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Chapter 8

Milk Casein Alleles, Haplotypes and QTL Effect on Protein and Fat Content and Milk Yield in Argentinean Criollo and Cross Goats

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Additional information is available at the end of the chapter

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1. Introduction

Globally, most of the goats are in marginal areas and hostile environments, raised by rural poor, smallholders and small producers (Morand-Fehr & Boyazoglu, 1999).

In Argentina, the existence of goats according to data released by SENASA (National Agrarian Health Service) is 4,256,716 animals (existence until March 2011), which are held by not more than 50,000 farmers, mostly the rural poor.

The predominant activity is to produce offsprings, followed in importance of fiber, milk and hides.

The production systems are essentially extensive with grazing on natural degraded grasslands. Most of the population is in the center-north, where production is oriented mainly to meat and milk, while in northern Patagonia are most of the hairs producing goats (mohair). In the north of the province of Buenos Aires there are intensive production systems, which mainly engaged in milk production and less production of meat.

According to data published by the Ministry of Agriculture, Livestock and Fisheries Argentina milk production reaches the 3,200 tons/year from about 10,000 goats with an average production of 300 liters per animal for 210 days lactation. The production structure is divided into two groups: first, business-oriented dairy large-scale productions, which use technologies and breeds of potentially high milk yield (Toggenburg, Pardo Alpina, Saanen and Anglo Nubian) and secondly small and medium producers, who have mostly Criollo goats which produce milk and meat on a seasonal basis.

The dairy goats for cheese making have been an ancient activity in the Argentinean regions of the arid valleys of the Northwest and Cuyo, a craft developed by producers in subsistence conditions.

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The Figure 1 shows Northwest Argentina area (Salta, Jujuy, Tucumán, Santiago del Estero and Catamarca provinces).

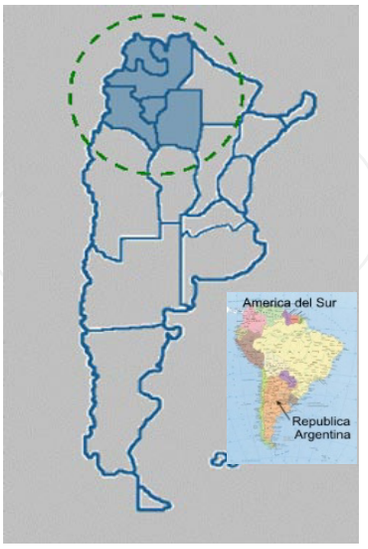


Figure 1. Map of Argentina. Northwest area highlighted

The production systems are based on the use of natural pastures and less often, irrigated pasture implanted. The herd is managed so that the kids after calving remain part of the day with the goats, thus allowing the animals to milk to obtain milk intended for cheese making. These cheeses are intended for family consumption, barter or sell the local market.

In Argentina, the Criollo goat is a "native" breed which can be considered as like-dairy breed that lives in isolated and very hard areas. Up to now, this breed has not been artificially selected for any specific trait and it has only been subjected to natural selection since brought by the Spanish people nearly 500 years ago (Rodero et al., 1992).

In the Northwest (NW) region of Argentina there are 91,532 goats and it is around of 21.4 % of the country (SENASA, existence until March 2011). Their great adaptation to specific environments allows for the exploitation in low rural areas, providing rural communities with typical products of animal origin. Moreover they constitute a potential genetic resource to be evaluated and preserved before some characteristic can be lost due to the unsystematic crosses with other highest selected breeds. Most breeders from NW region milk their goats to produce and trade a "homemade" cheese which is an important familiar economic income.

2. Milk goat proteins

Due to the molecular and genomics structure and organization of the milk protein are deeply described in a special chapter in this book, here we only give a general overview of milk protein.

In ruminants the four caseins represent about 80% of the protein in milk. It is well known that caseins are encoded by four linked and clustered genes including α_{s1}-casein (*CSN1S1*),

β-casein (*CSN2*), α_{s2}-casein (*CSN1S2*) and κ-casein (*CSN3*) genes. In goats, the entire casein gene cluster region spans about 250 kb on chromosome 6 (Hayes et al., 1993).

In the last years, the genetic polymorphism of goat α_{s1}-casein has been intensively studied because of its extensive variability and α_{s1}-casein its direct relationships with milk quality and composition (review by Grasclaude et al., 1994; Martin et al., 2002). So far, 18 alleles associated with different rates of protein synthesis have been identified. On the basis of the milk content of caseins, the variants can be classed into four groups: "high" alleles (A, B1, B2, B3, B4, C, H, L and M) producing almost 3.5 g/L of α_{s1}-casein each; "intermediate" alleles (E and I: 1.1 g/L); "low" alleles (D, F and G: 0.45 g/L) and "null" alleles (O1, O2, O3 and N) producing almost 0 g/L of α_{s1}-casein each (Moioli et al., 2007).

Owing to the importance of κ-casein in the technological properties of milk, the polymorphisms in the κ-casein gene have been extensively studied in ruminants. The κ-casein fraction plays a crucial role in the formation, stabilization, and aggregation of the casein micelles and thus affects the technological and nutritional properties of milk. Cheese-making is based on the cleavage of the κ-casein Phe-Met peptide bond by enzymes or heat.

In goats, the gene *CSN3*, like that of *CSN1S1* is polymorphic, which is being studied intensively. Further polymorphisms in exon 4 of the κ-casein locus were detected. Several studies, using various techniques, have reported polymorphisms in the goat κ-casein gene. Eight polymorphisms sites have been detected (Yahyaoui et al., 2003; Jann et al., 2004).

Both in cattle (Boettcher et al., 2004) and goats (Caroli et al., 2004; Prinzenberg et al., 2005) are discussed the possibility that contributions be found not only the genes specific to each casein, but the haplotypes.

3. Allele and haplotype frequency of α_{s1}-casein and κ-casein

In the last years the *"animal breeding world"* has been facing to the new paradigma quantitative-molecular for improvement. Over the past decades, unequivocal evidence has emerged for the existence of genes with major effects on many performance and fitness characteristics. The opportunity to use molecular screening of individual animals to rapidly increase the frequency of such genes is now a reality. The use of genetic markers to efficiently introgress genes into different genetic backgrounds likewise can potentially change specific genetic characteristics of a population without greatly diluting other established adaptation and product-quality traits. But the first step to use a molecular marker in any breding plan is to know the allele variability and its population frequencies.

3.1 α_{s1}-casein allele frequency and genotypes

In her Master of Science Thesis, Suárez (2003) described the polymorphism at the *CSN1S1* gene in a population of Criollo goats from the NW region. Blood samples were taken in four provinces of Argentina and genomic DNA was extracted from leukocytes following a protocol by Madisen et al. (1987). All samples were used to estimate the allelic frequencies at the *CSN1S1* gene.

The genotyping at the *CSN1S1* locus was carried out by a multiplex amplification using fluorescent primers. The PCR products were analyzed with an ABI PrismTM 310 (Applied Biosystem Inc., USA) automated sequencing system equipped with GenScanTM (version 2.1) and the GenotyperTM software (Babilliot and Amigues, personal communication). This procedure was developed by Labogena (Jouy-en-Josas, France). Also, some DNA samples were amplified by an allele specific PCR for allele E (Amills, 1996).

