View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by IntechOpen

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 1

Genetic Factors that Regulate Milk Protein and Lipid Composition in Goats

Marcel Amills, Jordi Jordana, Alí Zidi and Juan Manuel Serradilla

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/51716

1. Introduction

The mammary gland fulfills the essential role of providing all the nutrients needed to sustain the life and growth of the newborn under the form of milk, a white fluid composed primarily by water, carbohydrates, lipids, proteins and minerals. Domestication of cow, sheep and goats in the Near East 9,000 YBP and the subsequent creation of breeds specialized in milk production allowed humans to take profit of this rich source of proteins and minerals, becoming an important component of their diet either in the form of fresh milk or derived products such as cheese, yogurt, kefir, butter and many others (**Figure 1**). Because of their adaptability to a harsh climate and scarce vegetation, dairy goats occupy an important niche in the economy of tropical countries such as India, Bangladesh and Sudan, which happen to be the three main goat milk producers at a worldwide scale (FAOSTAT 2009). In Europe, France, Spain and Greece are the largest goat milk producers and, in comparison with Asian and African countries, have a much more intensified production system (FAOSTAT 2009).

Proteins and lipids are essential components of milk and they can have a very strong impact on milk nutritional and technological properties (Bauman et al. 2006). Milk casein content, for instance, is one of the main determinants of cheese yield and both traits are positively correlated (Remeuf and Hurtaud 1991). Similarly, fat content and composition are key factors determining milk and cheese attributes. In this way, milk with a low fat percentage is associated with a reduced cheese yield and firmness as well as with negative effects on flavor and color (Lamberet et al. 2001). Moreover, short-chain fatty acids (FA), such as C4:0-C12:0, have been implicated in the appearance of a rancid soapy flavor in milk, whilst the hardness and melting point of fat is largely determined by its unsaturated FA content (Fox and Sweeney 2003). Importantly, a relevant fraction (around 70%) of goat milk fat is composed by saturated FA that have detrimental effects on human health because they are associated with an increased risk of suffering cardiovascular diseases (Pfeuffer and

INTECH
open science | open minds

© 2012 Amills et al., licensee InTech. This is an open access chapter distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Schrezenmeir 2000). It is also worth to mention that hydrolysis of milk proteins releases a wide array of short bioactive peptides which might have many beneficial effects on human health, such as (i) hypotensive, antithrombotic, antioxidative, antimicrobial, and immunomodulatory activities (Fitzgerald and Meisel 2004, Korhonen and Pihlanto 2001), (ii) enhancement of mineral absorption (Meisel 1998), and (iii) antitumoral properties (Matar et al. 2003). Milk protein and fat contents vary from breed to breed due to both environmental and genetic factors (**Figure 2**)

Figure 1. Portray of a woman making butter (Paris, 1499). Source: *Compost et Kalendrier des Bergères*. Robarts Library, University of Toronto.

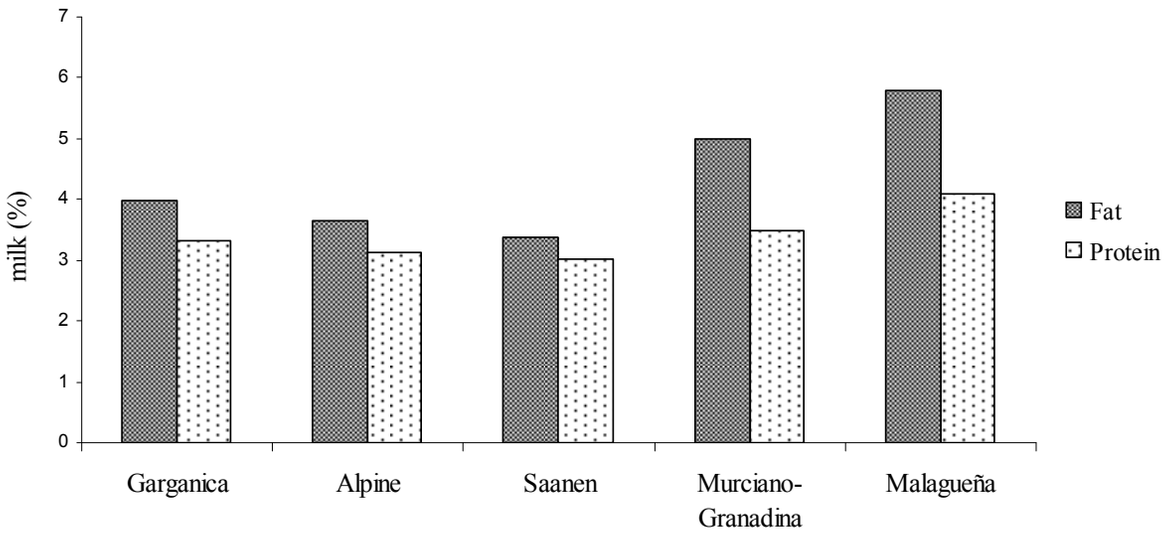

Figure 2. Milk protein and fat content in diverse goat breeds. Sources: Martini et al. (2010), Rupp et al. (2011), Fernández et al. (2005) and website of the Asociación Española de Criadores de la Cabra Malagueña (http://www.cabrama.com)

The major protein milk fraction (around 80%) is constituted by caseins, *i.e.* insoluble phosphoproteins organized in complex multi-molecular aggregates, named micelles, that at certain conditions of temperature and acidity (T ~ 20 ºC, pH = 4.6), precipitate from skim milk (Thompson et al. 1965). Besides caseins, micelles contain inorganic materials such as calcium phosphate and calcium citrate (Smiddy et al. 2006). In ruminants, four casein types have been distinguished so far (Martin et al. 2002): α_{S1}-casein (CSN1S1), α_{S2}-casein (CSN1S2), β-casein (CSN2) and κ-casein (CSN3). CSN1S1, CSN1S2 and CSN2 are considered to be calcium-sensitive caseins because they have a high phosphate content and precipitate in the presence of calcium (Grosclaude 1991). Loci encoding these three caseins have been shown to descend, through successive gene duplication events, from an ancestral locus encoding the secretory calcium-binding phosphoprotein proline-glutamine rich 1 (*SCPPPQ1*) molecule, that plays a key role in dental enamel mineralization (Kawasaki and Weiss 2003). In contrast, CSN3 is a calcium-insensitive casein responsible of micelle stabilization and whose molecular ancestry is completely different, since it evolved from the follicular dendritic cell secreted peptide (*FDCSP)* gene, which is expressed in fibroblasts producing periodontal ligament (Grosclaude 1991, Kawasaki and Weiss 2003). The enzymatic hydrolysis of CSN3 by chymosin involves the destabilization of micelles and the subsequent coagulation of milk, which is the initial step in the manufacturing of cheese (Jollès 1975, Remeuf et al. 1991).

Whey proteins represent around 20% of the total protein content of milk and their common denominator is that they remain soluble after milk coagulation (Madureira et al. 2007). Examples of whey proteins are β-lactoglobulin (BLG), α-lactalbumin (LALBA), immunoglobulins, serum albumin, lactoferrin, and lactoperoxidase. Functions of these proteins are very heterogeneous (Madureira et al. 2007), affecting processes as different as lactose synthesis (LALBA), transport of hydrophobic molecules (BLG) and microbial immunity (lactoferrin and lactoperoxidase).

Protein synthesis in the mammary gland depends on the uptake of amino acids from the circulatory system and it is controlled by lactogenic hormones (insulin, prolactin, and glucocorticoids) as well as by the blood concentrations of circulating amino acids (Weekes et al. 2006, Rhoads and Grudzien-Nogalska 2007). Milk protein gene expression is strongly affected by the reproductive cycle, being activated at mid-pregnancy, peaking during lactation and declining after weaning. Generally, the conversion efficiency of dietary nitrogen to milk proteins is relatively poor in the mammary epithelial cells of goats (25-30%) for reasons that remain to be defined (Bequette et al. 1998). The transport of amino acids, and even short peptides, through the membrane of secretory cells is facilitated by a variety of molecular systems that have been broadly reviewed by Shennan and Peaker (2000).

With regard to milk lipids, the most abundant fraction (around 95%) is constituted by triglycerides, whilst the remaining 5% encompasses free FA, phospholipids, cholesterol esters, diglycerides and monoglycerides (Harvatine et al. 2009). A distinctive feature of goat milk is that medium chain FA (*e.g.* C8, C10 and C12) and C18:1 unsaturated FA are particularly abundant (Fontecha et al. 2000). Milk FA are either synthesized by mammary epithelial cells through the lipogenic pathway or uptaken from the circulating plasma

(Bauman and Griinari, 2003). In ruminants, lipogenesis contributes short and medium-chain FA (C4:0 to C16:0) encompassing 50% of the milk FA pool (Barber et al. 1997). Ruminal fermentation provides the main precursors (*i.e.* acetate and β-hydroxybutyrate) for the *de novo* synthesis of FA (Van Soest, 1994). In contrast, long-chain FA are mostly obtained through the hydrolysis of blood lipoproteins by lipoprotein lipase (Bauman and Davis 1974). These circulating lipids, in turn, come from the mobilization of adipose tissue stores as well as from dietary lipid absorption in the digestive tract (Bauman and Griinari, 2003).

Functional genomic studies have allowed to dissect the complex network of genes that drive forward fat synthesis in the bovine mammary gland (Bionaz and Loor 2008). This network is composed by genes that participate in a wide variety of metabolic pathways related with FA uptake and transport (*e.g. LPL, VLDLR, ACSL1, CD36, FABP3*), triglyceride synthesis (*e.g. LPIN1, DGAT1, AGPAT6, GPAM*), lipid droplet formation (*e.g. XDH, BTN1A1*), lipogenesis (*e.g. ACACA, FASN*), FA desaturation (*SCD1, FADS1*) and activation (*ACSL1, ACSS2*) and membrane-associated transport of metabolites *(ABCG2).* The multiple components of the milk fat synthesis machinery defined above are coordinated by diverse transcription factors with a well-known role on lipid metabolism such as *SREBF1, SREBF2, PPARG, INSIG1*, and *PPARGC1A* (Bionaz and Loor 2008).

2. Genetic parameters of milk protein and lipid traits in goats

Although casein content is a crucial determinant of cheese yield, its utilization as a selection criterion has been hindered by the fact that this phenotype cannot be easily measured with routine analytical methods. Advances in infrared spectroscopy techniques, however, may overcome this difficulty by providing accurate measurements of the clotting protein fraction at a reasonable cost and time expense (Díaz-Carrillo et al. 1993). Fat content, another important factor determining cheese yield, is routinely recorded and it has been included as an important selection objective in most of breeding programs (Barillet 2007).

