuscinosis (NCL)**: Batten disease is the most common of the neuronal ceroid lipofuscinoses. An ovine form of this storage disorder, which results in progressive neuronal degeneration and leads to blindness, deafness, and death, has been extensively characterized by Jolly and colleagues (1992) in South Hampshire sheep in New Zealand. Although a small nucleus flock of affected animals is maintained, a substantial archive of more than 300 DNA samples from 60 pedigrees has been established and is being used to genetically characterize the disease, initially by gene mapping. In humans, at least 6 variants of NCL have been described. The genes for only 3 of these are known at the time of this writing, but mapping has excluded them from involvement in the ovine NCL (Dr. M. Broom, Molecular Biology Unit, Biochemistry Department, University of Otago, Dunedin, New Zealand, personal communication, 1998). Analysis of regions of the genome harboring the other variants is under way at the time of this writing.

**Congenital cataract.** Sheep with congenital cataract were identified by Dr. R. D. Jolly, Department of Veterinary Pathology and Public Health, Massey University, Palmerston North, New Zealand. At the time of this writing, 3 carrier rams descended from these animals are being mated to unselected ewes at AgResearch Invermay, Mosgiel, New Zealand, to generate a nucleus flock in which the affected gene is segregating.

**Noneruption of incisor teeth.** It appears that a recessive gene originating in a carrier ram in an unselected line of Coopworth sheep (Broad and others 1996) results in noneruption of incisor teeth and leads to death after weaning. At the time of this writing, a nucleus flock harboring the gene is being established for subsequent candidate gene and clinical investigation.

**Inherited deafness.** Sheep obtained from at least 3 independent flocks have been demonstrated by electrophysiology testing to be profoundly deaf. Breeding of affected individuals is under way for candidate gene studies.

**Chromosome translocation flocks.** Nucleus flocks are being maintained of sheep carrying the following Robertsonian translocations: t1 (rob 6;24), t1 (rob 9;10), t1 (rob 7;25), and t2 (rob 8;22) (Ansari and others 1993; Pearce and others 1994). Sheep with the first 3 of these centric fusions are derived from those initially detected by Bruere and others (1974) in New Zealand Romney sheep. All except the last are maintained in a homozygous state, and a flock carrying multiple translocations has been established in which the 2n chromosome number of several animals is 48.

**Body Composition Traits**

**Backfat.** Beginning in 1981, high (fat), low (lean), and control lines of Coopworth sheep were established at Invermay based on ultrasonic fat depth scans over the last rib, corrected for body weight. In birth years 1991 and 1992—the last 2 yr of selection—the fat and lean lines had diverged 2.08 and −0.85 mm in fat depth from the control line (equivalent to +2.50 and −1.03 phenotypic standard deviations, respectively). Large responses were recorded in live weight between the lines, with the fat and lean lines averaging 34.0 and 40.2 kg compared with 38.0 kg for the controls (Morris and others 1997). In 1993, the fat and lean lines were crossed: F1 rams were subsequently backcrossed with both selection lines in 1995 and 1996 (Jopson and others 1998). At the time of this writing, progeny born from these reciprocal backcrosses are being subjected to candidate gene genotypic analyses. High and low backfat Southdown selection lines of sheep were also established in 1979 (Carter and others 1989), but these have been the subject of limited physiological analyses.

**Glucose clearance.** A nucleus is being maintained of a flock of Coopworth sheep that were selected on the basis of the plasma clearance of a bolus intravenously injected dose of glucose. There was an initial but no subsequent divergence of the selection lines, with the slow-clearance line having a 3% higher basal plasma glucose level than the control line and the fast line 10% lower than the controls. The fast-clearance line had higher plasma insulin levels during the test and 11% more subcutaneous fat at the same carcass weight than the slow-clearance line (Francis and others 1994).
MUSCLING. The Callipyge gene, which produces muscular hyperplasia in sheep (particularly of the hindquarters), has been mapped to the distal region of sheep chromosome 18. Only the paternally inherited copy of Callipyge appears to be expressed (Cockett and others 1996). The gene was first detected in a ram called “Solid Gold” in a commercial Dorset flock in Oklahoma and was subsequently found to transmit the unusual phenotype to its descendants. Several flocks containing the gene have now been established in the United States, Canada, and Europe. Work is under way to identify the gene by positional cloning.