The *CSN1S1* allelic distribution present in this breed shows the most frequency of "high" alleles (0.68) is predominant over the "intermediate", "low" and "null" alleles (0.19, 0.23 and 0.02, respectively). The "high" alleles, A and B, have the highest frequencies, 0.30 and 0.31, respectively, followed by the E allele with a frequency of 0.19. The F allele and the O allele were found at a frequency of 0.04 and 0.02, respectively. During the genotyping process a pattern that does not belong to any known alleles was found. We checked the inheritance of this "new" variation in a heterozygous buck family with 13 kids and 11 does. We have preliminary designated it as "X allele" which was present at a frequency of 0.07.

The polymorphic information content (PIC) is a measure of informativeness related to expected heterozygosity and likewise is calculated from allele frequencies (Botstein et al., 1980; Hearne et al., 1992).

The PIC value found for the *CSN1S1* locus was 0.73 and the expected hetorozygosity 0.77. From the 28 possible genotypes (7 alleles) 23 (82%) were found. The A/B genotype had the highest frequency (0.19) and the C/X, F/F and O/X genotypes the lowest (0.005). Both A/B and B/B genotypes accounted for 31.7 % of all the genotypes analyzed. The genotypes B/O, C/C, C/O, F/O and O/O were absent. From the 17 goat breeds in which *CSN1S1* frequencies were evaluated (Table 1), the Criollo and Canaria breeds were the most similar for the A allele (0.30 and 0.28, respectively), B allele (0.31 and 0.32, respectively) and E allele (0.19 and 0.20, respectively) but were very different in the O allele (0.02 and 0.20, respectively). Although the Jónica breed seems also similar for the A, B and C allele frequencies to the Criollo breed, the F allele frequency was quite different (0.04 Criollo and 0.28 Jónica). Within "high" casein content alleles the C allele was found only in a few breeds and its frequency was always very low, but in the Criollo breed we found a frequency of 0.07, higher than any other breed.

Taken into account the historical information, that states that: " . . . during the first decade of America colonization European introduced different species of animals and some of them (swine, chicken, sheep, goats, cattle and horses) were boarded in the Canarias Island La Gomera in 1493 by Cristóbal Colón, . . ." (Gonzalez-Stagnaro, C. 1997) and considering also the phenotypic similarities between the Criollo and the Iberian breeds like Murciana-Granadina, Malagueña, Canaria and Payoya, we run a Principal Components Analysis (PCA).

The central idea of PCA is to reduce the dimensionality of a data set consisting of a large number of interrelated variables, while retaining as much as possible of the variation present in the data set (Jolliffe, I. 2002). In the PCA we found that the Criollo breed is away

Breed	*n*	A	B	C	E	F	O
Alpina (Fr)[1]	213	0.14	0.05	0.01	0.34	0.41	0.05
Alpina (It) [1]	80	0.00	0.00	0.00	0.35	0.59	0.06
Saanen (Fr) [1]	159	0.07	0.06	0.00	0.41	0.43	0.03
Saanen (It) [1]	70	0.05	0.00	0.00	0.49	0.46	0.00
Poitevine (It) [1]	209	0.05	0.35	0.00	0.45	0.14	0.00
Corse (Fr) [1]	106	0.06	0.13	0.00	0.14	0.59	0.08
Rove (Fr) [1]	147	0.12	0.05	0.00	0.62	0.10	0.11
Gargánica (It) [2]	38	0.28	0.41	0.03	0.00	0.22	0.08
Maltesa (It) [2]	70	0.41	0.16	0.00	0.06	0.37	0.00
Murciana Granadina(Sp) [1]	77	0.08	0.25	0.00	0.62	0.05	0.00
Malagueña (Sp) [1]	56	0.00	0.25	0.00	0.70	0.05	0.00
Payoya (Sp) [1]	39	0.04	0.14	0.00	0.82	0.00	0.00
Canaria (Sp) [1]	74	0.28	0.32	0.00	0.20	0.00	0.20
Vallesana (It) [2]	83	0.03	0.13	0.00	0.28	0.39	0.17
Roccaverano (It) [2]	77	0.23	0.12	0.00	0.21	0.38	0.04
Jónica (It) [2]	110	0.35	0.30	0.00	0.06	0.28	0.00
Norway Multicolor[3]	147	0.00	0.11	0.00	0.00	0.03	0.86
Criolla (Ar) [4]	214	0.30	0.31	0.07	0.19	0.04	0.02

Table 1. Allelic frequencies at the *CSN1S1* locus in different breeds *n*: Sample size; Fr: French; It: Italy; Sp: Spain; Ar: Argentina. [1] Grosclaude et al. (1994); [2] Sacchi et al. (2003); [3]Adnoy et al. (2003); [4]Suárez (2003).

from the 4 Iberian breeds (Figure 2). The Murciana-Granadina, Malagueña and Payoya were the most important breeds in the first axe (about 41% of the total variability). In axe 2, the Criolla breed account for 20% of the total variability and in axe 3 the Canaria breed also account for 20% of the total variability.

Although the PCA results from α_{s1}-casein show that Criolla breed is quite different from Iberian breeds morphometric measures and zoometric characteristics can help to establish any phylogenetic relationship between the Criollo breed and Iberian goats. Nevertheless 500 years in the America continent under natural selection process and eventual population contraction and expansion periods, one would not expect to observe so much genetic similarities between the Criollo breed and its Iberian ancestors.

In other study, Caffaro (2007), described the polymorphisms at the *CSN1S1* and *CSN3* genes in a population of Criollo in CriolloxCriollo and CriolloxSaanen crosses.

The allelic variants for the *CSN1S1* gene were detected using the PCR-AS and PCR-RFLP technique. The B and C alleles were gathered in B-(C) groups since they are indistinguishable with the methods developed in this study.

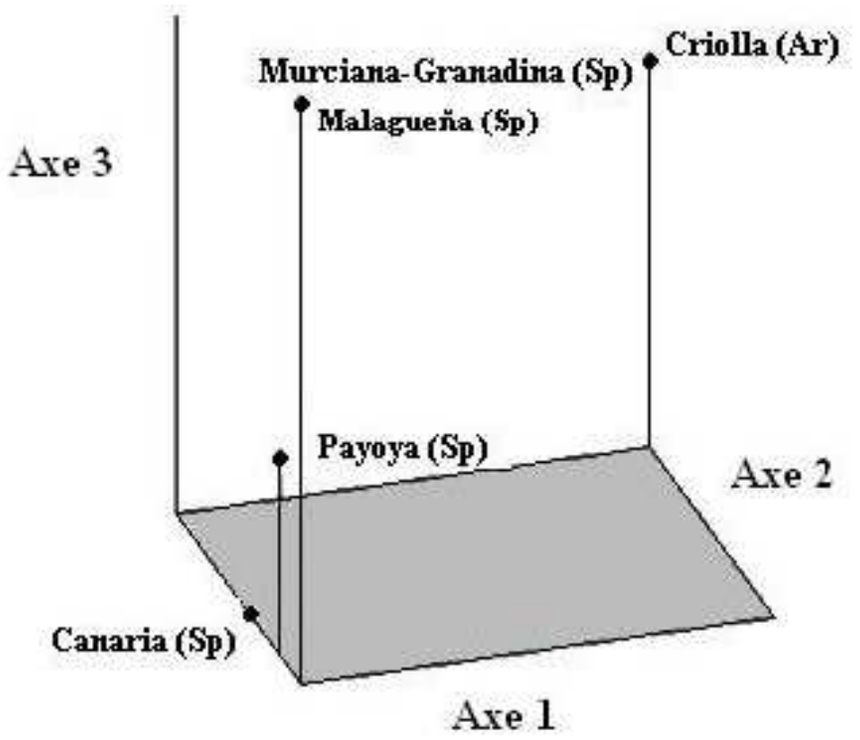


Figure 2. Results of principal component analysis by goat breeds

For *CSN1S1* gene, "high" alleles were found with most frequency (A, B and C) with 0.66. The "intermediate" allele presented by 0.17. The "low" allele was present in 0.03. Finally, the "null" allele was presented at 0.02.