Genetic parameters of milk traits under selection need to be accurately defined in order to implement breeding strategies (selection vs. crossbreeding), estimate breeding values and predict selection responses. Many of the heritability and genetic correlation estimates that have been reported in the scientific literature for milk protein and fat contents of dairy goats are listed in Tables 1 and 2. Large parameter ranges can be observed, a feature that might be likely explained by the fact that multiple breeds and methods have been used to estimate them. Another important difference amongst studies is the lactation time point at which phenotypes are obtained, an environmental factor that can have dramatic effects on genetic parameter estimation. With regard to the heritability of total casein and casein fraction contents, very few estimates have been reported so far. Worth to mention those obtained for casein content in the Alpine (h^2 = 0.65-0.66), Murciano-Granadina (h^2 = 0.13-0.19) and Malagueña (h^2 = 0.29) breeds (Ricordeau and Bouillon 1971, Sigwald et al. 1981, Benradi et al. 2007 and 2009). It is also necessary to highlight the study of Benradi et al. (2007), where heritabilities of CSN1S1 (h^2 = 0.25) and CSN1S2 (h^2 = 0.09) contents were estimated in the Murciano-Granadina breed.

Breed (Country)	Protein content	Fat content	Reference
Saanen (Norway)	-	0.28	Ronningen (1965)
Saanen (Norway)	-	0.40-0.59	Ronningen (1967)
Alpine (France)	0.59	0.62	Ricordeau et al. (1979)
Saanen, Alpine, Toggenburg (USA)	-	0.54	Kennedy et al. (1982)
Alpine (France)	0.52	0.50	Boichard et al. (1988)
Alpine (France)	0.49-0.53	0.46	Bouloc (1987)
Alpine (France)	0.67	0.56	Bouillon & Ricordeau (1975)
La Mancha (USA)	-	0.63	Iloeje et al. (1981)
Nubian (USA)	-	0.66	Iloeje et al. (1981)
Toggenburg (USA)	-	0.54	Iloeje et al. (1981)
Saanen (France)	0.41	0.47	Boichard et al. (1988)
Saanen (France)	0.42	0.42	Bouloc (1987)
Saanen (México)	0.38-0.63	0.32-0.64	Torres-Vázquez et al. (2009)
Saanen (South Africa)	0.44	0.21	Muller et al. (2002)
Alpine (France)	0.58	0.58	Bélichon et al. (1998)
Saanen (France)	0.50	0.60	Bélichon et al. (1998)
Local breeds (Greece)	0.51	0.38	Zygoyiannis (1994)
Murciano-Granadina (Spain)	0.25-0.47	-	Analla et al (1996)
Alpine (France)	0.66-0.85	0.58-0.77	Barbieri et al. (1995)
Verata (Spain)	0.14-0.42	0.30-0.32	Rabasco et al. (1993)
Murciano-Granadina (Spain)	0.30	-	Benradi et al. (2009)
Murciano-Granadina (Spain)	0.50	0.15	Benradi (2007)
Malagueña (Spain)	0.30	-	Benradi (2007)

Table 1. Heritability estimates of milk protein and fat content traits in goats

The main trend that emerges from these analyses is that protein, casein and fat contents have moderate heritabilities, so they can be improved at a reasonable pace by using classical selection. These traits show, in general, positive medium or high genetic correlations among themselves; being, consequently, also positive their respective correlated responses to selection. However, they display negative genetic correlations with milk yield, a circumstance that is quite unfavourable given the high economic impact of this phenotype. In spite of this, protein and fat contents are important selection criteria and they are frequently included in selection indexes (Manfredi et al. 2000; Montaldo and Manfredi 2002)

Another interesting issue that deserves to be discussed is the effect that the highly polymorphic *CSN1S1* gene has on the estimation of genetic parameters of milk traits in goats. In this way, Barbieri et al. (1995) reported that heritability of protein content was

reduced from 0.66 to 0.34 and that the genetic correlation between protein yield and content dropped from 0.09 to -0.22 when the *CSN1S1* genotype was taken into account as a fixed effect. This would mean that a substantial part of the genetic variance of goat protein content is explained by the polymorphism of the *CSN1S1* gene.

An important methodological advance in the estimation of genetic parameters of dairy traits has consisted in the use of random regression models applied to test day records (Schaeffer, 2004)). This approach has allowed to obtain estimates of heritabilities at, and genetic correlations among, different timepoints throughout the lactation curve in a wide variety of populations such as Norwegian dairy goats (Andonov et al. 1998), Spanish Payoya and Murciano-Granadina goats (Menéndez-Buxadera et al. 2008, 2010) and Canadian dairy breeds of Alpine origine (Bishop et al. 1994). To illustrate this concept, evolution of variance components for milk yield, fat, protein and dry matter contents in Murciano-Granadina goats is shown in **Figure 3**. From these data it can be inferred that estimates of heritability of yields and contents of milk components do not have stable values but, on the contrary, they vary throughout the lactation curve, being more variable near parturition and drying off. Moreover, genetic correlations between adjacent records are much higher (0.70-0.99) than those between records far apart (0.00-0.40). With no doubt, this statistical methodology allows a better genetic evaluation of dairy goats anf facilitates the selection of improving genotypes for lactation persistency (the ability of a goat to maintain as high as possible milk daily yield during lactation).

Trait	**Protein**	**Total casein**	**CSN1S1**	**CSN1S2**	**Fat**
Protein	-	0.39-0.90	0.65	0.55	0.45-0.93
Total casein	0.88	-	0.91	0.57	0.41
CSN1S1	0.04	0.01	-	-0.39	NA
CSN1S2	0.27	0.32	0.57	-	NA
Fat	-0.015-0.54	NA	NA	NA	-

Table 2. Genetic (above diagonal) and phenotypic (below diagonal) correlations between milk fat, protein and casein traits in goats (Benradi 2007, NA = data not available)

Genetic correlations between milk components and rheological traits as well as cheese yield have been also studied by Benradi et al. (2009). These authors reported high positive genetic correlations of protein, total caseins and CSN1S1 contents with time to curdling onset, curd firmness and curdling speed and a moderate positive correlation of the aforementioned milk components with cheese yield, so confirming the important influence of protein, and especially of total caseins and CSN1S1 contents, on the efficiency of cheese manufacture and quality.

3. Genomic architecture of protein and lipid phenotypes in goats and other ruminants

The lack of appropiate molecular tools in goats, such as large microsatellite panels uniformly covering the goat genome, microarrays and high throughput genotyping SNP

chips, has indered the fine mapping of genes related with milk protein and lipid traits at a genomic scale. While dense quantitative trait loci (QTL) maps of dairy traits have been obtained in cattle and sheep, a single partial genome scan for milk yield and fat and protein contents has been performed so far (Roldán et al. 2008). However, many of the findings obtained in cattle can be probably extrapolated to goats, so they will be commented in the following paragraphs. First of all, it should be highlighted that relative chromosomal contributions to protein and fat genetic variance are quite uneven. In cattle, strong evidences of protein content QTL have been obtained on chromosomes 3, 6 and 20, whilst protein yield QTL map to bovine chromosomes (BTA) 1, 3, 6, 9, 14 and 20 (Khatkar et al. 2004). Khatkar et al. (2004) have also reported QTL hotspots for milk fat content and yield (BTA6 and BTA 14). Second, many of the reported protein and fat content QTL just segregate in specific populations or families, meaning that they have a very restricted distribution (Khatkar et al. 2004). Third, and with a few exceptions, the identity of the genes and mutations explaining these QTL remain unsolved. The BTA14 QTL is one of the few cases where the underlying causal polymorphism has been identified *i.e.* a non-conservative amino acid substitution (K232A) in the DGAT1 enzyme that explains 51% of the daughter yield deviation variance of fat percentage (Winter et al. 2002, Grisart et al. 2002). The lack of success in finding causal mutations underlying milk trait QTL might be partly explained by the low resolution of microsatellite-based QTL mapping (confidence intervals usually encompass 20 cM or more).

Low resolution QTL detection methods have been (cattle, sheep) or will be (goats) progressively replaced by high throughput single nucleotide polymorphism (SNP) genotyping platforms. In this way, the recent advent of a bovine 50K SNP BeadChip has allowed to perform genome-wide association analyses of dairy traits at an unprecedented resolution (Hayes and Goddard 2010). As an example of the power of this approach, Schopen et al. (2011) analysed the segregation of 50,228 SNP in 1,713 Dutch Holstein cows with records for milk CSN1S1, CSN1S2, CSN2, CSN3, LALBA and BLG contents. Their results showed highly significant associations between polymorphisms mapping to BTA5, 6, 11 and 14 and protein percentage. With regard to specific protein fractions, the number of associated regions varied from three (CSN2 and BLG) to 12 (CSN1S2) and the percentage of additive genetic variance explained by the joint sets of significant SNP oscillated between 25% and 35%. Strong associations were observed between SNP mapping to casein genes and the corresponding casein fraction contents, but evidences of SNP acting in *trans* were also obtained *e.g.* SNP with effects on CSN1S1 content were detected in BTA11 and BTA14 (whilst the *CSN1S1* gene resides on BTA6). As a general conclusion, valid not only for cattle but also for sheep or goats, we can state that casein content is regulated not only by polymorphisms located within the casein genes but also by mutations mapping to other loci and chromosomes.

In goats, the precise position of genes with effects on milk lipid or protein composition or their contributions to phenotypic variance are mostly unknown. One of the few exceptions is the caprine casein gene cluster, which is known to have strong effects on milk composition and that has been finely dissected at the genomic and sequence levels (Martin et al. 2002). The four caprine casein genes are tightly clustered in a 250 kb region mapping to

chromosome 6, in the order *CSN1S1-CSN2-CSN1S2-CSN3* (Rijnkels et al. 2002). Genomic organization and gene structure are highly conserved in all mammals (Rijnkels et al. 2002), with the only exception of the *CSN1S2* gene that might contain from 11 to 19 exons depending on the species under consideration (Rijnkels et al. 2002). Moreover, *CSN1S2* is duplicated in human and rodents but not in ruminants.

