Chapter 5

Detection of QTL Underlying Milk Traits in Sheep: An Update

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Additional information is available at the end of the chapter

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1. Introduction

The worldwide production of sheep milk was 9,246,922 tonnes in 2009, whereas dairy cows produced 583,401,740 tonnes (FAOSTAT, at http://faostat.fao.org; accessed July 2011). The dairy sheep production is based on the utilization of local breeds of small or moderate effective and well adapted to local conditions in the different Mediterranean countries. This peculiarity contrasts with the "Holsteinization" which is observed in dairy cattle, where a single breed with small effective number and breed in very similar conditions throughout the world is responsible for most of the production of milk at the global level. Sheep milk is mainly addressed to the manufacturing of high quality artisanal cheese in most of the cases commercialised under Protected Designation of Origin (PDO) or other quality labels. Traditionally, classical dairy sheep breeding schemes have been mainly focused on increasing production traits. As in dairy cattle, the successful implementation of classical selection models on dairy sheep breeding schemes has led to an increased milk yield and milk fat and protein contents. In the case of dairy sheep the time and degree of selection progress are greatly variable depending on the population that the selection scheme is addressed to, especially when compared with the global/homogenous genetic improvement of the world-wide spread Holstein cattle breed. Nowadays, however, dairy sheep industry needs to face new challenges such as offering healthy and attractive products to consumers at the same time that providing local farmers the ability to keep their competitiveness. With this purposes, new selection objectives taking into account animal's overall health, mammary and body conformation traits need to be defined with the aim of ensuring the progress of the dairy sheep industry. Also traits such as milk fatty acid composition may be of great interests from the consumer point of view.

At the same time that the initial idea of addressing new selection objectives in dairy sheep selection schemes has become a requirement for the dairy sheep industry, great advances have taken place in the field of sheep genomics, following those reached on other species,

especially human, mouse and cattle. From the initial studies on milk protein polymorphisms (Reviewed by Barillet et al., 2005), and the first description of a QTL in a dairy sheep breed (Diez-Tascón et al., 2001), some few reports of genome scans to identify QTL influencing milk production traits in this species can be found (Gutiérrez-Gil et al., 2009a; Raadsma et al., 2009). The lower number of projects searching milk-related QTL in sheep when compared with the number of studies carried out in dairy cattle can be partially explained by the funding limitations that exist, for example, to establish a sheep experimental population as has been done in cattle in several occasions (Gutiérrez-Gil et al., 2009c; Eberlein et al., 2009). Other reasons contributing to the limited number of genome scans carried out in sheep are the great diversity of productive breeds and the different management systems that can be found in this species, which suggest that the implementation of molecular information in different sheep populations will not be as straightforward as in the case of dairy cattle. On the other hand, the size of the experimental designs based on the analysis of commercial sheep populations has important inherent limitations related to the power of the experiment due to reduced family sizes, as artificial insemination is not an overspread practice in sheep as it is in dairy cattle.

This chapter is intended to review the population designs (experimental crosses and commercial populations) used to map QTLs in dairy sheep. Also a review on the genetic markers and maps used in both whole genome studies and candidate gene approaches will be achieved. Finally the main results obtained by different projects searching for genes underlying milk production traits will be covered.

2. Genetic determination of milk production traits in sheep

2.1. Current selection objectives

In the dairy sheep industry, milk yield is the first criterion to establish milk payment systems. Hence, increasing milk yield is still the first selection objective for dairy sheep breeds. Cheese yield is directly influenced by milk protein and fat contents, which are traits showing negative genetic correlations with milk yield. This has led some dairy sheep breeding schemes (Lacaune, French Pyrenean and Churra) to take into account, at some extend, milk composition traits when estimating selection breeding values (Carta et al., 2009). On the other hand, quality and sanitary safety of products are nowadays major challenges for dairy sheep breeders. In dairy sheep subclinical mastitis occurrence has been estimated at between 16 and 35%, representing one of the most important reasons for culling prematurely. In addition to the economical losses due to medical treatment and decreased milk production, subclinical mastitis in dairy sheep is linked to the presence of contaminants in milk (pathogens or antibiotics). Somatic cell score (SCS), which has been shown as an accurate indirect measure to predict udder infection, may be used for selection in favour of mastitis resistance. Up to day, SCS is included as a selection objective for increased mastitis resistance only in the Lacaune breeding schemes (Barillet, 2007).

In addition, we should take into account that based on the European Decision Nº 100/2003 (European Commission, 2003) the most important dairy sheep breeds in Europe have been

subjected during the last years to national breeding programs aiming at increasing resistance against scrapie (Carta et al., 2009). This is a transmissible spongiform encephalopathy (TSE), akin to bovine spongiphorm encephalopathy (BSE) in cattle and Creutzfeldt–Jakob disease (CJD) in humans. Due to the potential public health risk and based on known association between some allelic variants identified in the ovine *PRNP* gene and the susceptibility/resistance status of this disease in sheep, the goal of these programmes is to increase the frequency of the most resistant allele (ARR).

Genetic parameters for milk production traits in sheep have been widely studied and show a similar pattern than in cattle. On a lactation basis, moderate heritabilities for milk yield have been reported in Lacaune (0.30; Barillet, 1997) and Sarda (0.30; Sanna et al., 1997), whereas the estimates are slightly lower in Spanish breeds such as Manchega (0.18; Serrano et al., 1996), Latxa (0.21; Legarra & Ugarte, 2001) and Churra (0.26; Othmane et al., 2002). Protein and fat yield heritabilities range from 0.16-0.18 (Latxa; Legarra & Ugarte, 2001) to 0.32-0.35 (Manech). The estimates for milk protein and fat percentages show higher heritability estimates than the yields (Serrano et al., 1996; Barillet & Boichard, 1987; Sanna et al., 1997), especially in the Lacaune and Sarda breeds for which these estimates are close or even higher than 0.5-0.55 (Barillet & Boichard, 1987; Sanna et al., 1997). In general milk fat percentage shows a lower heritability than protein percentage in all the breeds, with one of the lowest estimates being found in Churra sheep (0.10; Othmane et al., 2002). The same set of studies show that the genetic correlations between milk yield and milk fat and protein yields are close to one, whereas there are negative genetic correlations between milk yield and milk protein percentage (range -0.32/-0.53) and between milk yield and milk fat percentage (-0.27/-0.63). For SCC in dairy sheep heritability estimates reported range between 0.06 and 0.18 (Othmane et al., 2002; Rupp et al., 2003; Legarra & Ugarte, 2005).