For *CSN1S1* gene allelic frequencies were similar to the reported by Suárez (2003) for Creole goats in the NW. Furthermore, it is showing the X allele (0.10), as found by Suárez (2003), with a frequency slightly higher.

3.2. κ-casein allele frequencies and genotypes

In the same Criollo population described above, Caffaro (2007) using the PCR technique amplified the *CSN3* gene. The PCR products were purified by commercial kits and then the purified product was sequenced in both senses. The consensus sequence of each animal was aligned whit different alleles.

In the *CSN3* locus was found only 3 of 8 allelic variants described. The highest frequency was for the B allele (0.74), then the A allele (0.24) and lower D allele frequency (0.02) and only in heterozygous state. Moreover, the emergence of the state homozygous the allele B is significantly higher than other alleles. The number of individuals homozygous for this locus was approximately three times higher than in heterozygous (116 on 42 animals).

Two animals were also found (dam and daughter) with allele B′ (subtype B allele) and an animal with a substitution at nucleotide 91 (for the sequence of allele B) not yet reported in the literature.

Comparing the allelic frequencies found in Criollo goats with that reported for the different breed from different countries shows that the frequencies of three alleles in Criollo goats have a similar behavior to that reported in most other breed, i.e., most often found for the B allele, followed by the A allele and low frequency D allele was found.

In the Table 2 allele frequencies are presented for 26 goat breeds in different countries. Allele frequencies of this Table were taken from the following works: Chessa et al. (2003); Yahyaoui et al. (2003); Prinzenberg et al. (2005), Sacchi et al. (2005), Caroli et al. (2006 and 2007).

Breed	*n*	A	B	C	D	E	F	G	M
Murciana-Granadina[1]	30	0.37	0.63	-	-	-	-	-	-
Canaria[1]	30	0.58	0.42	-	-	-	-	-	-
Malagueña[1]	11	0.45	0.55	-	-	-	-	-	-
Teramana[3]	28	-	0.70	0.02	0.10	-	0.14	0.04	
Montefalcone[3]	17	-	0.59	-	-	0.41	-	-	-
Girgentana[3]	19	0.34	0.45	-	0.05	-	0.05	0.11	-
Sarda[3]	19	0.31	0.61	-	-	-	0.08	-	-
Alpina[2]	28	0.34	0.66	-	-	-	-	-	-
Saanen[2]	28	0.39	0.48	0.13	-	-	-	-	-
Saanen[3]	22	0.25	0.66	0.09	-	-	-	-	-
Gargania[3]	72	0.10	0.75	0.01	0.13	-	-	-	0.01
Jonica[3]	229	0.13	0.73	0.02	0.11	-	-	-	0.01
Maltesa[3]	105	0.08	0.70	0.01	0.20	-	-	-	0.01
Camosciata[3]	45	0.36	0.63	-	0.01	-	-	-	-
Vallesana[3]	83	0.37	0.60	0.03	-	-	-	-	-
Roccaverano[3]	77	0.25	0.60	0.06	0.07	-	-	-	0.01
Frisa[3]	70	0.33	0.65	0.01	0.01	-	-	-	-
Orobica[3]	66	0.08	0.55	0.02	0.35	-	-	-	-
Verzasca[3]	67	0.28	0.72	-	-	-	-	-	-
Camasciata[3]	88	0.39	0.61	-	-	-	-	-	-
Angora[4]	43	0.15	0.67	0.04	0.11	-	-	0.02	-
Weisse Deutsche Edelziege[5]	32	0.34	0.55	0.06	0.05	-	-	-	-
Borno[5]	66	0.46	0.54	-	-	-	-	-	-
Red Sokoto[5]	88	0.40	0.58	-	-	-	-	-	0.02
West African Dwarf[5]	92	0.36	0.64	-	-	-	-	-	-
Cabra de pelo[5]	50	0.31	0.26	0.04	0.25	-	-	0.14	-
Criolla[6]	137	0.24	0.74	-	0.02	-	-	-	-

Table 2. Allelic frequencies at the *CSN3* locus in different breeds N: Sample size. [1]Spain; [2]French, [3]Italy, [4]Turkey, [5]Germany, [6]Argentina

3.3. Haplotype frequencies

Haplotype means a set of closely linked alleles (genes or DNA polymorphic) inherited as a unit.

To reconstruct the most probable haplotype they use the LSPH program (Baruch et al., 2006).

LSPH program assumes that no recombination between loci. The haplotypes are reconstructed in two stages: first, the haplotypes in the parental generation are determined and the progeny haplotype for more information (no missing genotypes) are assigned. Then, the origin of each haplotype (paternal or maternal) is determined.

Once built haplotype most likely, the relative frequency was estimated by procedure FREQ of program SAS (Institute, Inc., Cary, NC).

Haplotypes frequencies the *CSN1S1-CSN3* cluster are reported in Table 3. A total of 12 possible haplotypes resulted from the alleles combination considered, 6 were highest frequency than 0.05. And the most frequent haplotypes were E-B (n=89) and B(C)-B (n=62).

	Haplotype											
	A-A	**A-B**	**A-D**	**B(C)-A**	**B(C)-B**	**E-A**	**E-B**	**F-A**	**F-B**	**O-A**	**O-B**	**X-B**
Frec (%)	0.035	0.116	0.013	0.038	0.200	0.087	0.289	0.025	0.071	0.011	0.025	0.090
NH	11	36	4	12	62	27	89	8	22	3	8	28

Table 3. Haplotype found. Frec (%): relative frequencies. NH: number of animals in each haplotype

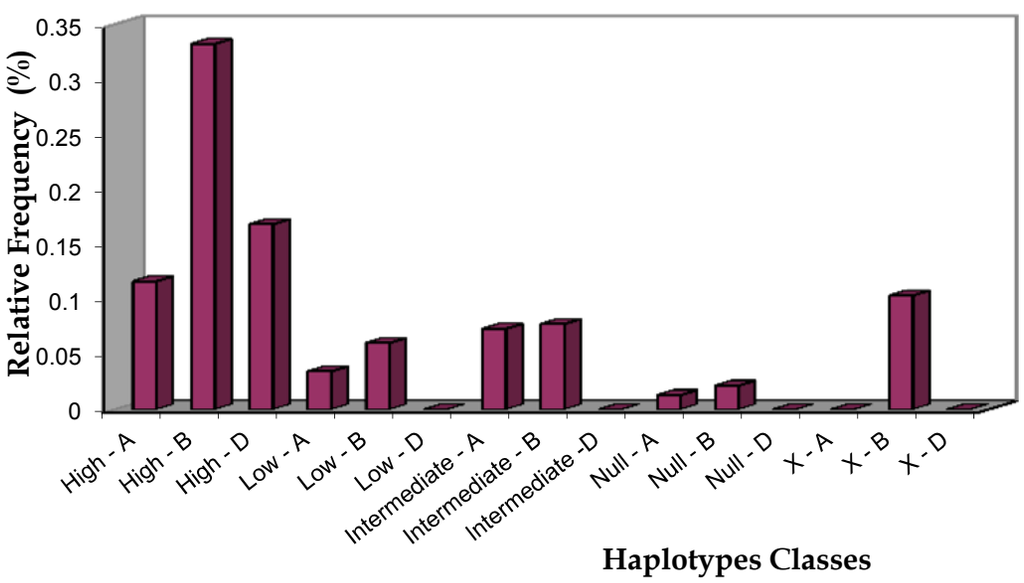


Figure 3. Relative frequency of haplotype grouped into haplotypes classes.