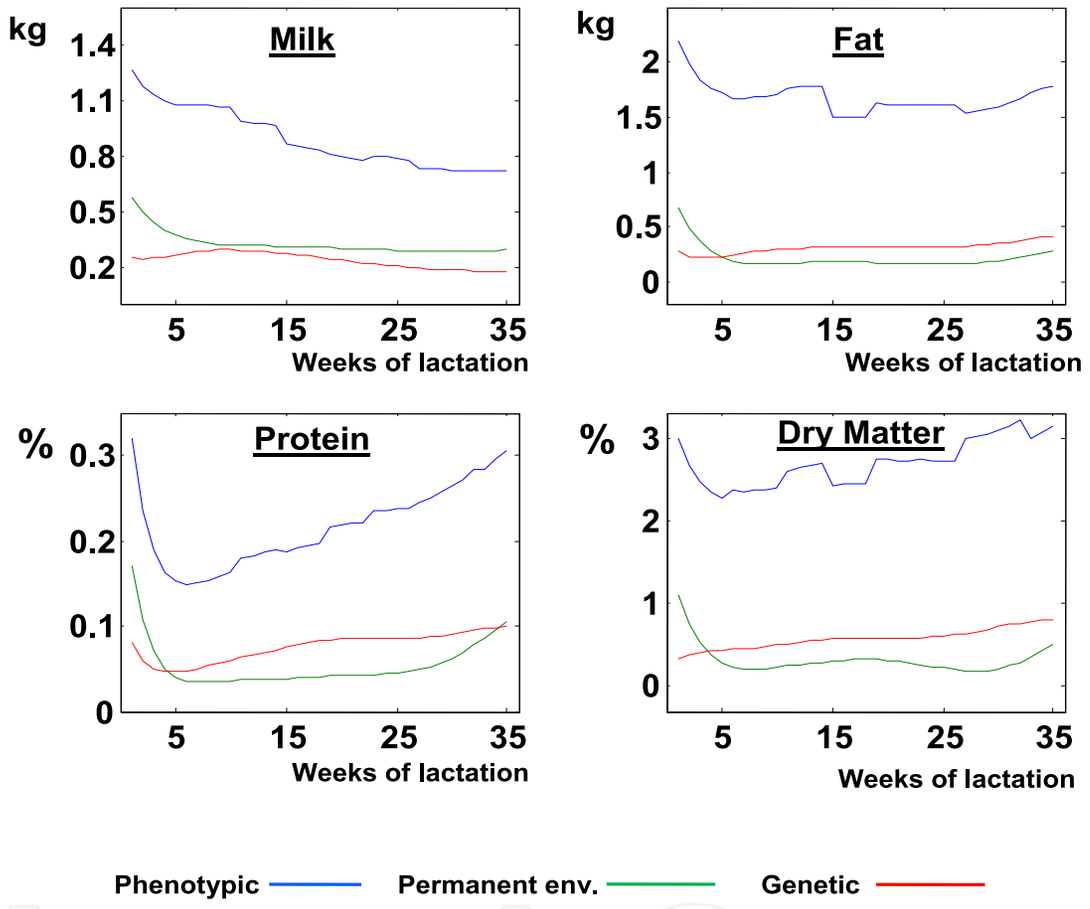

Figure 3. Variation through lactation curve of variance components for milk yield, fat, protein and dry matter contents in Murciano-Granadina goats. Source: Prof. Alberto Menéndez-Buxadera (unpublished data).

The goat *CSN1S1* gene encodes a 199 amino acid protein and it was completely sequenced by Ramunno et al. (2004). This gene is 16.7 kb long and contains 19 exons with sizes that go from 24 to 385 bp. The signal peptide and the first two amino acids of the mature protein are encoded by exon 2, whilst the stop codon is located at the boundary of exons 17 and 18. Leroux and Martin (1996) demonstrated that the goat *CSN2* gene is located 12 kb apart from the *CSN1S1* gene and that both are convergently transcribed (Leroux and Martin 1996). The transcription unit of *CSN2* contains 9 exons and encodes a 1.09 kb mRNA. The translation initiation site is located at exon 2, which encodes the signal peptide plus two amino acids of the mature protein (Roberts et al. 1992). The caprine *CSN1S2* and *CSN3* genes have been also characterized at the molecular level by Bouniol et al. (1993) and Coll et al. (1993).

The whey protein genes *LALBA* and *BLG* have been mapped to goat chromosomes 5 (Hayes et al. 1993) and 11 (Folch et al. 1994), respectively. The *LALBA* gene contains four exons and encodes a 123 amino acid protein. Structural characterization of the goat *BLG* gene has shown that it contains seven exons as previously described in other ruminant species (Folch et al. 1994). Two short interspersed nucleotide elements were found in the 3'end of the gene Moreover, a duplicated goat *BLG* pseudogene with a genomic organization very similar to *BLG* and also mapping to caprine chromosome 11 has been identified by Folch et al. (1996).

4. Candidate genes and their association with milk protein traits

From a structural and functional point of view, the casein cluster is one of the best studied genetic systems in goats. As outlined above, casein genes have been sequenced and their variability has been characterized in depth (Martin et al. 2002, Moioli et al. 2007). Even more, in several cases consistent association between this variability and milk composition traits has been firmly established (**Table 3**). In this regard, the most paradigmatic case is represented by the *CSN1S1* gene, where causal relationships between regulatory polymorphisms and CSN1S1 synthesis rate have been found. In the following sections, we will describe the variability of the casein and whey protein genes and its impact on the phenotypic variation of dairy and rheological traits.

4.1. The caprine α_{S1}-casein gene

This locus is highly polymorphic in goats (reviewed in Martin et al. 2002 and Moioli et al. 2007), with 17 alleles (**Table 3**) that can be classified as strong (A, B1, B2, B3, B4, C, H, L and M), medium (E and I), low (F, D and G) and null (01, 02 and N). The existence of this remarkable level of variability was firstly outlined by Boulanger et al. (1984). By means of starch gel protein electrophoresis, these authors evidenced the existence of one variant A, two B variants (associated with different electrophoretic band intensities) and one variant C. These results suggested the existence of a polymorphism with quantitative effects on CSN1S1 synthesis. This interpretation was subsequently confirmed by Grosclaude et al. (1987), who identified two additional alleles (F and 0) and provided a first estimate of quantitative differences amongst *CSN1S1* genotypes based on rocket immunoelectrophoresis *i.e.* strong, medium, low and null alleles were distinguished (**Table 3**). These two studies have become classics in goats genetics because they pionereed the discovery of genetic variants with effects on milk traits in this ruminant species.

The advent of DNA-based methods allowed to characterize the specific mutations causing this variability as well as to identify new variants not detectable through electrophoresis techniques. Strong variants A, B and C were shown to differ by several amino acid substitutions *i.e.* B vs A: P16L and E77N and B vs C: H8I, R100K and T195A, but none of these polymorphisms seemed to have quantitative effects. Protein variants H and L were identified and characterized by Chianese et al. (1997) by using a variety of proteomic techniques, whilst variant M was reported by Bevilacqua et al. (2002). The main feature of the M variant is the loss of two phosphate residues in the multiple phosphorylation site

consecutively to a S66L substitution. Likely, this allele emerged as a result of an interallelic recombination event between A and B2 alleles followed by a C to T transition at exon 9 (Bevilacqua et al. 2002).

Gene	**Allele**	**Synthesis rate (g casein /L/allele)**
CSN1S1	A, B1, B2, B3, B4, C, H, L, M	3.5
	E, I	1.1
	D, F, G	0.45
	01, 02, N	0
CSN1S2	A, B, C, E, F	2.5
	D	~ 1.25
	0	0
CSN2	A, A1, B, C, D, E	5
	0, 01	0

Table 3. Polymorphism of the *CSN1S1*, *CSN1S2* and *CSN2* genes and its relationship with the synthesis levels of the corresponding casein fractions (Martin et al. 2002, Moioli et al. 2007).

Variants E and I have been associated with an intermediate level of CSN1S1 synthesis (Boulanger 1984, Pérez et al. 1994, Chianese et al. 1997). Extensive sequencing of the E-allele revealed the existence of a 457 bp insertion at exon 19 caused by a truncated long interspersed nucleotide element (Pérez et al. 1994). This insertion might destabilize the corresponding *CSN1S1* mRNA diminishing 3-fold the synthesis of the corresponding protein (Pérez et al. 1994). Interestingly, the bovine *CSN1S1* allele G, that also contains a retrotransposon insertion at exon 19, has been associated with a lower milk CSN1S1 concentration (Rando et al. 1998). These results clearly indicate that the retrotransposon insertion is the causal mutation explaining the reduced levels of CSN1S1 in milk. However, the exact molecular mechanism by which the retrotranposon insertion represses CSN1S1 synthesis has not been elucidated yet, although a RNA interference mechanism might be suspected.

Low synthesis of CSN1S1 is explained by a defective processing of the corresponding transcript due to mutations that promote exon-skipping events and, in consequence, result in internally deleted CSN1S1 proteins (Martin et al. 2002). As much as nine different transcripts seem to be associated with allele F, the most abundant of which lacks exons 9, 10 and 11 and provokes a 37 amino acid deletion encompassing the multiple phosphorylation site (Leroux et al. 1992). A single nucleotide frameshift deletion in exon 9 (that induces the appearance of a premature stop codon at exon 12) and two 11 and 3 bp insertions at intron 9 might explain the defective processing of allele F. Similarly, the D allele is characterized by skipping of exon 9, while the G allele displays a G to A mutation in the 5′ splice site consensus sequence of intron 4 that causes the skipping of exon 4 and the synthesis of a protein lacking amino acids 14 to 26 (Martin et al. 1999).

The complete absence of CSN1S1 in milk is explained by a couple of genetic mechanisms. In the case of the 01 allele, a genomic deletion of at least 8.5 kb, that encompasses intron 12 to exon 19 of the *CSN1S1* gene, abrogates the synthesis of the corresponding protein (Cosenza et al. 2003). In close similarity with the F variant, the N allele contains a 1 bp deletion at the 23rd site of exon 9 determining a premature stop codon at exon 19. Sequencing of RT-PCR clones revealed that this variant is represented by at least 12 different transcripts lacking combinations of exons 9, 10, 11, 16 and 17 as a result of the defective processing of the mRNA. The abundances of transcripts carrying a premature stop codon are 30% and 14% for the N and F alleles, respectively (Ramunno et al. 2005). This finding might explain why the synthesis rate of the N-allele is 3-fold lower than that of the F-allele

Genotyping techniques have been developed to characterize the polymorphism of the *CSN1S1* gene in diverse goat populations. Initially, CSN1S1 variants were typed through the analysis of milk samples by SDS-polyacrylamide gel electrophoresis combined with isoelectric focusing (Grosclaude et al. 1987). The main inconvenient of this approach was that only lactating females could be typed, whilst in breeding schemes the main contributors to genetic improvement are bucks. To circumvent this problem, molecular techniques were developed. The first one was based on Southern blotting and restriction fragment length polymorphims analysis (Leroux et al. 1990). Although useful, this approach was very time consuming and not applicable to the large throughput genotyping required in breeding schemes. Later on, PCR-based techniques were published (Pérez et al. 1994, Ramunno et al. 2000) allowing the fast genotyping of the most abundant *CSN1S1* alleles.

With the aid of these molecular tools, the segregation of *CSN1S1* alleles has been studied in a wide array of breeds. Estimation of allelic frequencies in the Spanish Murciano-Granadina and Malagueña breeds showed that the E-allele was the most frequent one, followed by the B variant (Jordana et al. 1996). In contrast, in the French and Italian Saanen and Alpine breeds as well as in the French Corse breed the low content F-allele was predominant, while the E-allele would rank second (reviewed in Trujillo et al. 1998). It should be taken into account, however, that these estimates are quite outdated and that selection for *CSN1S1* variants might have changed their frequencies dramatically (at least in French breeds). In African, Canarian, Maltese and Garganica breeds, strong CSN1S1 content alleles are the most frequent ones (reviewed in Trujillo et al. 1998). A recent survey of American goat breeds highlighted the coexistence of different allelic CSN1S1 frequency patterns, with breeds in which the F (*e.g.* Alpine), E (*e.g.* Saanen and Oberhasli) and A+B alleles (*e.g.* LaMancha, Nigerian dwarf and Nubian) were predominant (Maga et al. 2009). These differences in the frequencies of *CSN1S1* variants might be explained by a combination of effects produced by genetic drift, selection and other evolutionary and demographic factors.