2.2. Opportunities derived from the use of molecular genetics

The genetic parameter estimates summarized above support that substantial genetic gains can be achieved on milk production traits following classical genetic selection based on standardized national recording systems. However, selection based on the phenotype is hampered for these traits due to the repetitive nature of the phenotype, which requires multiple measurements for an accurate description. The inclusion of composition traits as selection goals that some breeding schemes have already performed seems to be recommendable for other breeds based on the negative genetic correlation between these traits and milk yield. Increasing mastitis resistance through classical selection seems, however, more difficult to reach due to the low heritability estimates described for this trait. On this regard, it must be taken into account that marker- or gene- assisted selection (Dekkers, 2004) could be of great assistance to speed up selection response for milk production traits and to reach appreciable genetic gains regarding ewes´ mastitis resistance. For this to be a reality we need to identify the genetic basis of the phenotypic variation observed in dairy sheep flocks. Although this may involve complex mechanisms regarding the control of gene expression and epigenetics (Jaenisch & Bird, 2003), up to now the main efforts of the sheep research community have been addressed to identify the genes

influencing these quantitative traits, which are called *Quantitative trait loci* (QTL). Like most of the traits of interest in livestock species, milk traits in sheep are classical quantitative traits often described by the infinitesimal model, which assumes that the number of loci showing effect on them is infinitely large (Lynch & Walsh, 1998). Although this model produces good predictions of short-term selection response, the QTL mapping experiments have shown that the number of genes controlling the phenotypic variance of these traits is limited. A study in cattle has shown that about 30 QTL were likely to be segregating for milk production traits in a half-sib Holstein population (Chamberlain et al., 2007). In dairy sheep populations, where selection programmes started more recently and with a lower selection pressure than in dairy cattle, we would expect a slightly higher number of segregating loci to explain the phenotypic variation observed in the flocks, although always limited. With the aim of identifying these loci or QTL, low-medium genome scans based on the analysis of microsatellite markers have been undertaken in dairy sheep since 2001. These studies will be referred from now on as classical QTL mapping experiments and the description of their methodology, experimental designs and main results will be the main objective of the chapter. In addition, we must consider the great advances that are taking place nowadays in the field of sheep genomics such as the ongoing progress of the sheep genome sequencing project (International Sheep Genomics Consortium et al., 2010) and the availability of the Ovine SNP50BeadChip (Illumina). The search of QTL based on high-throughput genotyping assays will be commented in the last section of the chapter.

3. Analytical tools for classical detection of QTL for milk traits in sheep

QTL mapping experiments require the analysis of genetic markers across appropriate mapping populations to follow the segregation of markers and QTL within family structures. The development of the sheep linkage maps including an increasing number of markers has been an irreplaceable tool for the studies aiming the detection of QTL for milk traits in sheep.

In this section a brief description of the elements required for classical QTL mapping is presented (genetic markers, phenotypes, experimental design and statistical methods) with reference to the different approaches used in the different QTL studies reported so far for sheep milk traits. A detailed review of classical QTL mapping experiments for milk traits carried out in sheep and their results is provided in the next section.

3.1. Genetic markers and linkage maps

Most classical QTL mapping experiments carried out in livestock species, including sheep populations, have been based on the analysis of microsatellite markers across the resource mapping population. Microsatellites are a subclass of eukaryote tandemly repeated DNA that contains very short simple sequence repeats such as (dCdA)n, (dG-dT)n (Weber & May, 1989). Microsatellite blocks are polymorphic in length among individuals of the same species and therefore represent a vast pool of potential genetic markers. These genetic markers show a high level of polymorphism, and are uniformly spaced throughout the

genome at every 30-60 kb (Weber & May, 1989). Function for microsatellites is unknown, but it has been proposed that they serve as hot spots for recombination or participate in gene regulation (Hamada et al., 1984). However, they are mainly considered as "neutral phenotypic markers". The availability of the Polymerase Chain Reaction (Mullis et al., 1986) allowed the development of linkage maps of acceptable density in livestock species (Crawford et al., 1994).

Over the 1990s decade, great efforts were made by the international sheep genetics research community to develop a useful linkage map (Crawford et al., 1994; De Gortari et al., 1998). The establishment of several mapping flocks comprising three-generation full-sibling families allowed the construction of low-density autosomal (Crawford et al., 1994) and X chromosome (Galloway et al., 1996) linkage maps. The second generation map comprised 512 loci with an average spacing of 6 cM (de Gortari et al., 1998). In 2001, an enhanced linkage map of the sheep genome comprising 1093 loci was published (Maddox et al., 2001). This medium-density linkage map included 550 new loci merged with the previous sheep linkage map. The average spacing between markers for this map was 3.4 cM with an average of 8.3 cM between highly polymorphic autosomal loci. The third generation sheep linkage map shows strong links to the cattle linkage map, with 572 of the loci common to both maps. Also 209 of the loci mapped by Maddox et al. (2001) could be mapped in the goat map (Maddox et al., 2005). This third-generation linkage map has been expanded periodically with the different versions being available in the Australian Sheep Gene Mapping Web Site at http://rubens.its.unimelb.edu.au/~jillm/jill.htm. The latest available version, v5, includes 2515 loci, 344 of which are linked to a described gene, whereas most of the reported QTL mapping experiments in sheep have taken versions 4.0 to 4.7 as reference.

Also the development of comparative maps between sheep and other species such as cattle and human at the different stages of the progress on the sheep linkage map (http://rubens.its.unimelb.edu.au/~jillm/jill.htm) has provided great assistance to identify candidate genes for the QTL mapped in the different experiments.

3.2. Experimental designs

Detection of QTL is based on the study of segregation of a heterozygous QTL within a family through the analysis of informative markers. As in other livestock populations, the experiments designs used to map the genes underlying milk traits in sheep are based on the use of experimental crosses or, alternatively, in the analysis of commercial populations.

3.2.1. Cross-bred experimental populations

In this case, the experimental design is based on the establishment of experimental populations by crossing two breeds that show clear phenotypic differences for the traits of interest. By crossing founders of these divergent founder "lines" the resulting F1 individuals can be used to generate large segregating F2 or backcross (BC) populations. The complete resource population is genotyped for the genetic markers that will be used to identify QTL, whereas phenotypic measures of the traits to study are recorded from the second generation

animals (F2 or BC). Once the experimental population is established, many phenotypes for a wide-range of economical interesting traits are usually recorded in the cross-bred animals. The fact that the animals are reared in an experimental farm make easy obtaining phenotypes that could not be routinely recorded in commercial flocks. The power of these designs is maximized when the founder "lines" show alternative and fixed or nearly fixed alleles for the mutation that underlie the genetic control of the traits under study. Also the management of these populations under properly controlled environmental conditions may drastically reduce the environmental noise with the consequent increase of QTL mapping accuracy. The main disadvantages of these experimental designs are the time-consuming and expensive efforts required for the establishment of the experimental populations, and the fact that the results may not be directly implemented in commercial populations (Georges, 1998). Experimental cross populations have been widely used in pig and chicken populations. Also in cattle, there are some examples exploiting this kind of design by crossing the highly specialized dairy Holstein breed with a beef producer breed although published results are relative to other traits different to dairy traits (Eberlein et al., 2009; Gutiérrez-Gil et al., 2009c). In sheep, genome scans for mapping QTL influencing milk traits based on experimental crosses have been performed using a Sarda x Lacaune backcross population (Carta et al., 2002; Barillet et al., 2006) and a Awassi × Merino backcross family population (Raadsma et al., 2009). Also a genome scan based on a backcross pedigree using dairy East Friesian rams and non dairy Dorset ewes has been reported (Mateescu & Thonney, 2010).

The backcrosss Sarda x Lacaune resource population mentioned above was established in the framework of a European funded project (*GeneSheepSafety*, QL K5 CT2000 0656). Fourteen AI elite Lacaune rams were crossed with Sarda ewes to produce F1 rams. Ten of these F1 rams and 10 different Lacaune sires were mated to Sarda ewes to obtain 980 backcross females. Family size ranged from 76 to 121. Phenotypes were recorded for many traits from the second-generation backcross ewes. In addition to classical milk production traits, other phenotypes of interest in dairy sheep production such as milk fatty acid composition, kinetics of milk emission, udder morphology and resistance to mastistis and nematode infections were measured in this cross-population (Casu, 2004; Barillet et al., 2005; 2006).