The Carwell locus, which increases the size of the rib-eye (longissimus dorsi) muscle in sheep, has been detected in the progeny of rams derived from the Carwell Poll Dorset stud, Armidale, NSW, Australia (Nicoll and others 1998). The Carwell locus maps to a similar region of sheep chromosome 18 as the Callipyge gene. Work is under way to study the inheritance of the locus in commercial synthetic flock of sheep (Nicoll and others 1997) and to determine whether it is allelic to Callipyge.

Milk and meat traits. In 1995, Raadsma and Nicholas at the University of Sydney began the establishment of a resource flock for milk, fleece, and meat traits by crossing Awassi rams with fine wool Merino ewes. Backcross progeny are being scored for the widest possible range of traits: Female progeny are being scored for all the important milk yield and composition traits throughout a lactation; male progeny are being scored for food intake, growth, and meat quality traits; and all progeny are being recorded for a wide range of scoreable traits including coat color, breed type, and tail length. All progeny are also being subjected to a genome scan with 150 markers. A recessive pigmentation gene suspected to be a homologue of the mouse agouti gene has been reported in the progeny derived from a “self color” grandsire crossed to white dams and subsequently backcrossed to self-color ewes (Parsons and others 1997).

Fecundity Traits

The Booroola fecundity gene appears to have arisen de novo in the “Booroola” Merino commercial flock in which the Seears brothers in Australia selected to increase its frequency. By 1980, it was regarded as a single autosomal mutation, and it is now known to increase litter size by 1 lamb per gene copy due to an additive effect on ovulation rate. The gene has subsequently been mapped to sheep chromosome 6 using a whole genome scanning approach (reviewed in Montgomery and others 1994), and work is under way to find more closely linked markers and to isolate the gene by positional cloning methods.

The Inverdale prolificacy gene was first discovered in 1984 in a prolific family of Romney sheep that descended from 1 ewe. Progeny testing of her male descendants carried out from 1985 to 1990 indicated the presence of the Inverdale fecundity gene on the X chromosome. One copy of the gene increased ovulation rate by about 1.0 and litter size by about 0.6. However, in 1991 it was found that ewes with 2 copies of the gene have small nonfunctional “streak” ovaries and are infertile. Then in 1993, the gene was found in a second independent prolific flock of Romney sheep (Davis and others 1995). Mapping is under way to find markers linked to the gene (Galloway and others 1995, 1996).

WOOL TRAITS

Ultrafine Merino rams were mated in 1991 with high fleece weight-selected Romney ewes to generate F1 rams that were mated over 2 yr with Merino ewes to generate backcross progeny. A similar series of matings was performed with Romney ewes to produce reciprocal backcross progeny. Genomic scans are being performed to detect linkage with the following wool traits: fleece weight, fiber diameter, medullation, staple strength, staple length, fiber crimp, brightness, yellowness, bulk, and resilience (Wuliji and others 1995). A similar study involving genome scans is under way in Victoria, Australia, using a wool-trait selection flock generated from rams derived from superfine Merino grandsires mated with Border Leicester and strong-wool Merino ewes that were backcrossed to strong-wool Merino ewes to produce large family groups each containing at least 100 animals (Ward and others 1995).

Candidate gene studies are under way at the time of this writing for wool production and wool quality traits in animals of the CSIRO mapping flock (described in detail above). Material from this flock is available on request from Dr. Beryl van Hest, CSIRO, Prospect, NSW, Australia.

SCIENTIFIC CONTRIBUTIONS OF THE MAP

Mapping Successes

Genetic maps and markers are being applied in sheep to problems of parentage and individual identification, mapping genes affecting production, and studies of evolution. Markers have been used to check the accuracy of pedigree records (Crawford and others 1993) and to confirm the origin of offspring after cloning by nuclear transfer (Campbell and others 1996). The number of loci with phenotypic effects that have been mapped to specific locations is increasing (Table 3). Loci include those affecting carcass traits, milk production, ovulation rate, litter size, wool quality, and fleece weight. These traits have been mapped using a combination of candidate gene studies and genome scans.