There is substantial evidence that the aforementioned polymorphisms not only affect the synthesis rate of CSN1S1 but also a wide array of production traits. A within-sire analysis of the progeny of five Alpine bucks revealed significant effects of *CSN1S1* genotype on milk protein and fat content, with the A-allele showing a clear superiority over E and F (Mahé et al. 1994). A similar trend was observed by Manfredi et al. (1995) when surveying 184 Alpine

and 96 Saanen bucks. Moreover, Barbieri et al. (1995) demonstrated that the A-allele is associated with higher protein (AA > AE, AF > EE, EF > FF) and fat (AA, AE, AF > EE, EF) contents but also with a lower milk yield. Differences in protein content between genotypes might be in the order of 4 g/l (AA vs EE) to 6 g/l (AA vs FF). Chanat et al. (1999) offered a biological explanation to these findings by demonstrating that *CSN1S1* genotype has relevant effects on casein transport from the endoplasmic reticulum to the Golgi compartment (in goats with low or null *CSN1S1* genotypes this transport is severely impaired). An important question is if results obtained in French breeds can be safely extrapolated to breeds from other countries. In fact, milk composition is affected by many genetic and environmental factors that might differentially modulate the effects of goat *CSN1S1* genotype depending on the population under consideration. Results obtained in Spanish goat breeds are consistent with this hypothesis. Whilst significant differences were observed in the Malagueña breed when comparing milk CSN1S1 concentrations in BB (6.94 ± 0.38), BF (5.36 ± 0.22), EE (4.58 ± 0.13) and FF (3.98 ± 0.27 g/l) goats, in the case of the Murciano-Granadina breed only the BB genotype (8.50 ± 0.60 g/l) was significantly associated with increased levels of CSN1S1, whereas BF, EE and EF genotypes displayed non-significant differences when compared with each other (Caravaca et al. 2008). Even more, the *CSN1S1* genotype did not display any significant association with protein, casein or fat content (Caravaca et al. 2009). These results suggest that *CSN1S1* genotype has significant and consistent effects on the synthesis rate of the corresponding protein, but associations with other milk components might vary from breed to breed, likely due to differences in their genetic backgrounds and production systems. Interestingly, recent data suggest a certain level of dominance of strong alleles over the weak ones (Berget et al. 2010). In this way, CSN1S1 expression of goats carrying one strong and one weak allele at the *CSN1S1* locus is much more similar to those with a strong homozygous genotype than to goats with a weak homozygous genotype (Berget et al. 2010). Noteworthy, in cattle most of genetic correlations between casein fractions are negative or null (Schopen et al. 2009). As a whole, these findings suggest the existence of complex inter-loci and intra-locus interactions between casein genes that might impact their relative contributions to phenotypic variance of milk composition.

Not only fat content but milk FA composition has been reported to be affected by *CSN1S1* genotype. In this way, low-content *CSN1S1* alleles have been associated with less C8-C12 saturated FA, less stearic acid and more palmitic, linoleic and rumenic acids than their high-content counterparts (Chilliard et al. 2006). Low-content alleles have also been linked to an increased mammary desaturase activity (Chilliard et al. 2006). There is a certain controversy about the influence of *CSN1S1* polymorphism on the mRNA expression of lipid metabolism genes, with studies that support a regulatory effect (Badaoui 2008) and others that do not (Leroux et al. 2003). Since lipids and proteins are synthesized in the endoplasmic reticulum and their transport is, to a certain extent, coupled and co-regulated, it has been hypothesized that the perturbation of casein transport induced by the *CSN1S1* genotype might also alter lipid trafficking resulting in a reduced fat secretion (Ollivier-Bousquet et al. 2002).

Another trait influenced by *CSN1S1* genotype is micelle size, that happens to be lower in AA (221 nm) than in EE (265 nm) or FF (268 nm) milks (Remeuf 1993, Pirisi et al. 1994). This feature together with an augmented global protein content might explain the better coagulation properties and increased cheese yield of the AA milk (Ambrosoli et al. 1988, Vassal et al. 1994). In this way, AA milk produces a firmer curd and displays a slower coagulation time than FF milk (Ambrosoli et al. 1988). Moreover, corrected cheese yield (kg of cheese obtained from 100 kg of milk) was around 21-23 kg for AA, 20 kg for EE and 18 kg for FF goats (Vassal et al. 1994). These associations, however, may change depending on the breed under consideration. In this regard, Caravaca et al. (2011) were unable to find significant differences between the cheese yields of milks from BB, EE and FF Murciano-Granadina goats, whilst EE milk had a significantly higher curdling rate than its BB counterpart. As mentioned above, these differences amongst studies might be explained by a complex mixture of biological and technical factors.

From a sensorial point of view (Vassal et al. 1994), the AA cheese has been reported to display a higher hardness than the FF one (score of 3.23/5 vs 2.85/5), but a weaker goat flavor intensity (score of 2.10/5 vs 2.02/5). This means that the AA milk has better technological properties than the FF one in order to produce cheese but, unfortunately, the resulting product has a less intense taste and odour. It can be speculated that *CSN1S1* effects on cheese flavor might be caused by differences in the FA content and composition (goat flavor is mostly explained by the presence of volatile branched-chain 4-methyl and 4-ethyl octanoic FA) as well as in the lipolysis rate of AA vs FF milks (Chilliard et al. 2003, 2006),

4.2. The caprine α_{S2}-casein gene

Currently, five variants encoding "normal" levels of CSN1S2 have been found (**Table 3**), *i.e*. A and B (Boulanger et al. 1984), C (Bouniol et al. 1994), E (Veltri et al. 2000, Lagonigro et al. 2001) and F (Ramunno et al. 2001[a]). Two other variants D and 0 linked to reduced concentrations of CSN1S2 have also been detected (Ramunno et al. 2001[a,b]). The main feature of the D allele is a 106-nucleotide deletion, starting from the last 11 nucleotides of exon 11 and including 95 bp of intron 11, which causes the loss of three amino acid residues *i.e.* Pro122, Thr123, and Val124. Ramunno et al. (2001[a]) proposed that this variant might be associated with an intermediate level of CSN1S2 synthesis, but evidence is still preliminar and needs to be confirmed. The 0 allele contains a non-sense G>A mutation at exon 11 that changes the codon TGG (coding for Trp110) into a TAG stop codon (Ramunno et al. 2001[b]), thus hindering the synthesis of the corresponding protein. PCR-RFLP and PCR-SSCP protocols have been implemented in order to characterize *CSN1S2* variation (Ramunno et al. 2001[a,b], Chessa et al. 2008) but, to the best of our knowledge, association studies with milk and cheese traits are still lacking.

4.3. The caprine β-casein gene

Alleles at the *CSN2* locus can be classified in two main categories depending on the synthesis rate they are associated with (**Table 3**) *i.e*. alleles that are associated with "normal"

concentrations of CSN2 in milk (A, A1, B, C, D, E) and the null ones (0 and 01) in which CSN2 expression is completely abrogated. Cosenza et al. (2007) have also reported a single nucleotide polymorphism at the *CSN2* promoter but this variant has not been named yet. With regard to the A, B, C, D and E variants, they have been identified by means of proteomic techniques such as isoelectric focusing (Mahé and Grosclaude 1993), peptide mass fingerprinting and tandem mass spectrometry (Neveu et al. 2002), reversed phase HPLC/electrospray ionization mass spectrophotometry (Galliano et al. 2004) and immunoelectrophoretic analysis (Chianese et al. 2007). Molecular characterization of the null variants revealed that the 0 allele contains a 1 bp deletion in the 5'end of exon 7 that induces the appearance of a premature stop codon resulting in a 20-fold reduction in mRNA synthesis and the generation of a much shorter protein (72 vs 223 amino acids, Persuy et al. 1999). This variant has been found in Creole and Pyrenean goats (Persuy et al. 1999). Similarly, Ramunno et al (1995) identified a null 01 variant with a substitution at position 373 of exon 7 that converts a triplet encoding glutamine into a stop codon. This event results in a 10-fold reduction in *CSN2* mRNA synthesis and yields a non-functional protein truncated at position 181 (Ramunno et al. 1995). PCR-SSCP (Chessa et al. 2005, Caroli et al. 2006), allele-specific-PCR (Ramunno et al. 1995), and PCR-RFLP (Cosenza et al. 2005) methods have been developed to identify genetic variants A, A1, C, E, and 0 at the DNA level.

4.4. The caprine κ-casein gene

The caprine *CSN3* gene is extraordinarily polymorphic with 16 alleles (A, B, B′, B″, C, C′, D, E, F, G, H, I, J, K, L, and M) identified to date (Yahyaoui et al. 2003, Jann et al. 2004, Prinzenberg et al. 2005). Interestingly, most of the detected genetic variation is non-synonymous and preliminar evidence of positive selection acting on this locus has been found (Prinzenberg et al. 2005, Clop et al. 2009). This high genetic variation can be characterized with diverse molecular techniques, although multiplexed primer-extension analysis is particularly suitable in order to detect all alleles (Yahyaoui et al. 2003). The two most abundant *CSN3* alleles are A and B, while the remaining ones can be considered as low-frequency variants in the majority of caprine breeds. Interestingly, Caravaca et al. (2010) have reported that the *CSN3* genotype has significant effects on casein and protein contents (BB, AB > AA). Similar results have been obtained in the Orobica breed (Chiatti et al. 2007), where isolectric focusing variant B was associated with higher protein and casein contents than its A counterpart. The molecular basis of these associations is unclear because, as far as we know, the A and B variants only differ by a I119V substitution (Yahyaoui et al. 2003). *In silico* analyses with the Polyphen software have shown that in most mammalian species, Ile119 is a highly conserved residue, suggesting that it might have an important functional role (Caravaca et al. 2010). It is also worth to mention that associations between *CSN3* genotype and rennet coagulation time (BB>AB) have been recently reported (Caravaca et al. 2011). This finding is consistent with the key role of CSN3 in the initial phase of milk rennet coagulation, where 87–90% of CSN3 is enzymatically degraded before micellar aggregation takes place. However, it should be emphasized that *CSN3* genotype did not affect cheese yield, one of the main factors determining the economic income of goat farmers (at least in

Spain and other Mediterranean countries). In consequence, using *CSN3* genotype in marker-assisted selection schemes might not be advisable if cheese yield is a major breeding goal.