Another remarkable research programme for QTL detection based on an experimental ovine population has been performed in Australia (CRC funded project). This experiment was based on an extreme breed back-cross and inter-cross design between Awassi fat-tail sheep and Merino superfine and medium wool sheep (Raadsma et al., 1999). Due to the extreme difference between these two types of sheep in a range of production characteristics, this experiment aimed at identifying quantitative trait loci for wool, meat and milk production. Both super-fine and medium-wool Merinos were used in the present resource (Raadsma et al., 2009). This resource population was developed in three phases, coinciding with different stages of research. In Phase I, four sires from an imported strain of improved dairy Awassi were crossed with 30 super-fine and medium-wool Merino ewes. Four resulting F1 sires (AM) were backcrossed to 1650 fine and medium-wool Merino ewes, resulting in approximately 1000 second-generation backcrosses (AMM). In Phases II and III additional

crosses both within and across families were performed resulting in third- and fourth-generation animals. From the whole project a total of 2,700 progeny were produced over 10 years, representing four generations. In the genome scan for milk production traits reported by Raadsma et al. (2009) the QTL analysis was based on the information from the 172 ewe second-generation AMM progeny of one of the F1 sires.

Based on the increasing interest in the United States on sheep milk production, an experimental population of animals has been established by crossing East Friesian rams and Cornell Dorset ewes. This population has been established specifically to map QTL for milk production by crossing four East Friesian rams and 37 Dorset ewes to generate 44 F1 ewes, which were subsequently mated to 11 East Friesian rams to create 92 backcross ewes (Mateescu &Thonney, 2010).

An additional project exploiting line divergence between Awassi and Merino breeds has been performed in Hungary (FVM 46040/2003 project). In this case, the experimental population was initiated by crossing Awassi rams and Hungarian Merino ewes and then matting females in each subsequent generation back to new groups of purebred Awassi rams (Árnyasi et al., 2009). A total of 258 ewes with different proportions of Merino-Awassi genetic component were used to perform an association analysis with 13 microsatellite markers distributed on OAR6 (Árnyasi et al., 2009). This chromosome was selected as candidate for milk traits due to the large number of QTL detected in the orthologous bovine chromosome, BTA6, and because previous studies in sheep had identified significant effects on this chromosome (Díez-Tascón et al., 2001; Schibler et al., 2002). It should be noted that the casein cluster is located in this chromosome.

3.2.2. Outbred pedigrees

These experimental designs take advantage of the particular structure of some livestock commercial populations, such as those of dairy cattle and sheep where the use of artificial insemination (IA) results in large families of paternal half-sib families where the segregation of markers and QTL can be studied. In the classical "Daughter design", which was initially proposed by Neimann-Sörensen & Robertson (1961), the milk production records are obtained from the daughters, whereas all the population, including the sires, is genotyped for the genetic markers. In dairy cattle, where the IA has been extensively used for a large number of years, the "Granddaughter design" was suggested as a method to increase the statistical power of the "Daughter design" (Weller et al., 1990). In this case the availability of half-sib families of evaluated bulls allows the identification of QTL by genotyping only the founder sires and the bulls of each family whereas from the third-generation cows only the milk production phenotypes that are used to evaluate the second-generation bulls are obtained. This design allows a substantial reduction of animals to be genotyped, which is the most expensive part of the project, to reach an equivalent statistical power than the "Daughter design". Also getting biological samples for DNA extraction from the bulls localized in few insemination centres may be easier than collecting daughter samples from a wide range of different flocks. However, the selection of the design to be applied depends

on the characteristic of the population to be studied. Hence, despite the increased power that the "Granddaughter design" may offer, the daughter design may be more adequate for populations with a recent implementation of IA due to the lack of large half-sib families of evaluated sires.

Compared with the experimental cross designs QTL mapping experiments carried out in commercial populations may seem to show important limitations. For example marker and QTL heterozygosity are likely to be reduced when compared with a cross-population and, moreover, they may very between the different families. Also different QTL influencing the same traits may segregate in different families, which increases complexity of results (Georges, 1998). In addition, the phenotypic records obtained in field conditions may show the influence of environmental factors that should be taken into account in the QTL analysis model (year, season, flock, etc). As an advantage, the phenotype collection, at least, for milk traits, is usually performed on the basis of a national recording system, and therefore not additional funding efforts are required to obtain phenotypic measurements. However, the main advantage of these designs is that the QTL detected in a livestock commercial population could be subjected to a more straight forward "Marker Assisted Selection" as these QTL represent the allelic variants actually segregating in the studied population. Additional confirmation studies on independent sampling populations, however, are needed before trying to implement those results in different commercial sheep populations.

Both, the granddaughter and the daughter designs have been used to map QTL for milk traits in sheep through the 26 sheep autosomes (Barillet et al., 2006). French populations of Lacaune and Manech breeds have been studied following a granddaughter design, based on the large scale AI and progeny test performed as part of the breeding programmes of these breeds (Barillet et al., 2005). A total of 700 and 83 AI rams distributed in 22 families (18 in Lacaune and 4 in Manech breeds) were included in this QTL mapping population. Family size averaged 36 sons per sire and ranged from 24 to 56. The sons had 89 daughters on average (Barillet et al., 2005).

Churra sheep is one of the most important dairy sheep breeds in Spain. The selection programme of this population was started in 1986 (de la Fuente et al., 1995). Since them, flocks included in the Churra Selection Nucleus have made use of AI. Based on the daughter design a preliminary analysis focused on sheep chromosome 6 analysed 726 ewes distributed in 14 flocks and belonging to 8 half-sib families of the Selection Nucleus (Díez-Tascón et al., 2001). Based on the same design a genome scan included in the framework of the European funded *GeneSheepSafety* project was planned to scan the 26 ovine autosomes. A total of 1421 ewes sired by 11 IA rams and distributed among 17 different flocks were used in this project for detection of QTL underlying classical milk traits (Gutiérrez-Gil et al., 2009a). Other traits of interest in dairy sheep production such as morphology traits (Gutiérrez-Gil et al., 2008; 2011) and resistance to mastitis and nematode gastrointestinal infections (Gutiérrez-Gil et al., 2007; 2009b) were also recorded in the commercial population genotyped. The average family size in this daughter design was around 110, ranging from 47 to 223 daughters per sire.

Other QTL study for milk traits based on the daughter design has been performed in the Latxa breed, which is also an important dairy sheep located in the North of Spain. With the aim of reducing the genotyping effort, a "selective DNA pooling" approach was followed in this breed to search for QTL on sheep chromosome 6 (OAR6) (Rendo et al., 2003).

3.3. Phenotypes and dependent variables

The phenotypes considered in most of the QTL mapping studies mentioned above are the classical production traits, milk yield (MY), milk protein yield (PY), milk fat yield (FY), milk protein percentage (PP), milk fat percentage (FP) and somatic cell score (SCS).