Although not yet published at the time of this writing, a point mutation has been found (Beever and others 1998) in the fibroblast growth factor 3 receptor gene for spider lamb syndrome, which results in the excessive development of cartilage leading to bone deformities (Lauvergne and others 1996). Use of this genetic knowledge, and of the markers linked to these traits, is expected to contribute to the devol-
TABLE 3  Single gene and quantitative trait loci associations reported for sheep

<table>
<thead>
<tr>
<th>Trait</th>
<th>Locus</th>
<th>Chromosome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcass traits</td>
<td>Adipocyte fatty acid binding protein</td>
<td>NIa</td>
<td>Cockett and Medrano (1996)</td>
</tr>
<tr>
<td>Carcass traits</td>
<td>Lipoprotein lipase</td>
<td>2</td>
<td>Cockett and Medrano (1996)</td>
</tr>
<tr>
<td>Muscular hypertrophy</td>
<td>Callipyge</td>
<td>18</td>
<td>Cockett and others (1996)</td>
</tr>
<tr>
<td>Hypertrophy of L. dorsi muscle</td>
<td>Carwell</td>
<td>18</td>
<td>Nicoll and others (1998)</td>
</tr>
<tr>
<td>Milk production</td>
<td>Growth hormone</td>
<td>11</td>
<td>Gootwine and Olor (1996)</td>
</tr>
<tr>
<td>Milk production</td>
<td>OarJMP8</td>
<td>6</td>
<td>Diez Tascon and others (1996)</td>
</tr>
<tr>
<td>Prolificacy</td>
<td>Booroola fecundity gene</td>
<td>6</td>
<td>Montgomery and others (1994)</td>
</tr>
<tr>
<td>Prolificacy</td>
<td>Inverdale fecundity gene</td>
<td>X</td>
<td>Davis and others (1995)</td>
</tr>
<tr>
<td>Ovulation rate</td>
<td>Hemoglobin beta</td>
<td>15</td>
<td>Glazko and others (1997)</td>
</tr>
<tr>
<td>Wool fiber diameter</td>
<td>Fibroblast growth factor 1</td>
<td>NI</td>
<td>Robinson and others (1995)</td>
</tr>
<tr>
<td>Wool fiber diameter</td>
<td>Keratin-associated protein 6</td>
<td>1</td>
<td>Parsons and others (1994)</td>
</tr>
<tr>
<td>Wool fleece weight</td>
<td>Fibroblast growth factor 1</td>
<td>NI</td>
<td>Robinson and others (1995)</td>
</tr>
<tr>
<td>Wool strength</td>
<td>Keratin gene complex</td>
<td>11</td>
<td>Rogers and others (1994)</td>
</tr>
<tr>
<td>Horns</td>
<td>Horns</td>
<td>10</td>
<td>Montgomery and others (1996)</td>
</tr>
</tbody>
</table>

*NI, ovine chromosome not identified at the time of this writing.

Development of marker-assisted selection procedures to accelerate the genetic improvement of sheep. This subject has been reviewed by Montgomery and Kinghorn (1997).

Comparison with Other Genomes

The locations of 220 known genes on the sheep genome have been compared with their counterparts in cattle, pig, human, and mouse (Broad 1997). Displays of these data in Oxford grids illustrate the extent of conservation of chromosomal organization (conserved synteny) among these species—greatest with cattle and least with mouse. Thus, there is a one-to-one correspondence between chromosomes and chromosomal arms of the sheep and cattle genomes but increasing fragmentation compared with human and mouse, respectively. A total of 40 conserved chromosomal segments have been identified to date between sheep and human, and 55 between sheep and mouse.

There is also a high level of conserved synteny between the sheep and deer genomes (see below). Unlike comparisons of sheep with human and mouse, this conservation appears to extend to conserved linkage, that is, where the relative order of loci within these conserved segments is also conserved (Broom and others 1996). Thus the deer map may be useful in fine-mapping the sheep and possibly other artiodactyl or ruminant genomes.

ANTICIPATED FUTURE CONTRIBUTIONS OF THE MAP

Generation of a Generic Ruminant Map

An interspecies deer hybrid mapping panel has been generated from 346 1/4 Pere David’s deer × red deer hybrids (Tate and others 1997a). At the time of this writing, the deer map contains 251 mapped loci, of which 115 are mapped in human, 93 in sheep, and 113 in cattle. Comparison of the relative order of these loci in the different species has revealed very few rearrangements between sheep, cattle, and deer. However, comparison of the deer and human maps reveals considerable evidence for conserved synteny but not conserved linkage. Thus, for ruminants, the availability of the interspecies mapping panel provides an invaluable resource for mapping and ordering loci across a wide range of species (Tate and others 1997b).