4.5. Casein haplotypes and their association with milk traits

The most meaningful approach to investigate the effect of casein genes on milk composition implies the genotyping of haplotypes rather than individual locus-specific alleles. However, this methodological strategy has been rarely carried out, probably because of the technical challenge of simultaneously typing such highly polymorphic loci in a fast and reliable way. Casein haplotypes have been characterized in a number of breeds from Italy (Sacchi et al. 2005, Caroli et al. 2006, Finocchiaro et al. 2008, Gigli et al. 2008), Norway (Hayes et al. 2006, Finocchiaro et al. 2008, Berget et al. 2010), Germany (Küpper et al. 2010), Czech Republic (Sztankóová et al. 2009), West Africa (Caroli et al. 2007) and India (Rout et al. 2010). However, most of these studies just report the variability of the casein cluster in selected populations rather than analysing its impact on milk quality phenotypes. An exception to this general statement is the work performed by Hayes et al. (1996). These authors genotyped 436 goats for 39 SNP distributed in the casein loci. They found higher levels of linkage disequilibrium between SNP pairs within casein loci than between casein loci, meaning that levels of intragenic recombination in casein genes are somewhat low. Moreover, they found significant associations between *CSN1S1* haplotypes and protein percentage and fat yield, as well as between *CSN3* haplotypes and fat and protein percentages (Hayes et al. 1996). In the next future, extensive characterization of the variability of the casein cluster region with next generation sequencing techniques, construction of large casein SNP panels and genotyping with high throughput platforms will be instrumental to elucidate the influence of casein haplotypes on dairy traits.

4.6. The caprine α-lactalbumin and β-lactoglobulin genes

The *LALBA* gene has been poorly characterized in goats with a few polymorphisms described to date. Cosenza et al. (2003) reported a silent SNP at exon 3 that can be analysed by PCR-RFLP (*Mva*I). Another synonymous mutation has ben found at exon 1 (Ma et al. 2010). However, to the best of our knowledge none of these polymorphisms has been associated with milk traits in goats. With regard to the *BLG* locus, most of the polymorphisms that have been found so far lie at the promoter region. In this regard, Yahyaoui et al. (2000) reported a C>T change at position -60, while Ballester et al. (2005) found 9 SNP at the promoter region and 6 silent SNP at the coding region (exons 1,2,3 and 6). Pena et al. (2000) also found two SNP at exon 7 encoding the 3'UTR. In close resemblance with results contributed by Ballester et al. (2005), Sardina et al. (2011) reported extensive variability at the *BLG* promoter, with a total of 36 SNP identified in a panel of Sicilian goats. Several of the SNP identified by Ballester et al. (2005) and Sardina et al. (2011) have been mapped to potential transcription factor binding sites, so they might be good candidates to regulate *BLG* mRNA expression. Pending tasks are to investigate the existence of quantitative differences (in terms of *BLG* mRNA) between promoter alleles as well as to find out if they have a detectable influence on milk composition.

5. Candidate genes and their association with milk fat content and composition traits

The detection of electrophoretic variants of goat milk protein genes three decades ago gave a strong impetus to the identification of the underlying mutations and the performance of association analyses with milk traits. This has resulted in the establishment of a wide catalog of polymorphisms located in the casein and whey protein genes, several of which have well demonstrated causal effects on milk composition. In comparison, the study of the genetic basis of milk fat traits is much less advanced. So far, a reduced number of candidate genes have been characterized at the molecular level and associations with milk fat content and/or composition have been reported (**Table 4**). However, causality has not been demonstrated for any of these associations, that most likely are produced by the existence of linkage disequilibrium between the analysed SNP and the true causal mutation. This contrasts with results obtained in cattle, where causal effects have been proposed (and sometimes convincingly demonstrated) for polymorphisms located at the *DGAT1* (Grisart et al. 2002, Winter et al. 2002), *ABCG2* (Cohen-Zinder et al. 2005) and *PPARGC1A* (Weikard et al. 2005) genes. An important difference between studies performed in cattle and goats is that in the latter species candidate genes were exclusively selected on the basis of physiological criteria, since positional information (*e.g.* QTL landscape of traits under study) was not available. This is an important limitation that has severely hindered progress in goat genetics research

The acetyl-CoA carboxylase α (ACACA) enzyme catalyses the carboxylation of acetyl-CoA to form malonyl-CoA, that can be used by fatty acid synthase as a substrate. This is a key rate-limiting step in the synthesis of FA (Abu-Elheiga et al. 1997). Sequence analysis of 5.5 kb of the coding region of the caprine *ACACA* gene revealed a silent SNP at exon 45 that was suggestively associated with fat yield and other traits (Badaoui et al. 2007[a]). Moreover, Federica et al. (2009) found 3 SNP at promoter III of the caprine *ACACA* gene that map to putative transcription factor binding sites but none of them displayed significant associations with lipid traits. Lipoprotein lipase is another fundamental enzyme involved in FA release and absorption through the hydrolysis of triglycerides from chylomicrons and other lipoprotein particles (Olivecrona and Olivecrona 1998). One missense polymorphism involving a S17T change has been suggestively associated with milk fat content (Badaoui et al. 2007[b]). This polymorphism is located in the signal peptide so it has been hypothesized that it might alter protein localization or expression. Variability at the goat milk fat globule epidermal growth factor and butyrophilin genes has also been associated with milk fat yield (Qu et al. 2011).

Zidi and coworkers (2010[a,b,c,d]) pionereed the study of the genetic basis of milk FA composition in goats through the analysis of several candidate genes and the performance of association analyses. As said in previous sections, milk FA composition constitutes an important set of traits with a key influence on the nutritional and technological properties of milk. Results obtained by Zidi and colleagues are summarized in **Table 4**. Worth to mention the identification of a 3-bp indel in the 3'UTR of caprine stearoyl-CoA desaturase (*SCD1*) gene, previously reported by Bernard et al. (2001), that was suggestively associated with conjugated linoleic acid and polyunsaturated FA content. This deletion is predicted to cause

a dramatic change in the secondary structure of the 3'UTR so it has been hypothesized that it might exert its effect by influencing mRNA stability. In cattle, polymorphism at the *SCD1* gene has been associated with milk FA composition by several authors (Taniguchi et al. 2004, Schennink et al. 2008, Kgwatalala et al. 2009). A significant advancement in the dissection of the genetic factors that regulate milk fat content and composition in goats will necessarily involve the use of high throughput genotyping tools, such as the Illumina BeadChip that will be soon available, to type large goat populations with multiple records for these traits (throughout the lactation and/or successive lactations). This approach would allow to identify the genomic regions influencing milk lipid phenotypes, and then the daunting task of finding the causal mutations might begin with reasonable prospects of being successful.

Gene Name	Polymorphism	Association	References
Acetyl coenzyme A carboxylase α (*ACACA*)	C5493T in exon 45	fat yield, lactose content, and somatic cell count	Badaoui et al. (2007[a])
	1206 pb C/T at promoter III (locus AJ292286)	fat and protein percentages	Federica et al. (2009)
	1322 pb T/C at promoter III (locus AJ292286)	percentage, and fat and protein yields	
Growth hormone (*GH*)	SSCP patterns in exons 2, 4 and 5	milk, fat, and protein yields	Malveiro et al. (2001)
Lipoprotein lipase (*LPL*)	G50C (Ser17Thr)	milk fat content	Badaoui et al. (2007[b])
Stearoyl Co-A desaturase 1 (*SCD1*)	c.*1902_1904delTGT c.*3504G>A	trans-10, cis-12 CLA, PUFA, and total CLA	Zidi et al. (2010[a])
Malic enzyme 1 (*ME1*)	c.483C>T	C16:0 C17:0, C18:1n-9c, C20:1, SFA, MUFA and performed fatty acids.	Zidi et al. (2010[b])
	c.667G>A	C18:1n-9t, and C17:0, C18:0, C18:1n-9c, trans-10, cis-12 CLA, C20:1 and total CLA.	
	c.1200G>A	total CLA, and C17:0, C17:1, C18:0, C18:1n-9t, C18:1n-9c, cis-9, trans-11 CLA, and trans-10, cis-12 CLA.	
Hormone sensitive lipase (*LIPE*)	c.327C>A>T	C12:0 FA, C15:0 and *de novo* FA	Zidi et al. (2010[c])
	c.558C>T	fat content, trans-10, cis-12 CLA	
	c.1162G>T	C18:3n6g.	
Prolactin receptor (*PRLR*)	c. 1201G>A (R401G)	C16:1 FA and C16:1, C18:2n6c FA and PUFA	Zidi et al. (2010[d])
	c.1355C>T (T452I)	C16:1, C18:1n9t FA, SFA, MUFA, and omega 3	

Table 4. Associations between polymorphisms at candidate genes and milk fat traits

6. Conclusions

Milk protein and fat content and composition are key determinants of the nutritional and technological quality of goat dairy products as fresh milk, cheese and yogurt. Classical quantitative genetic studies have demonstrated that there is a remarkable amount of additive genetic variance for these dairy phenotypes, prompting the search of the causal mutations that explain the observed variability. These investigations have been particularly succesful when studying the genetic basis of casein concentrations in milk, since causal mutations have been identified in the goat CSN1S1 and relevant associations have been found for CSN3. These findings have allowed the implementation of marker assisted selection schemes to improve milk quality in goats. Milk fat related phenotypes have been much less studied, although we can anticipate that the development and application of high throughput genotyping and sequencing methods will revolutionize the field in the near future.

Author details

Marcel Amills and Alí Zidi
Department of Animal Genetics, Center for Research in Agricultural Genomics (CSIC-IRTA-UAB-UB), Universitat Autònoma de Barcelona, Bellaterra, Spain

Jordi Jordana
Departament de Ciència Animal i dels Aliments, Universitat Autònoma de Barcelona, Bellaterra, Spain

Juan Manuel Serradilla
Departamento de Producción Animal, Campus de Rabanales, Universidad de Córdoba, Córdoba, Spain

7. References

Abu-Elheiga L, Almarza-Ortega DB, Baldini A, Wakil SJ. 1997. Human acetyl-CoA carboxylase 2. Molecular cloning, characterization, chromosomal mapping, and evidence for two isoforms. J Biol Chem. 272:10669-10677.

Ambrosoli R, Di Stasio L, Mazzocco P. 1988. Content of α_{S1}-casein and coagulation properties in goat milk. J Dairy Sci. 71:24-28.

Analla M, Jímenez-Gamero I, Muñoz-Serrano A, Serradilla JM, Falagán A. 1996. Estimation of genetic parameters for milk yield and fat and protein contents of milk from Murciano-Granadina goats. J Dairy Sci. 79:1895-1898.

Andonov S, Kovac M, Kompan D, Dzabirski V. 1998. Estimation of covariance components for test day production in dairy goat. Proceedings of the 6th WCGALP. Armidale, Australia, pp. 145-148.