The dependent variables analysed for QTL detection are, in general, the measurements of the traits of interest adjusted for the specific environmental effects that show influence on the traits. This adjustment can be performed previously to the QTL analysis, or alternatively the fixed factors to be taken into account can be included in the QTL model when running the analyses. In commercial populations, where the trait is routinely recorded for other purposes and not only for the QTL mapping experiment, the phenotypic measures used in the QTL analysis can be breeding value estimates or deviations from the mean population. Using estimated breeding values (EBV) all the relationships among the animals are taken into account (Israel & Weller, 1998). Hence, the variability of the daughter productions is reduced and the estimated effect of a given QTL is reduced, which may make difficult QTL identification. Because of that several QTL studies use non biased measurements of the animals' productions such as the Yield Deviation (YD) or the Daughter Yield Deviation (DYD) (Israel & Weller, 1998). YDs are weighted averages of ewe's lactation yields minus solutions for management group, herd-sire, and permanent environmental effects (VanRaden & Wiggans, 1991). These are the quantitative measures that have been used in the QTL mapping experiments performed in Churra sheep (Díez-Tascón et al., 2001; Gutiérrez-Gil et al., 2007; 2009a). Because rams do not have yield deviations, DYD, which are adjusted for mates´ merit, can provide a usefull, unregressed measure of daughter performance to use in grand-daughter designs (VanRaden & Wiggans, 1991). These are the dependent variables used in the analyses performed in the Lacaune-Manech Granddaughter design (Barillet et al., 2006). In a commercial population of Latxa sheep, Rendo et al. (2003) used EBVs for milk production as quantitative measurements of the screening performed on OAR6. (Table 1).

In the experimental populations established by crossing divergent breeds the quantitative measures involve, in general, the phenotypic records adjusted for the corresponding fixed factors (Carta et al., 2002; Raadsma et al., 2009), whereas some other of these experiments use EBVs as the milk yield EBV analysed by Mateescu & Thonney (2010).

3.4. Statistical methods for QTL mapping

Most of the QTL mapping experiments for milk traits in sheep have followed an interval mapping approach for detection of QTL. Only the analysis performed on OAR6 in a backcross Awassy X Hungarian merino population (Árnyasi et al., 2009) has analysed one

locus at a time on each performance trait using a likelihood ratio test (Shaw, 1987) or a regression procedure (Ostergard et al., 1989). By adapting the method of LOD scores used in human genetic linkage analysis studies, Lander & Botstein (1989) proposed interval mapping to solve the problems shown by the initial QTL mapping experiments which studied single genetic markers one-at-a-time (Sax, 1923; Soller & Brody, 1976). Compared with these methods, interval mapping has been shown to provide some additional power and much more accurate estimates of QTL effect and position and to be relatively robust to failure of normality assumptions (Lander & Botstein, 1989; Knott & Haley, 1992). In the method of interval mapping the intervals between pairs of flanking markers in a linkage map are explored in turn for evidence of the presence of a QTL at various positions between the markers. Hence, the construction of a linkage map with the markers to analyse is required before performing the QTL mapping. The method described by Lander & Botstein (1989) is based in the maximum-likelihood analysis of the data. The likelihood ratio test is performed at regular intervals along the chromosome (e.g. 1 -cM), with the peak value representing the most likely position of a QTL. The significance threshold suggested is that applied in human genetics, LOD score ≥ 3 (Lander & Botstein, 1989). The disadvantage of maximum likelihood based methods for interval mapping is their computational complexity. Haley & Knott (1992) proposed a regression method applied to interval mapping. This methodology allows analysing more complex models for example to test the data for the presence of two or more linked or interacting QTL (Haley & Knott, 1992). In this case, the position which gives the best fitting model (i.e. produces the smallest residual mean square) gives the most likely position of a QTL and the best estimates of its effect.

However, the application of interval-mapping approaches to data from crosses between outbred lines would lead to the same situation observed in analyses within outbred populations that is that the power to detect a QTL varies from interval to interval depending upon the markers flanking that interval. This can lead to biases in the estimated position and effect of a QTL (Knott & Haley, 1992). Based on this, regression methods taking into account information from all of the informative markers in a linkage group (multimarker regression) were proposed for crosses between outbred lines (Haley et al., 1994) and half-sib outbred populations (Knott et al., 1996). Also Georges et al. (1995) presented a maximum-likelihood approach to QTL detection for use in half-sib populations by using information from all markers in a linkage group simultaneously, but analysed families separately. The method described by Knott et al. (1996) first calculate transmission probabilities in two-generation half-sib families and, second allow the linkage phase to differ from family to family. This analysis method is the one followed for milk traits QTL mapping in the commercial sheep populations previously described. The analyses performed in Spanish Churra sheep were performed using HSQM (Coppieters et al., 1998) which implements the multimarker regression method described by Knott et al. (1996) (Díez-Tascón et al., 2001; Gutiérrez-Gil et al., 2007, 2009a). In the Lacaune and Manech French populations, the QTL detection was carried out according to the methodology proposed by Knott et al. (1996) and Elsen et al. (1999) by within-sire linear regression (Barillet et al., 2006).

The analyses carried out in the Sarda X Lacaune cross population were performed with the INRA QTLMap software, which implements the methodology proposed by Elsen et al. (1999) by within-sire linear regression. The multimarker regression method for cross populations described by Haley et al. (1994) and implemented in the web-accessible programs QTL Express or GridQTL (Seaton et al., 2002; 2006; https://greidqtl.cap.ed.ac.uk/gridsphere) has been used to analyse the East Friesian X Dorset and Awasi x Merino backcross populations (Mateescu & Thonney, 2010; Raadsma et al., 2009). This later population was also analysed using a QTL maximum likelihood procedure suitable for the backcross design named QTL-MLE (Raadsma et al., 2009).

To determine chromosome-wise significance thresholds, most of the studies here referred have followed the permutation approach (Churchill & Doerge, 1994) for each trait and each chromosome using 10,000 permutations. Different methods have been used, however, to take into account the testing for 26 chromosomes in the genome scans reported. Hence, Bonferroni corrections have been used in some of the cases such as Churra sheep analysis of SCS (Gutiérrez-Gil et al., 2007), and the Sarda X Lacaune population (Barillet et al., 2006). Following the method described by Harmegnies et al. (2006) genome-wide permutations were implemented in the Churra sheep analysis for milk production traits (Gutiérrez-Gil et al., 2009a), In addition to the genome-wise significant QTL, these authors also considered the genome-wise suggestive linkage level, for which one false positive is expected in a genome scan (Lander & Kruglyak, 1995). On the other hand, Raadsma et al. (2009) adopted a false discovery rate (FDR) method (Benjamini & Hochberg, 1995) to adjust P-values for all traits to control for genome-wise error rates for the results obtained with the QTL-MLE analysis method. In most of the QTL experiments referred herein, the estimation of the confidence interval for the detected QTL was obtained by the bootstrapping method described by Visscher et al. (1996) (Gutiérrez-Gil et al., 2007; 2008; Barrillet et al., 2006; Mateescue & Thonney, 2010).

A summary of the populations studied for mapping of QTL for milk traits in sheep is provided Table 1. The experimental design, the number of markers analysed, the phenotypic traits analysed, and the statistical methods used for each of the QTL mapping experiments are detailed.