The X allele was only found associated with the B allele of *CSN3* (X-B). Also, the D allele of *CSN3* gene was only associated with *CSN1S1* A (A-D) and the B allele of *CSN3* was found associated with all *CSN1S1* alleles present in this study.

The results of this haplotype grouping in classes is similar those reported by other authors (Sacchi et al., 2005 and Prinzenberg et al., 2005), where they found that the B allele of *CSN3* appeared associated with two of the strongest *CSN1S1* alleles (A and B) (Figure 3).

4. Effect of α_{s1}-casein, κ-casein and haplotypes on production traits

Milk yield and milk components are influenced by a number of factors including animal genetic and environmental conditions. An association among physiological state of the animal, breed, parity number, season of kidding and level of production were reported by Gipson & Grossman (1990) and for milk composition by Soryal et al. (2005); Dimassi et al. (2005) and Fekadu et al. (2005).

In our study milk samples were collected from the Criollo goat belonging to the experimental flock (n=150) located in the Experimental Farm Leales – INTA (National Institute of Agricultural Technology), located 52 km southeast of the city of San Miguel de Tucumán, 27° 11′ latitude south and 65° 17′ west and at an altitude of 335 m above sea level. The majority of these Criollo goats were rescued from the different private flocks around the NW region and they can be considered the best representative of the breed. A sub set of 84 goats were milked. Milk samples were collected monthly by hand-milking into an individual container (50 ml) then refrigerated and analyzed for milk components (fat %-FP and protein %-PP) by Milkoscan using infrared procedures. Milk yield (MY) was recorded weekly.

To evaluate the effect of the *CSN1S1* genotypes on milk traits (MY, FP and PP) a set of 147 records from 84 milking goats was analyzed using the follow mixed model (1):

$$y = \boldsymbol{X}\beta + \boldsymbol{Z}u + \varepsilon \quad (1)$$

where y is the vector of phenotype data, $\boldsymbol{X}$ and $\boldsymbol{Z}$ are the design matrix, β is the unknown vector of fixed effects, u is the vector of random effects, and ε is the error vector. Records of MY, PP and FP were transformed to aggregate data by Fleishmann method (Peña Blanco et al., 2005). The influence of four fixed factors was considered: genotype (7 levels), kidding season (autumn or spring), parity number (6 levels) and number of kids (single and double) and every lactation was considered as a repetitive data. The PROC MIXED from SAS package was used (SAS, 2005). We wrote estimable functions and performing contrast to evaluate the differences between the available genotypic groups.

The average values estimated for MY, FP and PP were: 1.214 kg/day, 2.825 % and 2.672 %, respectively.

We did not detect any differences for the four fixed effects on MY or FP from aggregate data (Table 4), but we found a significant effect of season of kidding on PP. Angulo et al. (2002) reported that the season of kidding in Malagueña goats affected both MY and PP.

Fixed effects	MY	FP	PP
Genotype	0.2679	0.5370	0.0170 *
Kidding season	0.3907	0.0600	0.0008 **
Parity number	0.2468	0.6270	0.1974
Number of kids	0.6981	0.2890	0.2630

Table 4. Significance level for fixed effects of MY (milk yield), FP (fat percentage) and PP (protein percentage). * P≤0.05; ** P≤0.01

It has been reported that the difference in casein content between an homozygous animal for "high" alleles, like A/A, and an homozygous animal for "low" alleles, like F/F, is 6 g/l (Grosclaude *et al*., 1994), moreover the efficient transport of caseins seems to be dependent upon *CSN1S1*, thus animals with "low" alleles (F, G) would have a reduce solid content in milk (Chanat et al., 1999). In general goat milk with high levels of *CSN1S1* have been found to have better milk composition, not only protein content, but also regarding fat, total solids, phosphorous and lower pH than milks with low levels of *CSN1S1* (Grosclaude et al., 1987; Barbieri et al., 1995).

According to these results, we did not find any difference between genotypes for MY or FP. This result agree with those reported by Mahé et al. (1993); Vassal et al. (1994); Février et al. (2000) and Adnoy et al. (2003), but are rather uneasy to explain. The milk fat content is modulated by genetics and environmental factors (Barroso et al., 1999), and the regulation of gene expression in the mammary gland is not clear.

Leroux et al. (2003) investigated the association between the polymorphism at *CSN1S1* locus and lipid content in caprine milk with and they conducted RT-PCR and macroarrays analyses and concluded that milk fat content is not due to differences in the expression of some enzymes of the lipogenesis pathway but could be related to the expression of some genes encoding protein anchored in the milk fat globule membrane. An alternative hypothesis has been mentioned for a possible physical linkage between the *CSN1S1* locus and an unknown QTL that might influenced fat content (Manfredi, 2003), but this has not yet been investigated.

Regarding PP, significant differences exist with respect to the genotype in Criollo goats. This is also in agreement with previous results in French, Italian and Spanish breeds (Serradilla, 2003). To identify which genotype had the main influence for PP, we grouped the records according to the available genotypes and compared the differences between the estimated means (Table 5).

Milk samples having genotype for "high" alleles, A, B, C, had higher protein percentage (1.109 gr/kg) than homozygous samples for the "intermediate" allele E, as shown in Table 5. This is in agreement with the results reported by Angulo et al. (2002) for the Malagueña breed. In the Criollo goat from the NW region, although significative (P<0.05), the difference in protein content between "high" and "intermediate" genotypes was smaller than those reported in the literature.

In addition, we compare animals homozygous for the ¨X¨ allele and we did not find any significative difference between animals bearing "high" alleles and X/X goats, but we found

a difference with goats homozygous for the intermediate E allele (P=0.0154). This suggests that this "X" allele might belong to the "high" alleles group.

Genotype	PP Estimated (± sd)	p-value
AA-BB-CC-AC-BC vs EE	1.109 (± 0.430)	0.0140
AA-BB-CC-AC-BC vs XX	-0.915 (± 0.727)	0.2170
EE vs XX	-2.024 (± 0.789)	0.0154

Table 5. Estimated differences among *CSN1S1* genotypes for PP mean and standard deviation and p-value.

To evaluate the effect of the *CSN3* and haplotypes on milk traits (MY, FP and PP), records from 86 milking goats were analyzed using the follow lineal model (2)

$$y = Xb + e \tag{2}$$

where y is the vector that includes n records in each animal. Records of MY, FP and PP were transformed to aggregate data by Fleishmann method (Peña Blanco et al., 2005). b is the unknown vector of fixed effects, and e is the vector of residuals with covariance matrix $I\sigma_e^2$. X is the incidence matrix relating the vector data with the vector of fixed effects.