Badaoui B, Serradilla JM, Tomas A, Urrutia B, Ares JL, Carrizosa J, Sànchez A, Jordana J, and Amills M. 2007[a]. Goat acetyl-coenzyme A carboxylase α: Molecular

characterization, polymorphism and its association with milk traits. J Dairy Sci. 90:1039-1043.

Badaoui B, Serradilla JM, Tomàs A, Urrutia B, Ares JL, Carrizosa J, Sànchez A, Jordana J, Amills M. 2007[b]. Identification of two polymorphisms in the goat lipoprotein lipase gene and their association with milk traits. J Dairy Sci. 90:3012-3017.

Badaoui B. 2008. Genetic factors affecting milk composition in goats. PhD Thesis, Universitat Autònoma de Barcelona, Spain.

Ballester M, Sánchez A, Folch JM. 2005. Polymorphisms in the goat β-lactoglobulin gene. J Dairy Res. 72:379-384.

Barber MC, Clegg RA, Travers MT, Vernon RG. 1997. Lipid metabolism in the lactating mammary gland. Biochim Biophys Acta 1347:101-126.

Barbieri M, Manfredi E, Elsen JM, Ricordeau G, Bouillon J, Grosclaude F, Mahé M, Bibé B. 1995. Influence du locus de la caséine α_{s1} sur les performances laitières et les paramètres génétiques des chèvres de race Alpine. Genet Sel Evol. 27:437-450.

Barillet F. 2007. Genetic improvement for dairy production in sheep and goats. Small Rum Res. 70:60-75.

Bauman DE, Davis CL. 1974. Biosynthesis of milk fat. In Lactation: A Comprehensive Treatise. Academic Press, New York, USA, pp. 31-75.

Bauman DE, Griinari JM. 2003. Nutritional regulation of milk fat synthesis. Annu Rev Nutr. 23:203-227.

Bauman DE, Mather IH, Wall RJ, Lock AL. 2006. Major advances associated with the biosynthesis of milk. J Dairy Sci. 89:1235-1243.

Bélichon S, Manfredi E, Piacère A. 1998. Genetic parameters of dairy traits in the Alpine and Saanen goat breeds. Genet Sel Evol. 30:529-534.

Benradi Z. 2007. Análisis genético de los caracteres de rendimiento, composición, reología y rendimiento quesero de la leche en las razas caprinas Malagueña y Murciano-Granadina. Master Thesis, International Center for Advanced Mediterranean Studies, Zaragoza, Spain.

Benradi Z, Ares JL, Jordana J, Urrutia B, Carrizosa J, Baena F, Serradilla JM. 2009. Genetic parameters for milk yield, composition and rheological traits in Murciano Granadina goats. Proceedings of the 60th Annual EAAP Congress, Barcelona, Spain.

Bequette BJ, Backwell FR, Crompton LA. 1998. Current concepts of amino acid and protein metabolism in the mammary gland of the lactating ruminant. J Dairy Sci. 81:2540-2559.

Berget I, Martens H, Kohler A, Sjurseth SK, Afseth NK, Narum B, Adnøy T, Lien S. 2010. Caprine CSN1S1 haplotype effect on gene expression and milk composition measured by Fourier transform infrared spectroscopy. J Dairy Sci. 93:4340-4350.

Bernard L, Leroux C, Hayes H, Gautier M, Chilliard Y, Martin P. 2001.Characterization of the caprine stearoyl-CoA desaturase gene and its mRNA showing an unusually long 3'-UTR sequence arising from a single exon. Gene 281:53-61.

Bevilacqua C, Ferranti P, Garro G, Veltri C, Lagonigro R, Leroux C, Pietrola E, Addeo F, Pilla F, Chianese L, Martin P. 2002. Interallelic recombination is likely responsible for the occurrence of a new αs1-casein variant in the goat species. Eur J Biochem. 269:1293-1303.

Bionaz M, Loor JJ. 2008. Gene networks driving bovine milk fat synthesis during the lactation cycle. BMC Genomics 9:366.

Bishop S, Sullivan BP, Shaeffer LR. 1994. Genetic evaluation of Canadian dairy goats using test day data. Proceedings of the 29th Biennial Session of the International Committee for Animal Breeding (ICAR). Ottawa, Canada, pp. 299-302.

Boichard D, Bouloc N, Ricordeau G, Piacere A, Barillet F. 1988. Genetic parameters for first lactation dairy traits in the Alpine and Saanen goat breeds. Genet Sel Evol. 21:205-215.

Bouillon J, Ricordeau G. 1975. Paramètres génétiques des performances de croissance et de production laitière chez les caprins en station de testage. Estimation des réponses directes ou in directes à la séléction. 1ères Journées de la Recherches Ovine et Caprine. INRA-ITOVIC, Paris, France, pp. 149-155.

Boulanger A, Grosclaude F, Mahé MF. 1984. Polymorphisme des caséines α_{S1} et α_{S2} de la chèvre (*Capra hircus*). Genet Sel Evol. 16:157-176.

Bouloc N. 1987. Adéquation du critère de selection et possibilités d'allègement du contrôle laitier chez la chèvre. Mémoire de Fin d'Etudes. INRA, Toulouse, France.

Bouniol C. 1993. Sequence of the goat α_{s2}-casein enconding cDNA. Gene 125:235-236.

Bouniol C, Brignon G, Mahé MF, Printz C. 1994. Biochemical and genetic analysis of variant C of caprine αs2-casein (Capra hircus). Anim Genet. 25:173-177.

Caravaca F, Amills M, Jordana J, Angiolillo A, Agüera P, Aranda C, Menéndez-Buxadera A, Sánchez A, Carrizosa J, Urrutia B, Sànchez A, Serradilla JM. 2008. Effect of α_{S1}-casein (*CSN1S1*) genotype on milk CSN1S1 content in Malagueña and Murciano-Granadina goats. J Dairy Res. 75:481-484.

Caravaca F, Carrizosa J, Urrutia B, Baena F, Jordana J, Amills M, Badaoui B, Sànchez A, Angiolillo A, Serradilla JM. 2009. Short communication: Effect of α_{S1}-casein (*CSN1S1*) and κ-casein (*CSN3*) genotypes on milk composition in Murciano-Granadina goats. J Dairy Sci. 92:2960-2964.

Caravaca F, Ares JL, Carrizosa J, Urrutia B, Baena F, Jordana J, Badaoui B, Sànchez A, Angiolillo A, Amills M, Serradilla JM. 2011. Effects of α_{S1}-casein (*CSN1S1*) and κ-casein (*CSN3*) genotypes on milk coagulation properties in Murciano-Granadina goats. J Dairy Res. 78:32-37.

Caroli A, Chiatti F, Chessa S, Rignanese D, Bolla P, Pagnacco G. 2006. Focusing on the goat casein complex. J Dairy Sci. 89:3178-3187.

Caroli A, Chiatti F, Chessa S, Rignanese D, Ibeagha-Awemu EM, Erhardt G. 2007. Characterization of the casein gene complex in West African goats and description of a new α_{S1}-casein polymorphism. J Dairy Sci. 90:2989-2996.

Chanat E, Martin P, Ollivier-Bousquet M. 1999. α_{S1}-casein is required for the efficient transport of β- and κ-casein from the endoplasmic reticulum to the Golgi apparatus of mammary epithelial cells. J Cell Sci. 112:3399-3412.

Chessa S, Budelli E, Chiatti F, Cito AM, Bolla P, Caroli A. 2005. Short communication: Predominance of β-casein (*CSN2)* C allele in goat breeds reared in Italy. J Dairy Sci. 88:1878-1881.

Chessa S, Rignanese D, Chiatti F, Radeghieri A, Gigliotti C, Caroli A. 2008. Technical note: simultaneous identification of *CSN1S2 A*, *B*, *C*, and *E* alleles in goats by polymerase chain reaction-single strand conformation polymorphism. J Dairy Sci. 91:1214-1217.

Chianese L, Ferranti P, Garro G, Mauriello R, Addeo F. 1997. Ocurrence of three novel αs1 casein variants in goat milk. Proc. Int. Dairy Fed, Fed. Int. Laiterie Semin. Milk Protein Polymorphism II. Int. Dairy Fed., Palmerston North, New Zealand, pp. 259-267.

Chianese L, Caira S, Garro G, Quarto M, Mauriello R, Addeo F. 2007. Occurrence of genetic polymorphism at goat β-CN locus. 5th Int. Symp. Challenge to Sheep and Goats Milk Sectors, Alghero, Sardinia, Italy.

Chiatti F, Chessa S, Bolla P, Cigalino G, Caroli A, Pagnacco G. 2007. Effect of κ-casein polymorphism on milk composition in the Orobica goat. J Dairy Sci. 90:1962-1966.

Chilliard Y, Ferlay A, Rouel J, Lamberet G. 2003. A review of nutritional and physiological factors affecting goat milk lipid synthesis and lipolysis. J Dairy Sci. 86:1751-1770.

Chilliard Y, Rouel J, Leroux C. 2006. Goat's alpha-s1 casein genotype influences its milk fatty acid composition and delta-9 desaturation ratios. Anim Feed Sci Technol. 131: 474-487.

Clop A, Zidi A, Amills M. 2010. Identification of positively selected sites in the goat *kappa casein* (*CSN3*) gene. Anim Genet. 41:332.

Cohen-Zinder M, Seroussi E, Larkin DM, Loor JJ, Everts-van der Wind A, Lee JH, Drackley JK, Band MR, Hernandez AG, Shani M, Lewin HA, Weller JI, Ron M. 2005. Identification of a missense mutation in the bovine *ABCG2* gene with a major effect on the QTL on chromosome 6 affecting milk yield and composition in Holstein cattle. Genome Res. 15:936-944.

Coll A, Folch JM, Sànchez A. 1993. Nucleotide sequence of the goat κ-casein cDNA. J Anim Sci. 71:2833.

Cosenza G, Illario R, Rando A, Di Gregorio P, Masina P, Ramunno L. 2003. Molecular characterization of the goat *CSN1S1* (01) allele. J Dairy Res. 70:237-240.

Cosenza G, Pauciullo A, Gallo D, Di Berardino D, Ramunno L. 2005. A *Ssp*I PCR-RFLP detecting a silent allele at the goat *CSN2* locus. J Dairy Res. 72:456-459.

Cosenza G, Pauciullo A, Colimoro L, Mancusi A, Rando A, Di Berardino D, Ramunno. 2007. An SNP in the goat *CSN2* promoter region is associated with the absence of β-casein in milk. Anim Genet. 38:655-658.

Díaz Carrillo E, Alonso-Moraga A, Serradilla-Manrique JM, Muñoz-Serrano A. 1993. Near Infrared calibration for goat's milk components: protein, total casein, α_s-, β- and κ-caseins, fat and lactose. J Near Infrared Spectrosc. 1:141-146.

FAOSTAT. 2009 (http://faostat.fao.org/ site/ 339/ default.aspx).