4. QTL mapping results for milk traits in sheep

Based on the available scientific literature and the information stored in *Sheep*QTLdb (http://www.animalgenome.org/cgi-bin/QTLdb/OA/index), we present in this section a brief description of the QTL results reported so far for classical milk production traits in the different sheep populations previously mentioned (MY, PY, FY, PP, FP and SCS), considering the analysis of lactational or test-day records for the same phenotype as the same trait. Figure 1 shows a graphical representation of the milk QTL identified for these traits through the linkage analyses performed on the experimental populations previously described. Just to note that only across-family significant QTL have been considered, and therefore some effects identified in the within-family analyses are not here commented. Apart of these QTL detected on the basis of multimarker regression linkage analyses,

Árnyasi et al. (2009) and Calvo et al. (2004a, 2004b, 2006) performed association analyses for milk production traits on selected candidate chromosomes, OAR6 and OAR1 respectively. These results are mentioned in the candidate gene approach section. The map positions of the different QTL represented in Figure 1 are based on the position suggested by the Australian linkage map version 5.0 for http://rubens.its.unimelb.edu.au/~jillm/jill.htm) for the closest marker reported for each QTL.

	Breed – Design Population	**Target chromosomes (Nb of markers)**	**Analysis method**	**Reference**
Experimental cross-bred populations	Sarda X Lacaune (980 BC ewes)	1 to 26 (127 microsatellites)	Multimarker regression for half sibs[1]	Carta et al. (2003)
	East Friesian X Dorset (92 BC ewes)	1 to 26 (99 microsatellites)	Multimarker regression for cross populations [2]	Mateescu & Thonney (2010)
	Awasi x Merino (172 ewes)	1 to 26 (200 microsatellites)	Maximum Likelihood[3] Multimarker regression for cross populations [2]	Raadsma et al. (2009)
Commercial populations	Awassi x Hungarian Merino (258 ewes)	OAR6 (13 microsatellites)	Association analysis	Amyasi et al. (2009)
	Churra DD (1421 ewes)	1 to 26 (181 microsatellites)	Multimarker regression [1]	Gutiérrez-Gil et al., (2007; 2009a)
	Churra DD (726)	OAR6 (11 microsatellites)	Multimarker regression [1]	Díez-Tascón et al. (2001)
	Lacaune-Manech GDD (783 AI rams – 89 daughter on average)	1 to 26 (163 microsatellites)	Multimarker regression [1,4]	Barillet et al. (2006)

[1]Knott et al. (1996); [2]Haley et al. (1994); [3]Raadsma et al. (2009); [4]Elsen et al. (1999)

Table 1. Characterization of QTL mapping experiments performed in sheep for milk traits.

As a general observation, the QTL reported in the different experiments are not coincident among each other. This contrasts with the results published in dairy cattle (reviewed by Khatkar et al., 2004 and Smaragdov et al., 2006; see also CattleQTLdb at http://www.animal genome.org/cgi-bin/QTLdb/BT/index), and suggests a high diversity of causal mutations or QTN underlying milk production traits segregating in the different sheep populations. Attention, however, should be driven to chromosomes OAR3 and OAR20, where several studies have found significant linkage associations with milk production traits (Figure 1).

4.1. Milk yield

QTL affecting milk yield (MY) have been identified in different sheep populations, with no substantial coincidences regarding QTL location among these reports. Raadsma et al. (2009) described QTL for total milk in OAR2, OAR3, OAR20 and OAR24 segregating in the Awassi x Merino cross population. All these QTL were identified with the regression and maximum-likelihood analysis methods used by these authors. Focusing on the results of the QTL-MLE analysis, the most interesting QTL are those on OAR3 and OAR20 which reached genome-wide significance and mapped close to other QTL influencing other milk yield traits (Raadsma et al., 2009). In the Sarda X Lacaune population significant linkage associations with MY were found on OAR3, OAR4, and OAR20 (Barillet et al., 2006). These QTL were coincident with other genetic effects influencing PY and FY. Another QTL identified in this population for MY on OAR16 was closely linked to a QTL for FP (Barillet et al., 2006). In the commercial population of Churra sheep, a genome-wise suggestive QTL was detected for MY in the proximal end of OAR23. The effect detected seems the result of a pleiotropic QTL influencing also PY and FY (Gutiérrez-Gil et al., 2009a). The genome scan performed in the Friesian X Dorset backcross population studied by Mateescu & Thonney (2010) identified two chromosome-wise significant QTL for MY on OAR2 and OAR18, the later of these being also associated with effects on PY.

4.2. Protein percentage and protein yield

The initial analysis performed of chromosome 6 in Churra sheep allowed the detection of a putative QTL for PP showing chromosome-wise significance, which mapped close to the casein gene cluster region (Díez-Tascón et al., 2001). This QTL was not identified, however, in the genome scan performed in an extended design of this population some years later (Gutiérrez-Gil et al., 2009a). In this genome scan, the most significant QTL, which reached genome-wise significance, was that identified for PP on OAR3 in the second half of the chromosome, close to marker *KD103*. One other suggestive QTL for PP was identified in this analysis in the proximal region of OAR2. The genome scan performed in the Awassi x Merino Backcross population only detected a significant QTL for PP in the first half of OAR7 (Raadsma et al., 2009). The Sarda x Lacaune genome scan identified a genome-wise significant QTL for PP in the first third of OAR1 and another genome-wise suggestive QTL on the second half of OAR7. Three genome-wise suggestive QTL for PP were found in the Lacaune-Manech population on OAR2, OAR5 and OAR9. For PY, apart of the QTL linked to MY QTL previously mentioned, a genome-wise suggestive QTL was detected in Churra sheep, in the second half of OAR1 (Gutiérrez-Gil et al., 2009a).

4.3. Fat percentage and fat yield

In the Sarda x Lacaune experimental population, a genome-wise significant QTL for FP was found on OAR20, whereas genome-wise suggestive linkage associations were reported on OAR3, OAR7 and OAR16. Close to the OAR20 QTL detected in that population, Gutiérrez-Gil et al. (2009a) reported a genome-wise suggestive QTL for FP in Churra sheep. In this

population another suggestive QTL for FP was detected at the distal region of OAR2. In the Lacaune-Manech French genome scan genome-wise suggestive QTL for FP were detected on OAR1, OAR9 and OAR10. Raadsma et al. (2009) detected significant QTL for FP on OAR3, and OAR25, whereas a suggestive QTL was found on OAR8 for this trait. The first of these QTL, detected on OAR3, seems to be the result of a pleiotropic QTL linked to marker *DIK4796* that affects several milk production traits. As mentioned earlier, QTL for FY have been detected jointly with MY and PY QTL on OAR3, OAR4, and OAR20, in the Sarda X Lacaune population (Barillet et al., 2006), on OAR3 and OAR20 in the Awassi x Merino cross (Raadsma et al., 2009) and on OAR23 in Churra sheep (Gutiérrez-Gil et al., 2009a). Apart of these, the FY trait has shown genome-wise suggestive linkage associations on OAR14 in the Sarda x Lacaune population (Barillet et al., 2006), on OAR16 in the Lacaune-Manech commercial French population and on OAR25 in Churra sheep (Gutiérrez-Gil et al., 2009a).