The fixed effects considered in the matrix X were: racial biotype (Criollo and different percentages of crossing with Saanen), age of the animal (from 9 months to 14 years), calving season (2 levels, autumn and winter), lactation number (6 levels, from first lactation to number 6, assuming that animals born on the premises, had no previous lactations), number of kids (single and double), α_{s1}-casein genotype (23 levels according to genotypes present) genotypes κ-casein (4 levels: 1 = AA genotype, 2 = BB genotype, genotype 3 = AB, 4 = genotype AD). It also adjusted the interactions between genotype α_{s1}-casein and κ-casein genotypes.

The GLM procedure from SAS package was used (SAS, 2005). We wrote estimable functions and performing contrast to evaluate the differences between the available genotypic groups.

With respect to the *CSN3* gene, there was no significant effect on production variables. Contrary to these results, Chiatti et al. (2005), who studied the effect of *CSN3* gene on production variables in four Italian breeds of goats, they found that animals with BB genotype had a higher percentage of protein and casein in milk, and animals with genotype AB, had milk with higher fat content. These authors suggest that the results are independent of gene expression levels *CSN1S1*.

On the other hand, when we assessed the association of the haplotypes present in the population (α_{s1}-casein/κ-casein) with dairy character, significant effect on protein percentage was found

We found that animals with haplotypes "high" for *CSN1S1* and *CSN3* B allele were more frequent but also the presence of allele B was associated with higher protein levels

compared with the A allele when both were associated with alleles "high" for the gene *CSN1S1* (0.040 and 0.036, respectively). The milk from animals that contain the D allele of *CSN3* give values lower protein content than milk from animals with *CSN3* B allele when alleles are also associated with "high" locus *CSN1S1*.

Sacchi et al. (2005) and Prinzenberg et al. (2005) postulated that the B allele of *CSN3* occured most often associated with the "high" alleles *CSN1S*1, levels of casein in milk were higher than the presence of the A allele of *CSN3*. On the other hand, the average values were similar between different alleles found for *CSN3* gene when they were associated with "intermediate" *CSN1S1* gene.

5. QTL detection for milk production traits in goats

The use of quantitative information in livestock breeding programmes has become more sophisticated over time in order to allow breeders to make faster progress in a chosen set of traits. Quantitative information was initially used in mass selection, whereby individuals with better trait values were chosen to be parents of the next generation. This progressed to using information from relatives and multiple traits, by assuming an infinitesimal (and usually additive) model of inheritance.

This approach maybe criticized for the simplicity of this assumption with regard to the actual mechanisms of gene action, but has proven highly successful in generating genetic change in livestock populations.

Most of the economically important traits for breeding animals show a continuous distribution of observations as a result of the action of polygene and the environment (Falconer & Mackay, 1996; Lynch & Walsh, 1998). Turn polygene are the result of a large number of additive gene actions between quantitative trait loci (QTL) scattered throughout the genome. Each QTL shows a small effect on the total variation present in the character. Such genes could be detected as segregation in pedigrees, either by observation (in the case of extreme effects) or by sophisticated statistical analysis. The advent of easily scored genetic markers (i.e., microsatellites and SNPs-Single Nucleotype Polymorphism) spaced across the genome of a species has allowed the inheritance of each position in the genome to be traced from parents to progeny, and consequently has allowed more powerful tests of segregation to be developed. Then, we can define a QTL as a chromosomal region that contains one o more genes that encoded a quantitative trait (Andersson & Georges, 2004).

Linkage-based quantitative trait loci (QTL) mapping is based on the linkage disequilibrium observed within a family (Lynch & Walsh, 1998), exploiting recombination in pedigreed and genotyped generations. In livestock the most usual breeding system is to use one male mated with many females producing paternal half-sib family designs. This is the simplest and common commercial herds desing situation to QTL detection.

For mapping genes, there are basically two strategies: the candidate gene and genomic sweep. In the candidate gene locus identifies a polymorphism which is known to have effect on the phenotype in one species and, potentially, could have similar effect on others.

Genomic scanning strategy explores the association between a phenotype and selected markers across the genome, thus identifying chromosomal regions that include genes partly responsible for the expression of that character.

Figure 4 illustrates the principle of detecting a QTL when using a single marker M (with alleles M1 and M2) located at a distance of θ centiMorgan (cM) of QTL. Nevertheless, today the most frequent methodology used in animals for QTLs detection is the method of "multiple markers," which performs the mapping interval and estimated the position of a QTL located between two markers. This strategy is unbiased only if within the chromosomal segment bounded by the two markers there is a single QTL (Kinghorn & van der Werf, 2000).