Federica S, Francesco N, Giovanna de M, Carmela SM, Gennaro C, Carmela T, Bianca M. 2009. Identification of novel single nucleotide polymorphisms in promoter III of the acetyl-CoA carboxylase-{alpha} gene in goats affecting milk production traits. J Hered. 100:386-389.

Fernández C, Mocé ML, Latorre MA, Gómez E. 2005. Producción lechera de cabras Murciano-Granadinas de la región de Murcia. Ganadería 35:38-43.

Finocchiaro R, Hayes BJ, Siwek M, Spelman RJ, van Kaam JB, Adnøy T, Portolano B. 2008. Comparison of casein haplotypes between two geographically distant European dairy goat breeds. J Anim Breed Genet. 125:68-72.

Fitzgerald RJ, Meisel HM. 2003. Milk protein hydrolysis and bioactive peptides. In: Advanced Dairy Chemistry (3rd, Part B), Kluwer Academic/Plenum Publishers, New York, USA, pp. 675-698.

Folch JM, Coll A, Sànchez A. 1994. Complete sequence of the caprine β-lactoglobulin gene. J Dairy Sci. 77:3493-3497.

Folch JM, Coll A, Hayes HC, Sànchez A. 1996. Characterization of a caprine β-lactoglobulin pseudogene, identification and chromosomal localization by in situ hybridization in goat, sheep and cow. Gene 177:87-91.

Fontecha J, Ríos JL, Lozada L, Fraga MJ, Juárez M. 2000. Composition of goat's milk fat triglycerides analysed by silver ion adsorption-TLC and GC-MS. Int Dairy J. 10:119-128.

Fox PF, McSweeney PLH. 2006. Advanced Dairy Chemistry-2. Lipids, 3rd. Edition, Springer Publishers, New York, USA, pp. 801.

Galliano F, Saletti R, Cunsol V, Foti S, Marletta D, Bordonaro S, D'Urso G. 2004. Identification and characterization of a new *β*-casein variant in goat milk by high-performance liquid chromatography with electrospray ionization mass spectrometry and matrix-assisted laser desorption/ionization mass spectrometry. Rapid Commun Mass Spectrom. 18:1972-1982.

Gigli I, Maizon DO, Riggio V, Sardina MT, Portolano B. 2008. Short communication: casein haplotype variability in Sicilian dairy goat breeds. J Dairy Sci. 91:3687-3692.

Grisart B, Coppieters W, Farnir F, Karim L, Ford C, Berzi P, Cambisano N, Mni M, Reid S, Simon P, Spelman R, Georges M, Snell R. 2002. Positional candidate cloning of a QTL in dairy cattle: identification of a missense mutation in the bovine *DGAT1* gene with major effect on milk yield and composition. Genome Res. 12:222-231.

Grosclaude F, Mahé MF, Brignon G, Di Stasio L, Jeunet R. 1987. A Mendelian polymorphism underlying quantitative variations of goat α_{S1}-casein. Genet. Sel. Evol. 19:399-412.

Grosclaude F. 1991. Structure, détérminisme génétique et polymorphisme des 6 lactoprotéines principales des bovins, des caprins et des ovins. Journeés sur la Qualité des Laits à la Production et Aptitude Fromagère. Colloque INRA-ENSA, Rennes, France.

Harvatine KJ, Perfield JW, Bauman DE. 2009. Expression of enzymes and key regulators of lipid synthesis is upregulated in adipose tissue during CLA-induced milk fat depression in dairy cows. J Nutr. 139:849-854.

Hayes HC, Popescu P, Dutrillaux B. 1993. Comparative gene mapping of lactoperoxidase, retinoblastoma, and *α*-lactalbumin genes in cattle, sheep, and goats. Mamm Genome 4:593-597.

Hayes B, Hagesaether N, Adnøy T, Pellerud G, Berg PR, Lien S. 2006. Effects on production traits of haplotypes among casein genes in Norwegian goats and evidence for a site of preferential recombination. Genetics 174:455-464

Hayes B, Goddard M. 2010. Genome-wide association and genomic selection in animal breeding. Genome 53:876-883.

Iloeje MU, Van Vleck LD, Wiggans GR. 1981. Components of variance for milk and fat yields in dairy goats. J Dairy Sci. 64:2290-2293.

Jann OC, Prinzenberg EM, Luikart G, Caroli A, Erhardt G. 2004. High polymorphism in the κ-casein (*CSN3*) gene from wild and domestic caprine species revealed by DNA sequencing. J Dairy Res. 71:188-195.

Jollès P. 1975. Structural aspects of the milk clotting process. Comparative features with the blood clotting process. Mol Cell Biochem.7:73-85.

Jordana J, Amills M, Díaz E, Angulo C, Serradilla JM, Sánchez A. 1996. Gene frequencies of caprine α_{s1}-casein polymorphism in Spanish goat breeds. Small Rumin Res. 20:215-221.

Kawasaki K, Weiss KM. 2003. Mineralized tissue and vertebrate evolution: The secretory calcium-binding phosphoprotein gene cluster. Proc Natl Acad Sci USA 100:4060-4065.

Kennedy BW, Finley CM, Bradford GE. 1982. Phenotypic and genetic relationships between reproduction and milk production in dairy goats. J Dairy Sci. 65:2373-2383.

Kgwatalala PM, Ibeagha-Awemu EM, Mustafa AF, Zhao X. 2009. Influence of stearoyl-coenzyme A desaturase 1 genotype and stage of lactation on fatty acid composition of Canadian Jersey cows. J Dairy Sci. 92:1220-1228.

Khatkar MS, Thomson PC, Tammen I, Raadsma HW. 2004. Quantitative trait loci mapping in dairy cattle: review and meta-analysis. Genet Sel Evol. 36:163-190.

Korhonen H, Pihlanto A. 2001. Food-derived bioactive peptides-opportunities for designing future foods. Curr Pharm Des. 9:1297-1308.

Küpper J, Chessa S, Rignanese D, Caroli A, Erhardt G. 2010. Divergence at the casein haplotypes in dairy and meat goat breeds. J Dairy Res. 77:56-62.

Lagonigro R, Pietrola E, D'Andrea M, Veltri C, Pilla F. 2001. Molecular characterisation of the goat s_2-casein *E* allele. Anim Genet. 32:391-393.

Lamberet GA, Delacroix B, Degas C. 2001. Intensité de la lipolyse initiale des laits de chèvre et perception de l'arôme "chèvre" dans les fromages. In: Proc. Technical Symp. 7th Int. Conf. Goats: Recent Advances on Goat Milk Quality, Raw Material for Cheesemaking. Poitiers, France, pp. 130-139.

Leroux C, Martin P, Mahé MF, Levéziel H, Mercier JC. 1990. Restriction fragment length polymorphism identification of goat α_{S1}-casein alleles: a potential tool in selection of individuals carrying alleles associated with a high level protein synthesis. Anim Genet. 21:341-351.

Leroux C, Mazure N, Martin P. 1992. Mutations away from splice site recognition sequences might *cis*-modulate alternative splicing of goat α_{s1}-casein transcripts. Structural organization of the relevant gene. J Biol Chem. 267:6147-6157.

Leroux C, Martin P. 1996. The caprine α_{S1}- and β-caseins genes are 12 kb apart and convergently transcribed. Anim Genet. 27 (Suppl. 2):293.

Leroux C, Le Provost F, Petit E, Bernard L, Chilliard Y, Martin P. 2003. Real-time RT-PCR and cDNA macroarray to study the impact of the genetic polymorphism at the α_{s1}-*casein* locus on the expression of genes in the goat mammary gland during lactation. Reprod Nutr Dev. 43:459-469.

Ma RN, Deng CJ, Zhang XM, Yue XP, Lan XY, Chen H, Lei CZ. 2010. S-novel SNP of α-lactalbumin gene in Chinese dairy goats. Mol Biol. (Mosk) 44:608-612.

Madureira AR, Pereira CI, Gomes AMP, Pintado ME, Malcata FX. 2007. Bovine whey proteins-Overview on the main biological properties. Food Res Int. 40:1197-1211.

Mahé MF, Grosclaude F. 1993. Polymorphism of β-casein in the Creole goat of Guadeloupe, evidence for a null allele. Genet Sel Evol. 25:403-408

Mahé MF, Manfredi E, Ricordeau G, Piacère A, Grosclaude F. 1994. Effets du polymorphisme de la caséine α_{S1} caprine sur les performances laitières: analyse intradescendance de boucs de race Alpine. Genet Sel Evol. 26:151-157.

Maga EA, Daftari P, Kültz D, Penedo MC. 2009. Prevalence of α_{S1}-casein genotypes in American dairy goats. J Anim Sci. 87:3464-3469.

Malveiro E, Marques PX, Santos IC, Belo C, Cravador A. 2001. Association between SSCPs at Algarvia goat GH gene and milk traits. Arch Zootec. 50:49–57

Manfredi E, Ricordeau G, Barbieri ME, Amigues Y, Bibé B. 1995. Genotype caséine α_{s1} et sélection des boucs sur descendance dans les races Alpine et Saanen. Genet Sel Evol. 27:451-458.

Manfredi E, Serradilla JM, Leroux C, Martin P, Sánchez A. 2000. Genetics for milk production. Proceedings 7th World Conference on Goats. Tours, France, pp. 191-196.

Martin P, Ollivier-Bousquet M, Grosclaude F. 1999. Genetic polymorphism of caseins: a tool to investigate casein micelle organization. Int Dairy J. 9:163–171

Martin P, Szymanowska M, Zwierzchowski L, Leroux C. 2002. The impact of genetic polymorphisms on the protein composition of ruminant milks. Reprod Nutr Dev. 42:433-459.

Martini M, Salari F, Altomonte I, Rignanese D, Chessa S, Gigliotti C, Caroli A. 2010. The Garfagnina goat: a zootechnical overview of a local dairy population. J Dairy Sci. 93:4659-4667.

Matar C, LeBlanc JG, Martin L, Perdigon G. 2003. Biologically active peptides released in fermented milk: Role and functions. In: Handbook of Fermented Functional Foods. Functional Foods and Nutraceuticals Series. CRC press, Florida, USA, pp.177-201.

Meisel H. 1998. Overview on milk protein-derived peptides. Int Dairy J. 8:363-373.

Menéndez-Buxadera A, Romero F, González O, Arrebola F, Molina A. 2008. Estimación de parámetros genéticos para la producción de leche y sus componentes en la raza caprina Payoya mediante técnicas de regresión Aleatoria. Inf Tec Agr. 104:127-132.

Menéndez-Buxadera A, Molina A, Arrebola F, Gil MJ, Serradilla JM. 2010. Random regression analysis of milk yield and milk composition in the first and second lactations of Murciano-Granadina goats. J Dairy Sci. 93:2718-2726.

Moioli B, D'Andrea M, Pilla F. 2007. Candidate genes affecting sheep and goat milk quality. Small Rumin Res. 68:179-192.

Montaldo HH, Manfredi E. 2002. Organization of selection programs for dairy goats. Proc. 7th World Congress on Genetics Applied to Livestock Production. Montpellier, France, pp. 187-194.