4.4. Somatic cell score

Although this trait is not directly related with milk production its relation with subclinical mastitis incidence makes it of interest when trying to enhance productivity of sheep flocks. Hence, most of the genome scans performed for milk traits in this species have also studied this phenotype. The whole genome screening performed in Spanish Churra sheep identified a single genome-wise suggestive QTL for SCS on OAR20 (Gutiérrez-Gil et al., 2007). The best position suggested for this QTL is close to marker *OLADRBPS*, which is located in the major histocompatibility complex (MHC). In the Sarda x Lacaune population, several traits related to mastitis resistance were recorded (SCS in parity 1 to 4, SCS considered as a repeated trait within lactation and SCS considered as a repeated traits across four lactations). For these traits, together with 11 genome-wise suggestive QTL, two genome-wise significant QTL were found on OAR6 and OAR13 (Barillet et al., 2006). In the Lacaune-Manech population a suggestive genome-wise significant QTL was found on OAR14 for SCS (Barillet et al., 2006). In the case of the Awassi X Merino cross population a significant QTL for SCS was found on OAR14, whereas two suggestive QTL for this trait were reported on OAR17 and OAR22 (Raadsma et al., 2009).

4.5. Other traits of interest in dairy sheep

Apart of the classical milk yield and composition traits and SCS, QTL have been reported for other traits directly related to milk production. Raadsma et al. (2009) analysed the useful yield content. Some of the QTL detected for this trait were detected in the same regions that other milk production traits on OAR3 and OAR25. These authors also identified suggestive QTL for useful yield content on OAR6 and OAR9. In the Awassi x Merino cross population analysed by these authors QTL have been also been identified for milk lactose yield on OAR2, OAR3, OAR15, OAR20 and OAR24. These QTL were coincident with QTL influencing other milk traits (Raadsma et al., 2009).

Total lactation performance and length of lactation also have a significant economical impact on dairy sheep industry. Traits related with lactation persistency and extended

lactation in sheep have been analysed for QTL detection in the Awassi x Merino backcross population (Jonas et al., 2011). These authors identified five genome-wise significant QTL for these traits on OAR3 (fat persistency), OAR10 (extended lactation somatic cells) and OAR11 (extended lactation milk, milk persistency and extended lactation protein) together with five other suggestive QTL. Interestingly, on OAR11 where the most significant QTL were identified in this study, no other QTL for milk production traits had been described before. The lack of coincidence between the QTL identified for lactation persistency and extended lactation suggests that lactation persistency and extended lactation do not have a common genetic background.

In the last years the evident relationship between human health and animal fat content in the diet may have a negative impact on the consumption of sheep cheese because of its high fat content. Sheep milk has a high level of saturated fatty acids (SFA) when compared to polyunsaturated (PUFA) and monounsaturated FA (MUFA). However, sheep milk has some other beneficial components for human health such as ω_3-fatty acids and the conjugated linoleic acid (CLA). Considering genetics to improve the fatty acid (FA) composition of milk sheep and due to the difficulties to measure these traits in commercial populations, the detection of genetic markers associated with these traits would be of great interest. Analysing the experimental Sarda x Lacaune backcross resource population, Carta et al. (2008) identified several chromosome-wise QTL for milk fatty acid composition across the sheep autosomes. The most significant QTL were found on OAR11 and OAR6. Because of its interest in relation to human health benefices, it is worth mentioning the QTL identified for CLA content on AOR4, OAR14 and OAR19, whereas QTL for the ratio CLA/Vaccenic acid, which is an indicator of the proportion of CLA that is synthesised in the mammary gland from its precursor, were found on the same region of OAR4 and on OAR22. For the latter of this QTL the *SCD* (stearoyl-CoA desaturase) gene was suggested as functional and positional candidate (Carta et al., 2006). Based on the Sarda x Lacaune genome scan results, and the location of candidate genes related to milk fatty acid composition metabolic pathways, linkage analyses for these traits were performed on OAR11 and OAR22 in a commercial population of Spanish Churra sheep including 15 half-sib families (García-Fernández et al., 2010a; 2010b). These studies assessed the role of candidate genes in relation to fatty acid composition and will be described later.

Other traits of interest in dairy sheep are those related to udder and type morphology. Udder related traits may be considered the most important functional traits in dairy sheep, as they determine the machine milking efficiency of the animal (Labussière, 1998) and have a substantial effect on its functional lifetime (Casu et al., 2003). QTL for udder traits have been reported in the Sarda x Lacaune population, the Lacaune-Manech families (Barillet et al., 2006) and in Churra dairy sheep (Gutiérrez-Gil et al., 2008). In the Sarda x Lacaune population a detailed study of udder morphology traits was performed, with digital picture measures being recorded in the cross-bred animals and a large list of udder morphology related traits being analysed for QTL detection. Genome-wise significant QTL were detected on OAR3, OAR4, OAR9, OAR14, OAR16, OAR20, OAR22 and OAR26. In the Lacaune-Manech population, genome-wise suggestive QTL were identified on OAR6 and OAR17 for

udder cleft (Barillet et al., 2006). In this population, QTL were also detected for traits related to the kinetics of milk emission which are also directly related with the machine milking ability of the ewes. The difficulties to measure these traits in commercial populations make these analyses of great value for the sheep research community. Genome-wise suggestive QTL for these traits were detected on OAR9, OAR11, OAR15, OAR17 And OAR20, with the most significant QTL influencing maximum milk emission flow on OAR11.

In the commercial population of Spanish Churra sheep, a genome scan for udder morphology traits assessed according to the 9-point linear scale described by de la Fuente et al. (1996) identified chromosome-wise significant QTL on OAR7, OAR14, OAR15, OAR20 and OAR26. The most significant of these QTL was that identified in the proximal end of OAR7 for teat placement (Gutiérrez-Gil et al., 2008). In the same population QTL have also been identified for body conformation, which are functional traits of great interest in dairy sheep because its correlation with functionally productive life and overall productivity of the flock (Vukasinovic et al., 1995). Genome-wise suggestive QTL for these traits were identified on OAR2, OAR5, OAR16, OAR23 and OAR26 (Gutiérrez-Gil et al., 2011). The QTL reported on OAR16 was the most significant of these linkage associations and influenced the rear legs-rear view trait, which is related to leg conformation.

For dairy sheep reared on grazing systems, gastrointestinal nematode (GIN) parasite infections are diseases with a great impact on animal health and productivity. The selection of resistant animals to these infections might be a possible strategy for a sustainable control of this problem. Because of the low to moderate heritability estimated for indicator traits in adult dairy sheep (Gutiérrez-Gil et al., 2010) and the difficulties of routine collection of phenotypic indicators detection of genetic markers associated with these traits could be use to improve the efficiency of classical breeding. In Churra Spanish sheep, the genome scan reported by Gutiérrez-Gil et al. (2009b) describes a genome-wise significant QTL on OAR6 influencing faecal egg count. Four other chromosome-wise significant QTL were found for faecal egg count and anti-Teladorsagia circumcincta Larvae IV IgA levels. Many QTL for resistance to GIN infection have also been identified in the Sarda x Lacaune backcross population (Moreno et al., 2006; Barillet et al., 2006). Apart of several regions showing suggestive significance, genome-wise significant QTL were detected on OAR2, OAR3, OAR6, OAR12 and OAR13 (Barillet et al., 2006). QTL for host resistance against GIN parasite infections have been mapped in other non-dairy sheep populations (Davies et al., 2006; Coltman et al., 2001; Beh et al., 2002: Dominik, 2003).