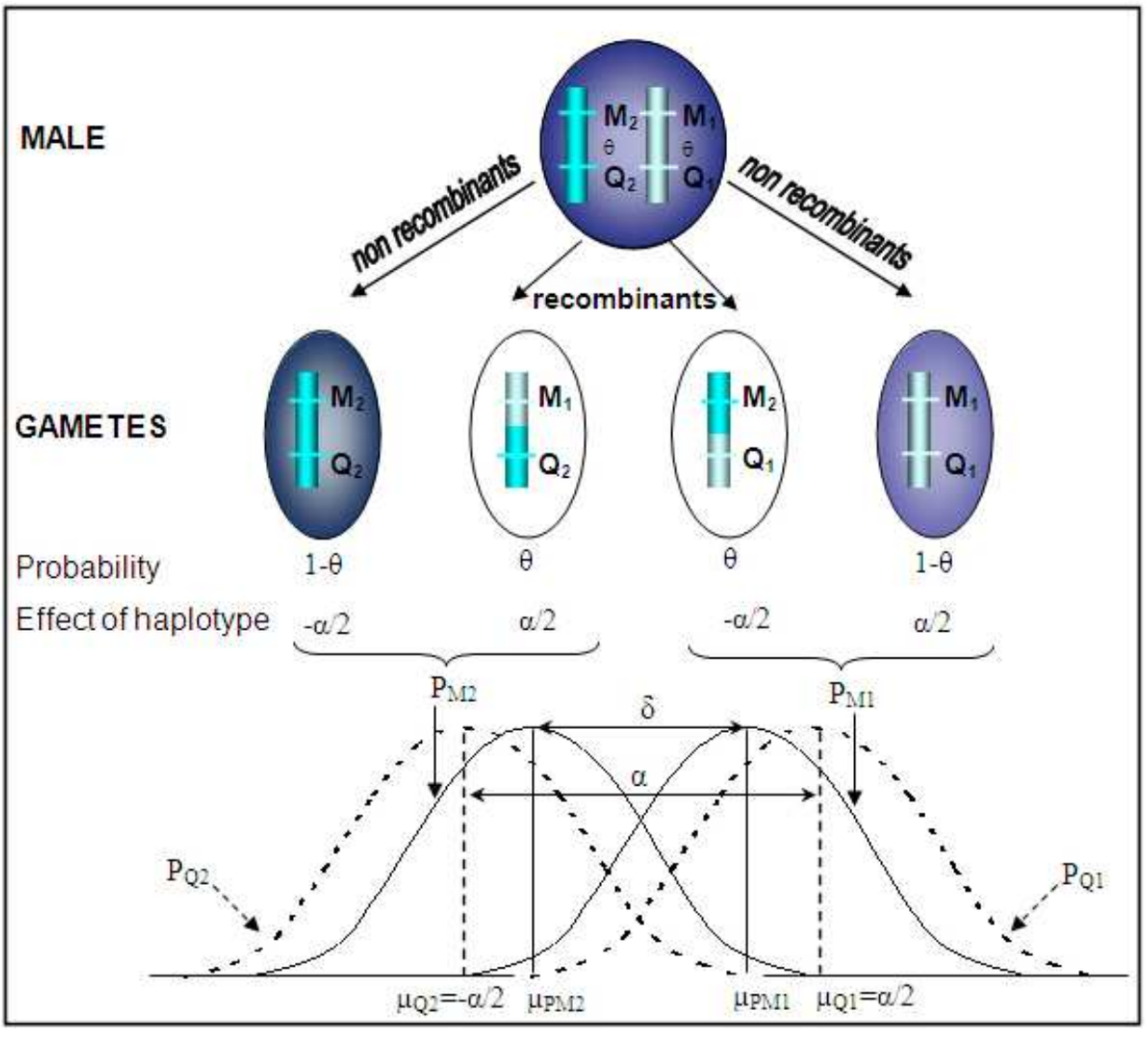


Figure 4. Detection of QTL with a single bi-allele marker. (Adapted to Gautier, 2003)

Most studies of QTL detection for milk production traits have been carried out in cattle, using mostly aggregated data (Zhang et al., 1998; Heyen et al., 1999; Plante et al., 2001; Viitala et al., 2003; Ashwell et al., 2004)). Moreover, Rodriguez-Zas et al. (2002) measured the

association between chromosomal regions and the scale and shape that describe the lactation curve in dairy cattle using a two-stage procedure: a random regression model to predict the elements of the lactation function on an animal basis, followed by a regression interval mapping using the predictions obtained in the first stage of the analysis. Work of QTL detection in goats is scarced (for a reviews of QTL mapping in goat see Maddox & Cocket, 2007). Analyses on QTLs affecting milk traits of dairy goats are lacking. However, the only well-documented genetic association with dairy traits in goats is the one related with the highly variable α_{s1}-casein polymorphisms (Grosclaude et al., 1994; Adnoy et al., 2003; Manfredi, 2003; Suárez, 2003; Sacchi et al., 2005; Caffaro, 2007).

In searching for QTLs in goats, one may look at those significant associations found between milk production traits and genetic markers in cattle (reviewed by Khatkar et al., 2004), and take advantage of the homology between the genetic maps of the cow and the goat. For example, Roldán et al. (2008) identified chromosomal regions associated with variation in the lactation function of goats using the two-stage procedure as employed by Rodriguez-Zas et al. (2002).

The goat population used in this study was established in 1998 at the Experimental Farm of Leales – INTA, in the province of Tucumán. Phenotypes recorded were milk yield (MY), fat percentage (FP) and protein percentage (PP) from 212 female goats. Milk samples were collected at the morning milking, at each of the two kidding seasons (fall-winter and spring-summer) during 6 years (1999–2004). Each goat was sampled for FP and PP once a month, either five or six times per lactation. Records of daily MY for a given test day were the averages of an entire week, with sampling taking place every month but on an irregular basis (up to 3 weeks a month). Lactations with three or fewer records were deleted, and the lactation stage ranged from 3 to 321 days. The total number of observations were 897 for MY, and 814 for FP and PP. Averages (standard deviations) across all families were 0.879 kg (SD 0.563) for MY, 4.382% (SD 1.864) for FP and 4.065% (SD 0.757) for PP.

Genotypic data from eight paternal half-sib families composed of 87 young females and 75 older goats were used for QTL detection. Whereas six families were purebred Criollo goats, the two other families consisted of Saanen by Criollo crosses.

Taking account the homologies between the genetic maps of cattle and goats and the significant associations between molecular marker and milk production traits summarized by Khatkar et al. (2004) in *Bos taurus* autosome (BTA) 3, 6, 14 and 20 a set of 37 microsatellite were selected. Details of molecular markers about map positions, distance can be see in the web.

The statistical analysis was conducted in two stages. They first calculated the predictions of the random regression coefficients, and then they tested the effects of the chromosome regions on those predictions. The random regression model used in the first stage included the goat-specific parameters plus the predictions of individual breeding values and permanent environmental effects. The model equation was as follows:

$$y_{ij\ln rs} = c_l + b_n + d_r + p_s + \sum_{m=1}^{5} \kappa_{(ns)m}\ \phi_{ij(ns)m}(t) + \sum_{m=1}^{5} \psi_{(n)m}\ \phi_{ij(n)m}(t)\ + \sum_{m=1}^{5} \tau_{ijm}\ \phi_{ijm}(t) + \sum_{m=1}^{5} \pi_{ijm}\ \phi_{ijm}(t) + \varepsilon_{ij\ln rs} \quad (3)$$

In (3), y_{ijlnrs} is the record of MY, FP, or PP, for the i^{th} animal measured on the j^{th} test-day taken on year l (l = 1999,…, 2004), under lactation number n (n = 1,…, 6), with the r^{th} number of kids at parturition (r = 1, 2), and in the s^{th} season (s = fall-winter, spring-summer). Fixed effects in the model were year (c_l), lactation number (b_n), number of kids at parturition (d_r), and season (p_s). Additionally, the parameters of the regression function of Ali & Schaeffer (1987) were fitted for each combination of lactation and season ($\kappa_{(ns)m}$). The regression coefficients ($\psi_{(n)m}$) in the Ali & Schaeffer (1987) function were also fitted as random variables that are associated with the permanent environmental effects that are common to the n^{th} lactation number. For animal i, the random variables τ_{ijm} and π_{ijm} are the regression coefficients for the breeding values and the permanent environmental effects, respectively, of the lactation curve proposed by Ali & Schaeffer (1987). For animal i measured on day j, the random regression function which mimics the model of Ali & Schaeffer (1987) can be written as

$$\sum_{m=1}^{5} \lambda_{ijm}\ \phi_{ijm}(\boldsymbol{t}) = \alpha_i + \beta_i \left(\frac{t_{ij}}{280}\right) + \gamma_i \left(\frac{t_{ij}}{280}\right)^2 + \delta_i \ln\left(\frac{280}{t_{ij}}\right) + \phi_i \left[\ln\left(\frac{280}{t_{ij}}\right)\right]^2$$

where λ_{ijm} is either τ_{ijm} or π_{ijm}, and $\boldsymbol{t}$ is a vector such that $\boldsymbol{t}'$ = [1,(t_{ij}/280), (t_{ij}/280)^2, (ln(280/t_{ij})), (ln(280/t_{ij}))^2], being t_{ij} the j^{th} test-day for animal i. The scale parameter that characterizes the overall level of the trait (MY, FP or PP) for the curve of individual i is α_i. The remaining parameters are responsible for the shape of the curve, and represent the rate of change of the trait at different stages of the lactation: β_i and γ_i are associated with a decreasing slope of the curve, and δ_i and ϕ_i with increasing slope. The lactation length was taken to be 280 days. The variance and covariance functions in the random regression model (3) were estimated by Restricted Maximum Likelihood using the program VCE5 (Kovac & Groeneveld, 2003). The permanent environmental matrix ($\boldsymbol{E}$) was estimated with a submodel of (3) in which the fifth and sixth terms were left out. To fit (3), $\boldsymbol{E}$ was split into 'across lactations' ($\boldsymbol{E}_B$) and 'within lactation' ($\boldsymbol{E}_W$) components, such that $\boldsymbol{E}_W$ = 0.4 $\boldsymbol{E}$ and $\boldsymbol{E}_B$ = (1-0.4) $\boldsymbol{E}$. The value 0.4 corresponds to the correlation between permanent environmental effects of first and second lactations. The estimates of the fixed effects, as well as of the additive genetic and permanent environmental effects were calculated by solving the mixed model equations using a program written in PROC IML (SAS, 2005).