It would be both novel and useful if the deer map became the generic map for ruminants such as sheep, goats, and cattle. Two main uses for it are immediately apparent: for efficiently establishing the order of loci within regions of conserved synteny and for efficiently mapping type I loci (known genes and expressed sequence tags) from other species precisely onto the ruminant chromosomes. In the context of this review, the latter application has great appeal since the availability of the deer interspecies mapping panel overcomes 2 important comparative mapping bottlenecks: marker heterozygosity and integration of new mapping data with existing physical and linkage mapping information. In the deer panel, variation can be readily demonstrated in most markers (saving considerable time and expense). In addition, using breakpoint mapping analysis, most syntenic markers can be rapidly ordered relative to each other or, at worst, grouped into “bins” of adjacent markers. This process facilitates the extrapolation of mapping information from human and mouse and other species into the ruminants and will accelerate positional cloning studies.

Sheep Models of Human Genetic Diseases

Although the relevance of any animal model depends on anatomical, physiological, and genetic similarity to the hu-
man disorder, sheep have several general advantages over mice and other laboratory animals as potential models for the study of human diseases and metabolic disorders. Physically, sheep are similar in size to human subjects, facilitating the development of new surgical procedures and the testing of therapeutic agents. Phylogenetically, sheep are more closely related to humans than are mice and other rodents. On some cultural and religious grounds, there are fewer restrictions to using sheep than pigs. In countries such as New Zealand and Australia, the cost of sheep is substantially lower than in Europe and many other regions. These comparative advantages have contributed to the development of ovine models for several human disorders (see below). Nicholas (1997) has listed 36 traits and inherited disorders in sheep that may be potential models for human disorders.

Conservation Biology

Mapped microsatellite markers have been used to determine evolutionary relationships between sheep breeds (Buchanan and others 1994) and parentage in wild populations such as Soays (Gulland and others 1993) and Rocky Mountain Big-horns (Forbes and others 1995). The sheep genome map and its associated resources can be used to help in the conservation of sheep breeds. It has been estimated that 148 breeds of sheep have become extinct in the last 100 yr (see Ponzoni 1997).

The issue of genetic resources conservation is becoming increasingly acute for sheep as well as for all other biota. For a comprehensive review of this area as it concerns sheep, see Ponzoni (1997). For information on the United Nations Food and Agriculture Organization (FAO) global program for management of farm animal genetic resources, see the FAO Web site (http://dad.fao.org/dad-is/library/programm/index.htm). As part of this developing global initiative, an expert committee is making recommendations for a panel of microsatellite markers to assist in identifying sheep breeds at risk of extinction by measuring the relative diversity of the existing breeds. At the time of this writing, the large Domestic Animal Diversity Information System (DAD-IS) database of relevant Web information has moved from the design to the implementation phase (http://dad.fao.org/dad-is/index.htm).

Fundamental Science

As the pace of gene mapping increases in sheep and in other species, evolutionary break points may be characterized that will help us understand the events associated with speciation. The sites of meiotic breakpoints may also be dissected and may assist in defining, or even manipulating, mechanisms of chromosome rearrangement. Ultimately, this information on chromosome structure and organization may lead to a more thorough understanding of gene expression, which may in turn result in the development of novel methods to control patterns of growth and development.

USES OF THE MAP AND ACCESSIBILITY

SheepBase

SheepBase is a database of publicly available, updated mapping information and associated data that are accessible on the Web (http://rubens.its.unimelb.edu.au/). The primary site of SheepBase is AgResearch Invermay, Mosgiel, New Zealand; secondary nodes are available at the Roslin Institute, Edinburgh (http://www.ri.bbsrc.ac.uk/sheepmap/), and at the US National Agricultural Library, Beltsville, Maryland (http://tetra.gig.usda.gov:8400/).