Selection programs towards scrapie resistance are being implemented in many European countries based on the genotyping of the *PRNP* gene alleles classically associated with the disease (Hunter, 1997). However, selection in favour of the ARR/ARR genotype could induce a simultaneous change in production traits due to either the pleiotropy of the *PRPN* gene or genetic linkage with dairy QTL. This possibility has been studied in East Friesian (Vries et al., 2005) and Churra (Álvarez et al., 2006) sheep breeds. The association and linkage analyses performed in Churra sheep suggested that increasing the ARR frequency in the Churra population will not have an adverse effect on selection for milk traits included in the breeding objectives of this breed. Similar conclusion was drawn by De Vries et al. (2005),

who did not identify any significant association between the prion protein genotypes and milk performance, type or reproduction traits. QTL other than *PRNP* for scrapie resistance have been reported on OAR6 and OAR18 in Romanov sheep (Moreno et al., 2008; 2010).

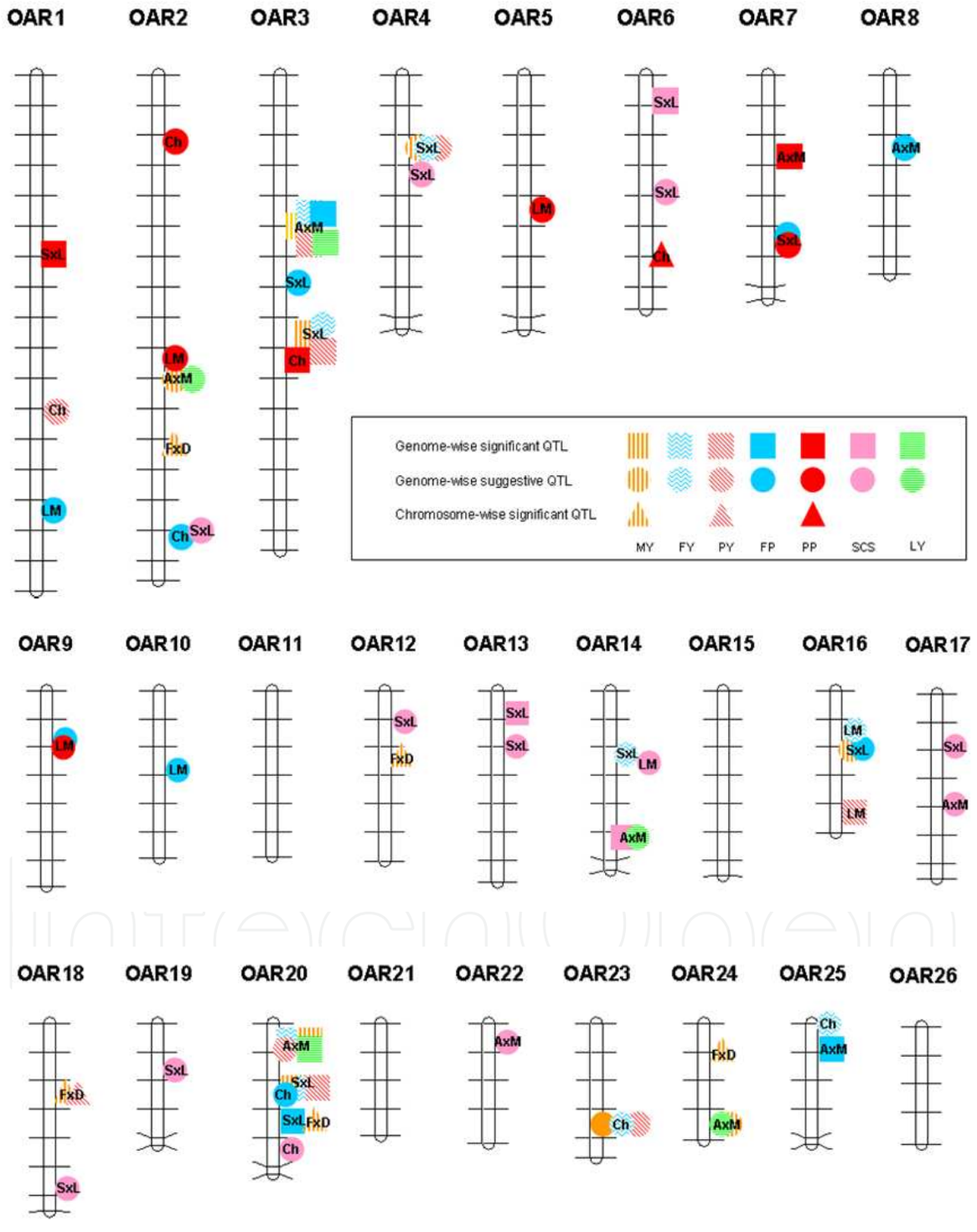

Figure 1. Graphical representation of QTL mapped on the sheep autosome for milk production traits and SCS. Legend abbreviations: MY: Milk yield; FY: Milk fat yield; PY: Milk protein yield; FP: Milk fat percentage; PP: Milk protein percentage; SCS: Somatic cell score; LY: Milk lactose yield.

4.6. Following-up studies on the QTL detected

Few fine-mapping studies have been reported in relation to QTL identified for traits of interest in dairy sheep whereas up to date no QTN explaining a previously identified QTL has been identified for milk traits in sheep. In order to validate the segregation of QTL previously detected on OAR7 in the Sarda x Lacaune population for milk fat and protein contents (Barillet et al., 2006), a new resource population was procreated by mating Sarda rams with BC ewes (Casu et al., 2010). The increased of informative meiosis and a higher marker density allowed to confirm the presence of a chromosome-wise significant QTL affecting milk contents by exploiting a similar approach than the great-grand-daughter design proposed by Coppietters et al. (1999). In Churra sheep, additional analyses have allowed the replication of the QTL detected on OAR20 for FP (García-Gámez et al., 2009) and on OAR3 for PP (García-Gámez et al., 2012) by analyzing additional half-sib families of the Selection Nucleus of Churra sheep commercial population. The increased of marker density reached on the OAR3 QTL region and the use of a combined linkage analysis and linkage disequilibrium analysis (LDLA) has allowed the refinement of the initially described confidence interval for this QTL from 40 to 13 cM (García-Gámez et al., 2012). Further research efforts are under way to perform a high density SNP screening on this QTL region and identify functional and positional candidate genes (García-Gámez et al., under review). High resolution mapping has also been performed on OAR3 and OAR20 in relation to QTL affecting lactation persistency and protein yield segregating in the Australian Awassi X Merino cross population (Singh et al., 2007).

5. Functional candidate genes in dairy sheep

As an alternative approach to QTL mapping, the candidate gene strategy undertakes the study of genes that are supposed to be responsible for a considerable amount of the genetic variation of traits of interest based on their known physiological function (Moioli et al., 2007). More precisely, this is a functional candidate gene, whereas a positional candidate would be any gene mapping within the confidence interval of a described QTL. On this section, we will comment briefly studies performed on functional candidate genes in dairy sheep. In the 1990s, genes coding for milk proteins were studied as potential tools for selection in dairy sheep (see reviews by Barillet et al., 2005, Moioli et al., 2007). For example, for the αs1-casein five polymorphisms were identified (Chianese et al., 1996). Associations of this gene's allelic variants with milk composition traits and renneting properties were identified in different sheep breeds (Piredda et al., 1993; Pirisi et al., 1999). Other milk protein gene extensively studied in dairy sheep is β-lactoglobulin, for which three protein polymorphisms have been described (Erhardt, 1989). However, the lack of consistent results regarding the possible associations of β-lactoglobulin polymorphisms with milk production traits, have discarded this gene as a potential genetic marker.