In the second stage, we performed a QTL analysis using the half-sib regression interval mapping method of Knott et al. (1996), with the software QTL Express (Seaton et al., 2002). The test statistics were computed every centiMorgan (cM) over the mapped chromosome. *F*-statistic thresholds for chromosome-wise level were calculated from 10,000 permutations

(Churchill & Doerge, 1994). Families that displayed the highest evidence for a QTL at the location in the across-family analysis were taken from the QTL-express output (Knott et al., 1996).

5.1. Genetics parameters

The estimated heritability for MY ranged from 0.142 to 0.593, and the average estimated over the whole lactation period was 0.343. These values were in agreement to those reported in the literature for different goat breeds, and with estimates obtained from either single or multiple trait models.

Our results seem to be slightly lower than those of Weppert & Hayes (2004) for Nubian, Alpine, Saanen and Toggenburg goats, when maternal effects were included in the analysis. The estimated heritability of MY from a model without maternal effects was equal to 0.19 (Weppert & Hayes, 2004). Similar estimates of heritability to the values found in the current study were reported for South African Saanen goats (0.30, Muller et al., 2002), and for Alpine and Saanen females (0.23, Clément et al., 2002).

The average heritability estimate of FP was equal to 0.092 (ranging from 0.093 to 0.141), and the average heritability estimate of PP was 0.160 (ranging from 0.007 to 0.515). These values were lower than those obtained and reviewed by Muller et al. (2002) using data from several goat breeds: the range of FP was 0.160–0.540 (Spain, Alpine, Saanen and Toggenburg breeds) and the range of PP was 0.250–0.620 (Spain, Greece and Saanen goats).

5.2. QTL detection

5.2.1. Milk yield

Seven tests were significant for at least one parameter. In CHI6, we detected a significant effect for all parameters in the interval flanked for the MS BM4621 and BM415 (from 70 to 78 cM).

One chromosomal region was associated with δ and Φ on CHI14. Several studies based on cumulative single records in dairy cattle detected the presence of QTL at the genome-wise and suggestive thresholds on BTA3, in the interval from 16 to 32 cM (Heyen et al., 1999), at 39 cM (Plante et al., 2001), and at 40 cM (Vandervoort & Jansen, 2002).

On the other hand, neither Viitala et al. (2003) nor Ashwell et al. (2004), reported evidence of a QTL for MY on BTA3. Rodriguez-Zas et al. (2002) using test-day milk records reported a significant association between marker MS BL41 (32 cM) and the parameter that describes the shape of the function at the beginning of the lactation.

Additionally, these workers reported significant associations between the scale parameter and two chromosomal regions of BTA3 that were located in the centromere from 0 to 36 cM and in the telomere from 91 to 113 cM (close to MS HUJI177 at 100 cM and MS BR4502 at 113 cM).

An association with increasing slope parameters d and Φ was found at 70 and 71 cM, respectively, on CHI6. Also at 75 cM, the scale parameter (α) and the descriptor of the shape

at the end of the lactation (γ) were found to be significant. Another association with the remained descriptor of the decreasing slope (β) was detected at 78 cM. The correlation between the estimates of α, γ, δ and Φ was high (0.922 – 0.998).

Similarly, the correlation between β and the other parameters ranged from 0.652 to 0.758. Such correlations may suggest a QTL with pleiotropic effects on these parameters. Rodriguez-Zas et al. (2002) detected α putative QTL between 0 and 21 cM in dairy cattle that affected the scale parameter for MY. They also reported the finding of another QTL affecting the shape parameters for MY, which is located in the region from 108 to 129 cM. In dairy cattle, Zhang et al. (1998) reported a putative QTL in the interval between 30 to 50 cM on BTA6 (between MS BM1329 and BM143).

Remember, in goat, the casein gene cluster has been mapped to the distal region of CHI6 (Grosclaude et al., 1994), and is composed of four genes (α_{S1}- casein, α_{S2}-casein, β-casein, and κ-casein). Moioli et al. (2007) reviewed the several associations between casein genes, and dairy traits of goats have been reported in the literature.

This is especially so for the *CSN1S1* gene, which displays a higher level of polymorphism than the one observed in the bovine, and has been related to fat and protein contents (Grosclaude et al., 1994; Adnoy et al., 2003; Manfredi, 2003; Sacchi et al., 2005). However, the effect of α_{S1}-casein alleles on MY does not seem to be important (Moioli et al., 2007). In the current research, they used α_{S1}-casein gene as a marker gene (MS CSN) and did not find association to MY. These results and previous described by Suarez (2003) and Caffaro (2007) suggest that the effect of *CSN1S1* and *CSN3* gen or the haplotypes are not very important for MY but they could have an effect on lactation curve shape.

Moving to CHI14, there was evidence for a QTL at 14 cM (the interval flanked by ILSTS011 and RM011) related to δ and Φ. This result suggests that there may be a QTL with pleiotropic effects on both parameters. It may also be the case that, due to the high correlation (0.996) between the estimates of those parameters, one of the associations observed may be a false positive.

Similarly, Rodriguez-Zas et al. (2002) reported an association between the chromosomal region at about 13 cM on BTA14 (marker CSSM66), and the shape parameters that describe the changes in milk yield during mid and late lactation. However, in dairy cattle a QTL affecting MY was seemingly associated with BTA14 by Khatkar et al. (2004).

Several studies in cattle reported QTLs for MY on BTA20. The chromosomal regions in the bovine were at 21 cM (Plante et al., 2001), 82 cM (Viitala et al., 2003) and 68 cM (Ashwell et al., 2004). In the current study, no microsatellite marker on CHI20 was associated with some lactation descriptors.

5.2.2. Fat percentage

Although several studies in dairy cattle reported a putative QTL on BTA3 and BTA6 affecting FP (Khatkar et al., 2004), we did not find evidence for the effects of a chromosomal

region in either CHI3 or CHI6, at the chromosomal-wise threshold. However, for FP they detected significant effects from CHI14 and CHI20.

When analyzing CHI14, one chromosomal region at 63 cM (between CSSM66 and CSSM36) associated with variation of the parameter β was found significant.

Conversely, analyses with dairy cattle found strong evidence for a putative QTL affecting FP near the centromere of BTA14, being the MS CSSM66 the nearest marker (Coppieters et al., 1998; Zhang et al., 1998; Heyen et al., 1999; Ashwell et al., 2004).

A QTL proximal to the centromere on BTA14 with an effect on FP has consistently been reported (Grisart et al., 2002 and Winter et al., 2002), and the mutation underlying this QTL has been identified (Winter et al., 2002) as the K232A substitution in exon VIII of acylCoA / diacylglycerol acyltransferase 1 enzyme (DGAT1).

This enzyme is considered to be of importance in controlling the synthesis rate of triglycerides in adipocytes. Nevertheless, no associations with several microsatellite markers on BTA14 were found by Rodriguez-Zas et al. (2002) using a longitudinal mapping model. Comparing the goat and bovine linkage maps, CHI14 shows a partial homology with BTA14 from MS CSSM66 to the telomere.