The software platform for SheepBase is ARKdb, the same as that for PigBase, ChickBase, and BovBase. This platform—Anubis, the graphical map display, and the Web interface—were developed by Chris Mungall and Dr. Jian Hu of the Roslin Institute, Edinburgh, and Dr. Alan Hillyard, formerly of the Jackson Laboratory, Maine. SheepBase initially used the GBASE (mouse) database developed by Jackson Laboratory. ARKdb has been designed as a generic single-species genome database. It is hoped that its adoption by an increasing number of species mapping groups will establish a common foundation that will facilitate between-genome comparisons.

In the new ARKdb platform, the stored information includes chromosomal locations and relative positions (where reported) of loci, full reference citations, and details of DNA polymorphisms, clones, and probes. The addition of links to other databases is planned.

Other Useful Sheep Databases

A wealth of sheep genome data organized, collated, and annotated by Frank Nicholas and colleagues (University of Sydney, NSW, Australia) is now available on the Web at the Australian National Genome Information Service (http://www.angis.su.oz.au). Based on McKusick’s online database of human disorders entitled Mendelian Inheritance in Man (http://www3.ncbi.nlm.nih.gov/omim/), Nicholas has created Mendelian Inheritance of Animals (MIA) online at the Web address http://angis.su.oz.au/Databases/BIRX/omia/, where more than 139 ovine traits and disorders are listed together with a complete list of references. Some of this material has been published (Nicholas 1997). Also online at the same address are the COGNOSAG catalogs of loci, which have been published under the title Mendelian Inheritance in Sheep MIS96 (Launverge and others 1996). In the database entitled Online Chromosomes of Animals, Nicholas has also made available a complete bibliography of sheep and other animal karyotypes.

At the CAB Web site (http://rubens.its.unimelb.edu.au/-jillm/JILL.HTM), Jillian Maddox has made available her compilations of detailed comparative mapping data of sheep and other mammals in addition to reports of Australasian linkage mapping meetings.
CONCLUSION
Coordination of Action

Sheep genome research is being pursued actively in many countries around the world at the time of this writing; however, no formal mechanism exists to coordinate this effort. Research findings are widely communicated in a broad range of scientific journals and at equally diverse conferences, workshops, and other forums. In addition, a national sheep mapping program entitled SheepMap™ has been established in New Zealand. For full details, click on http://agresearch.cri.nz and http://biochem.otago.ac.nz:800/panzora/mbu/mbu3.html. In the United States, the sheep genome initiative is coordinated by Professor Noelle Cockett, Utah State University, Logan, Utah, under the US Department of Agriculture National Animal Research Program.

Future Perspectives

Although funded relatively modestly compared with cattle and pig genome programs, the sheep genome mapping initiative has already contributed substantially to knowledge of the organization and evolution of the vertebrate genome and has laid solid foundations for developing a better understanding of the genetic basis of the biology of the sheep. As more detailed investigations proceed in the future of those regions of the sheep genome that are shown to be important economically to the sheep industry or medically to human health, there will be increasing opportunity for comparisons with the genomes of other species. These finely mapped regions of the sheep genome will, of necessity, be rich in information about the coding regions and other landmark loci and of the spatial organization and distances between these loci. Data such as these will provide the substance rather than the flavor of comparative genome analyses. For this we are all impatient!

ACKNOWLEDGMENTS

We gratefully acknowledge Dr. A. L. Archibald, C. Mungall, Dr. Jian Hu, and colleagues of the Roslin Institute, Edinburgh, for making the software platform ARKdb available to us and for their help in establishing SheepBase. The work of T. E. B., D. F. H., and G. W. M. was funded as part of a program grant to AgResearch from the New Zealand Foundation for Research, Science and Technology. J. F. M.’s work was funded as part of a grant for the Australian Meat Research and Development Council.

REFERENCES

Broom JE, Tate ML, Dodds KG. 1996. Linkage mapping in sheep and deer identifies a conserved pecora ruminant linkage group orthologous to two regions of HSA16 and a portion of HSA7q. Genomics 33:358-364.


Lord EA, Lumsden JM, Dodds KG, Henry HM, Crawford AM, Ansari HA, Pearce PD, Maher DW, Stone RT, Kappes SM, Beattie CW, Montgomery GW. 1996. The linkage map of sheep chromosome 6 compared with the orthologous regions in other species. Mamman Genome 7:373-376.


Raadsma HW, Attard GA, Nicholas FW, Egerton JR. 1996. Disease resistance in Merino sheep: Genetic heterogeneity in response to vaccination...