Based on previously described QTL in the bovine orthologous chromosome (BTA3), Calvo et al. (2004a; 2006) reported a preliminary assessment of genes located on the orthologous ovine chromosome, OAR1, for milk traits in 13 half-sib families of Spanish Manchega sheep.

The genes studied included two α-amylase (*AMY*) genes, annexin A9 (*ANXA9*), solute carrier family 27 member 3 (*SLC27A3),* cingulin *(CGN)* and acid phosphatise 6 lysophophatidic *(ACP6).* However, only within-family associations were detected for *AMY* and *SLC27A*, suggesting the need of larger resource populations to confirm the preliminary results reported. Similar results were found in this population in relation to the heart type *FABP3* gene, studied as a candidate gene for milk fat content (Calvo et al., 2004b). The candidate chromosome approach based on QTL detected in sheep and cattle was also followed by Árnyasi et al. (2009), who looked for any relationship between microsatellite markers localised on OAR6 and milk production traits in a backcross Awassi X Hungarian Merino population. Significant associations were detected for the lactation milk traits studied, with the most significant associations being found for marker *BM143* and lactation milk yield and lactation lactose yield.

A simplistic approach was presented by García-Fernández et al. (2011a) when assessing in Churra dairy sheep the role of genes previously identified to harbour causal mutations or QTN in dairy cattle. Hence, these authors searched for polymorphisms in the genes encoding the acylCoA:diacylglycerol acyltransferase 1 (*DGAT1*; Grisart et al., 2002), the growth hormone receptor (*GHR;* Blott et al., 2003) and the breast cancer resistance protein (*ABCG2*; Cohen-Zinder et al. 2005; Olsen et al., 2007). Also the osteopontin (*SPP1*) gene was considered in this work, as initial candidate gene in dairy cattle (Schnabel et al. 2005) and because its known influence on the expression of milk protein genes (Sheehy et al. 2009). This analysis revealed only significant associations at the nominal level for allelic variants of the *ABCG2* gene, whereas no significant association was found for the other studied genes. These results suggest that milk production traits show a different genetic architecture in sheep and cattle and highlight the need of increasing our knowledge on sheep genomics and not only building up on the advances previously reported in dairy cattle. Scatà et al. (2009) also studied the influence of *DGAT1* polymorphisms on milk traits in three Italian sheep breeds. These authors identified a SNP in the 5`UTR region of the gene showing a significant negative association with milk fat content in the Sarda sheep whereas this allelic variant was rare in Altamurana and Gentile di Puglia breeds, which have a higher milk fat content than Sarda.

Several genes encoding enzymes directly involved in fatty acid metabolism have been studied in the last years. In Churra sheep linkage and association analyses have been performed to assess the influence of the stearoyl-CoA desaturase (*SDS*), acetyl-CoA carboxylase α (*ACACA*) and fatty acid synthase (*FASN*) genes on milk fatty acid composition (García-Fernández et al., 2010a, 2010b, 2011b). Although some significant nominal associations were detected between some of the allelic variants identified in these genes, these analysis did not reveal any major effect of these genes on the fatty acid profile of Churra sheep milk. Crisà et al. (2010) have also studied polymorphisms in genes encoding enzymes putatively involved in the synthesis and metabolism of milk fat in three Italian breeds (Altamurana, Gentile di Puglia and Sarda). These authors identified genes such as α-1-antichymotrypsin-2 (*SERPINA3*), diacylglycerol O-acyltransferase homolog-2 (*DGAT2*), propionyl Coenzyme A carboxylase, β polypeptide (*PCCB*), sulin-like growth factor-1 (*IGF1*) and *FASN* to influence on the variability of the fatty acid profile of sheep

milk. Two other genes, *GHR* and zona pellucida glycoprotein-2 (*ZP2*), were found to affect the variability of the total fat content.

6. Short future research and expectations

Despite the moderate number of QTL identified in dairy sheep, the identification of genetic markers to use in marker- or gene- assisted selection programmes is still hampered by the large confidence intervals of the QTL identified by classical linkage analyses based on medium-density microsatellite maps. In the last years, high-density SNP genotyping has become feasible in livestock species, whereas genome sequencing projects for cattle and sheep are now are reality. Whereas the last version of the bovine assembly (btau_4.0; http://www.ensembl.org/Bos_taurus/Info/Index?db=core) is of acceptable quality, the sequencing project of the sheep genome is still ongoing (International Sheep Genomics Consortium et al., 2010). The great research efforts of the International Sheep Genomics Consortium (ISGC; http://www.sheephapmap.org/) to develop public genomic resources to be used by sheep geneticists are providing the research community with the tools required to assist dairy sheep breeding with edge-cutting genomic technology. The Sheep HapMap project allowed the identification of millions of allelic variants in the sheep Genome, part of which have been used for the development of the ovine SNP50 BeadChip. Current efforts of the ISGC are being addressed to progress on the sheep genome sequencing project, with v3.0 of the sheep genome assembly (http://www.livestock genomics.csiro.au/sheep/oar3.0.php) being available, and to develop a high density SNP chip to allow the study of structural variants (J. Kijas, personal communication).

In cattle, several studies can be found already in the literature using high-throughput SNP genotyping platforms to study the genetic basis of milk production traits (Mai et al., 2010; Schopen et al., 2011). In this species, Genomic Selection seems a feasible way of using the advances of the genomic era for a straight-forward implementation in breeding schemes. In dairy sheep, however, the great genetic diversity of the populations makes this approach more difficult to implement in current breeding programmes. In any case, the screening of high density SNP distributed along the sheep genome will, for sure, facilitate the identification of allelic variants directly associated with milk production traits and other traits of interest in dairy sheep. The whole genome association study (GWAS) approach, which directly exploit linkage disequilibrium between markers and causative mutations, together with scans based on the LDLA methodology (Legarra & Fernando, 2009; Druet et al., 2008), are currently under way in some of the resource populations previously used to map classical QTL detection. Several of these genome screenings are included in the framework of the European funded project *Sustainable Solutions for Small Ruminants* (3SR) where the genetic basis of resistance to mastitis, parasite infections and paratuberculosis in different European populations are under dissecting using the last genomic advances. International collaborations with research groups from Australia, China and USA have made of this project a major international effort to increase our knowledge on the field of sheep genomics (see http://www.3srbreeding.eu/ for further details about this project). Another collaborative project performed under the Seventh Framework Programme (FP7) of

the European Commission is Quantomics, which aims to deliver a step-change in the availability of cutting edge technologies and tools for the economic exploitation of livestock genomes (http://www.quantomics.eu).

7. Conclusion

Dairy sheep has been the subject of several studies trying to decipher the molecular architecture of milk production traits. Due to dairy sheep production systems characteristics (based on a wide range of local breeds reared under a variety of management systems) and its minor economic importance related to dairy cattle, the results are only modest but provide an initial picture of the genetic basis of milk production in sheep. The development of molecular tools derived from the increasing knowledge on the genome of this species make us envision a promising future where genomic information will assist sheep breeders to analyze their pedigrees and make informed decisions to enhance the improvement of sheep milk production.

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