The centromeric region of CHI14 flanked between MS ETH225 and MS BM757, corresponds to the same region of chromosome 9 in cattle. Therefore, it is likely that an association with FP could be found near the centromeric end of CHI9.

At 72 cM on CHI20, where the nearest marker is BMS1719, we detected an association with parameter α ($p < 0.00002$). Many additional QTL with significant effects on FP and FY has been reported for chromosome 20 in dairy cattle (Khatkar et al., 2004).

5.2.3. Protein percentage

Chromosomal regions associated with β for PP were found in CHI3. For this chromosome and close to MS INRA023 (at 59 cM), we detected a chromosomal region affecting β. A QTL for PP located in an area of about 40 cM in BTA3 was reported in several studies (Khatkar et al. 2004).

We did not find significant associations among chromosomal regions of CHI6 and any parameter when looking at PP. Nevertheless, many studies in dairy cattle have detected the presence of a QTL close to MS BM143 in BTA6 that is related to PP, and the marker position agrees in all these studies (Spelman et al., 1996; Zhang et al., 1998; Ron et al., 2001; Viitala et al., 2003). Using longitudinal phenotypic data, Rodriguez-Zas et al. (2002) found significant association between MS BM143 and the scale and the shape parameters at middle and late lactation for PP in dairy cows.

Schnabel et al. (2005) performed a fine-mapping study of BTA6 of dairy cattle and identified the osteopontin (OPN) gene as an ideal functional candidate gene for a QTL very close to BM143. The OPN is a secreted glycoprotein and its expression in the murine mammary

gland depends on the stage of postnatal development, which in turn suggests a role for OPN in mammary involution.

5.2.4. Lactation patterns

We use the expression longitudinal mapping model to refer to those statistical models for mapping QTLs of a longitudinal (or functional value) trait. The ability of the model used in the current study to detect associations between markers and lactation stages may contribute to explain the different lactation patterns among individuals.

Although breeders do not usually breed for lactation shape, some traits such as persistence that are described by lactation curve parameters are economically relevant.

6. Conclusions and perspectives

The casein cluster gene is today the most studied chromosomal region related with milk characteristics - quality and quantity -in goats but there are a lot of to come.

The genetic variability and alelle distribution at the *CSN1S1* and *CSN3* in the Criollo and crosse breed showed in this chapter reveal large differences between breed specialy with those highly selected. Althougth the number of animals, families and the design used in all works presented here are not very large compared with those used in the dairy cattle experiments, they were good enough to show the usefull and potenciallity of both quantitative and molecular data analysis together in differents aspects and with differents methodologies to be used in animal breeding.

Molecular markers are more commonly being used in other ruminant - cattle and sheep - than in goat breeding programmes, due to the animal economic value and the technology costs ratio is more profitable in cattle and sheep than in goat. Nevertheless some laboratories now are offering DNA test mainly for paternity and inherited diseases in goats.

There are a number of research programmes endeavouring to detect additional gene effects most of them to genetic resitance and reproductive traits (i.e. 3SR ; CRC FAO-IAEA) and it is highly likely that these will yield further targets for Marker Asisted Selection(MAS) / Gene Assisted Selection (GAS). The application of MAS/GAS to date has mainly been in the form of introgression programmes or for selection within a few flocks with a high emphasis on the gene of interest.

The strong association found here between some allele at *CSN1S1* locus and haplotypes of *CSN1S1* and *CSN3* and PP suggest that Criollo goat is a breed with good milk quality for cheese production and that they can be use for MAS. The molecular information at the *CSN1S1* and *CSN3* could be useful for genetic improvement of dairy traits in Criollo goats by contributing to design breeding schemes able to fit selection goals. In addition, this breed is well adapted to harsh environments and it has a great potential for increasing production without loss of local adaptation, being a highly valuable genetic resource for the region.

The methodology used by Roldán et al. (2008) to detect QTL for milk production traits using a longitudinal model identified nine map positions affecting any parameter of the lactation function of dairy goats: one in CHI3, four in CHI6, two in CHI14 and two in CHI20. Some of these results were consistent with QTLs found in dairy cattle while using either aggregate lactation records, or longitudinal-linkage analysis. This is one example in goats of integration between molecular and quantitative information to enhance rates of genetic improvement in small ruminants. As was stated by Notter & Baker (2007) a quantitative-molecular paradigm for livestock improvement is badly needed and is gradually emerging. This paradigm aspires to provide a structure to combine established strategies for prediction of breeding values from performance records on individuals and their relatives with modern molecular techniques to determine parentage, identify major genes or genetic markers associated with desirable phenotypes, and utilize the power of functional genomics to improve understanding of the genetic mechanisms that control expression of complex traits.

When the cattle genome was sequenced (The bovine genome consortium.Science, April 24, 2009), it puts that species on the threshold of a new era in which the challenges of health, production and sustainability can be addressed far more effectively through selective breeding than was previously possible. The whole genome sequencing and the subsequent characterisation of densely spaced genetic markers, such systems may eventually be superceded by 'genome selection-GS' techniques (Meuwissen et al., 2001).

Through use of genome assisted selection improved selection response can be expected for most traits of interest, but especially for traits where the routine collection of accurate phenotypes is difficult, costly or possible only late in an animal's life or only in one sex. Such traits include many health characteristics as well as reproductive efficiency.

Despite a slow start to the development of genomic tools, the goat genome assembly is running. In January 2010 was "officially" constituded the International Goat Genome Consortium (IGGC - http://www.goatgenome.org/doku.php?id=start). Goat whole genome reference sequence began with *de novo* assembly into high quality contigs and continue with information from EST-based virtual goat genome and BAC clones. Additionally, SNP discovery using next-generation sequencing technology is underway to develop initial genetic polymorphism database and SNP chip(s). A 50-60K goat SNP chip will be available by November 2011 from Illumina company. RH panel, mapping of markers for RH map and HapMap development will be utilized in the following version of the reference genome.

Despite the widespread excitement about the potential for GS to provide new approaches for the improvement of sustainability traits there are a number of reasons to be cautious about this approach in goat. Firstly, there is the challenge of many different breeds and production environments: whilst it is entirely feasible to 'train' GS for Holstein dairy cattle where there are relatively few variations in production environments, very little is currently known about the 'portability' of GS algorithms across different breeds or environments. Early results for beef and dairy cattle indicate that more dense SNP arrays than are currently available are likely to be needed. This brings us to the second concern, *viz*. cost. Moreover

only about 1/3 of the SNP associated with any productive traits in one breed can be used in another breed (Boichard et at., 2010; Lopez-Villalobos, pers com.).

Nevertheless, as technology development will never stop, we will face in a few years to the new challenge, that is the use of the whole genome sequence data for QTL mapping and genomic selection instead of dense SNPs chips. As was stated by Meuwissen (2010), future technologies are predicted to reduce cost by about 100 fold that today and we can expect to have whole genome sequence data available on substancial number of animals at reasonable low cost.

At the same time as these valuable new genomic resources for goat are being developed, livestock breeders are facing real challenges in delivering more balanced breeding objectives that seek to broaden selection goals beyond traditional productivity traits to include sustainability and welfare traits such as disease resistance, robustness, reproductive efficiency and longevity.

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