Muller CJC, Cloet SWP, Schoeman SJ. 2002. Estimation of genetic parameters for milk yield and milk composition of Saanen goats. Proc. 7th World Congress on Genetics Applied to Livestock Production. Montpellier, France, pp. 259-262

Neveu C, Mollé D, Moreno J, Martin P, Léonid J. 2002. Heterogeneity of caprine β-casein elucidated by RP-HPLC/ MS: Genetic variants and phosphorylation. J Protein Chem. 21:557-567.

Olivecrona G, Olivecrona T. 1998. Clearance of artificial triacylglycerol particles. Curr Opin Clin Nutr Metab Care 1:143-151.

Ollivier-Bousquet M. 2002. Milk lipid and protein traffic in mammary epithelial cells: joint and independent pathways. Reprod Nutr Dev. 42:149–162.

Pena RN, Sánchez A, Folch JM. 2000. Characterization of genetic polymorphism in the goat β-lactoglobulin gene. J Dairy Res. 67:217-224.

Pérez MJ, Leroux C, Bonastre AS, Martin P. 1994. Occurrence of a LINE sequence in the 3' UTR of the goat α_{S1}-casein E-encoding allele associated with reduced protein synthesis level. Gene 147:179-87.

Persuy MA, Printz C, Medrano JF, Mercier JC. 1999. A single nucleotide deletion resulting in a premature stop codon is associated with marked reduction of transcripts from a goat β-casein null allele. Anim Genet. 30:444-451.

Pfeuffer M, Schrezenmeir J. 2000. Bioactive substances in milk with properties decreasing risk of cardiovascular diseases. Br J Nutr. 84 (Suppl 1):S155-159.

Pirisi A, Colin O, Laurent F, Scher J, Parmentier M. 1994. Comparison of milk composition, cheesemaking properties and textural characteristics of the cheese from two groups of goats with a high or low rate α_{S1}-casein synthesis. Int Dairy J. 4:329-345.

Prinzenberg EM, Gutscher K, Chessa S, Caroli A, Erhardt G. 2005. Caprine κ-casein (*CSN3*) polymorphism: new developments in molecular knowledge. J Dairy Sci. 88:1490-1498.

Qu Y, Liu Y, Ma L, Sweeney S, Lan X, Chen Z, Li Z, Lei C, Chen H. 2011. Novel SNPs of butyrophilin (*BTN1A1*) and milk fat globule epidermal growth factor (EGF) 8 (*MFG-E8*) are associated with milk traits in dairy goat. Mol Biol Rep. 38:371-377.

Rabasco A, Serradilla JM, Padilla JA, Serrano A. 1993. Genetic and non-genetic sources of variation in yield and composition of milk in Verata goats. Small Rum Res. 11:151-161.

Ramunno L, Mariani P, Pappalardo M, Rando A, Capuano M, Di Gregorio P, Cosenza G. 1995. Un gene ad effetto maggiore sul contenuto di caseina β nel latte di capra, XI Convegno ASPA, Grado, Italy, pp. 185-186.

Ramunno L, Cosenza G, Pappalardo M, Pastore N, Gallo D, Di Gregorio P, Masina P. 2000. Identification of the goat *CSN1S1F* allele by means of PCR-RFLP method. Anim Genet. 31:342–343.

Ramunno L, Cosenza G, Pappalardo M, Longobardi E, Gallo D, Pastore N, Di Gregorio P, Rando A. 2001[a]. Characterization of two new alleles at the goat *CSN1S2* locus. Anim Genet. 32:264-268.

Ramunno L, Longobardi E, Pappalardo M, Rando A, Di Gregorio P, Cosenza G, Mariani P, Pastore N, Masina P. 2001[b]. An allele associated with a non-detectable amount of α_{S2}-casein in goat milk. Anim Genet. 32:19-26.

Ramunno L, Cosenza G, Rando A, Illario R, Gallo D, Di Berardino D, Masina P. 2004. The goat α_{s1}-casein gene: gene structure and promoter analysis. Gene 334:105-111.

Ramunno L, Cosenza G, Rando A, Pauciullo A, Illario R, Gallo D, Di Berardino D, Masina P. 2005. Comparative analysis of gene sequence of goat *CSN1S1* F and N alleles and characterization of *CSN1S1* transcript variants in mammary gland. Gene 345:289-99.

Rando A, Di Gregorio P, Ramunno L, Mariani P, Fiorella A, Senese C, Marletta D, Masina P. 1998. Characterization of the *CSN1A G* allele of the bovine α_{S1}-casein locus by the insertion of a relict of a long interspersed element. J Dairy Sci. 81:1735-42.

Remeuf F, Cossin V, Dervin C, Lenoir J, Tomassone R. 1991. Relations entre les caractères physico-chimiques des laits et leur aptitude fromagère. Le Lait 71:397-421.

Remeuf F, Hurtaud C. 1991. Relationship between physicochemical traits of milk and renneting property. In: Qualité des Laits à la Production et Aptitude Fromagère, INRA-ENSAR, Rennes, France, pp. 1-7.

Remeuf F. 1993. Influence du polymorphisme génétique de la caséine α_{s1} caprine sur les caractéristiques physico-chimiques et technologiques du lait. Le Lait 73:549-557.

Rhoads RE, Grudzien-Nogalska E. 2007. Translational regulation of milk protein synthesis at secretory activation. J Mammary Gland Biol Neoplasia 12:283-292.

Ricordeau G, Bouillon J, Sánchez F, Mocquot JC, Lajous A. 1979. Amélioration génétique de caprins. Facteur favorisant ou limitant le progrès génétique. 5ème Journées de la Recherche Ovine et Caprine. INRA-ITOVIC, Paris. pp. 403-426.

Rijnkels M. 2002. Multispecies comparison of the casein gene loci and evolution of casein gene family. J Mammary Gland Biol Neoplasia 7:327-345.

Roberts B, DiTullio P, Vitale J, Hehir K, Gordon K. 1992. Cloning of the goat beta-casein-encoding gene and expression in transgenic mice. Gene. 121:255-262.

Roldán DL, Rabasa AE, Saldaño S, Holgado F, Poli MA, Cantet RJ. 2008. QTL detection for milk production traits in goats using a longitudinal model. J Anim Breed Genet. 125:187-193.

Ronningen K. 1965. Cases of variation in the flavor intensity of goat milk. Acta Agric Scand. 15: 301-342

Ronningen K. 1967. A study of genetic parameters for milk characteristics in goats. Meld Norg Landbr Hogsk. 46:1-17.

Rout PK, Kumar A, Mandal A, Laloe D, Singh SK, Roy R. 2010. Characterization of casein gene complex and genetic diversity analysis in Indian goats. Anim Biotechnol. 21:122-134.

Rupp R, Clément V, Piacere A, Robert-Granié C, Manfredi E. 2011. Genetic parameters for milk somatic cell score and relationship with production and udder type traits in dairy Alpine and Saanen primiparous goats. J Dairy Sci. 94:3629-3634.

Sacchi P, Chessa S, Budelli E, Bolla P, Ceriotti G, Soglia D, Rasero R, Cauvin E, Caroli A. 2005. Casein haplotype structure in five Italian goat breeds. J Dairy Sci. 88:1561-1568.

Sardina MT, Rosa AJ, Davoli R, Braglia S, Portolano B. 2011. Polymorphisms of β-lactoglobulin promoter region in three Sicilian goat breeds. Mol Biol Rep. (in press).

Schaeffer LR. 2004. Applications of random regression models in animal breeding. Livest Prod Sci. 86:35-45.

Schennink A, Heck JML, Bovenhuis H, Visker MHPW, van Valenberg HJF, van Arendonk JAM. 2008. Milk fatty acid unsaturation: genetic parameters and effects of stearoyl-CoA

desaturase (*SCD1*) and acyl CoA: diacylglycerol acyltransferase 1 (*DGAT1*). J Dairy Sci. 91:2135-2143.

Schopen GC, Heck JM, Bovenhuis H, Visker MH, van Valenberg HJ, van Arendonk JA. 2009. Genetic parameters for major milk proteins in Dutch Holstein-Friesians. J Dairy Sci. 92:1182-1191.

Schopen GC, Visker MH, Koks PD, Mullaart E, van Arendonk JA, Bovenhuis H. 2011. Whole-genome association study for milk protein composition in dairy cattle. J Dairy Sci. 94:3148-3158.

Shennan DB, Peaker M. 2000. Transport of milk constituents by the mammary gland. Physiol Rev. 80:925-951.

Sigwald JP, Ricordeau G, Bouillon J, Grappin R, du Sartel C. 1981. Paramétres génétiques et phenotypiques de la valeur fromagère du lait de chévre: richesse en matiéres azotées totales et coagulables. 6éme Journées de la Recherche Ovine et Caprine, ITOVIC-SPEOC, Paris, pp. 415-426.

Smiddy MA, Martin JE, Kelly AL, De Kruif CG, Huppertz T, 2006. Stability of casein micelles cross-linked by transglutaminase. J Dairy Sci. 89:1906-1914.

Sztankóová Z, Mátlová V, Kysel'ová J, Jandurová OM, Ríha J, Senese C. 2009. Short communication: Polymorphism of casein cluster genes in Czech local goat breeds. J Dairy Sci. 92:6197-6201.

Taniguchi M, Utsugi T, Oyama K, Mannen H, Kobayashi M, Tanabe Y, Ogino A, Tsuji S. 2004. Genotype of stearoyl-CoA desaturase is associated with fatty acid composition in Japanese Black cattle. Mamm Genome 15:142-148.

Thompson MP, Tarassuk NP, Jenness R, Lillevik HA, Ashworth US, Rose D. 1965. Nomenclature of the proteins of cow's milk-second revision: report of the committee on milk protein nomenclature, classification, and methodology of the manufacturing section of ADSA for 1963-64. J Dairy Sci. 48:159-169.

Torres-Vázquez JA, Valencia-Posadas M, Castillo-Juarez H, Montaldo HH. 2009. Genetic and phenotypic parameters of milk yield, milk composition and age at first kidding in Saanen goats from Mexico. Livest Sci. 126:147-153.

Trujillo AJ, Jordana J, Guamis B, Serradilla J, Amills M. 1998. Review: Polymorphism of the caprine α_{s1}-casein gene and its effect on the production, composition and technological properties of milk and on cheese making and ripening. Food Sci Technol Int. 4: 231-237.

Van Soest PJ. 1994. Nutritional Ecology of the Ruminant. 2nd. Ed. Cornell University Press, USA, pp. 476.

Vassal L, Delacroix-Buchet A, Bouillon J. 1994. Influence des variants AA, EE et FF de la caséine α_{s1} sur le rendement fromager et les caractéristiques sensorielles des fromages traditionnels : prèmieres observations. Le Lait 74:89-103.

Veltri C, Lagonigro R, Pietrollà E, D'Andrea M, Pilla F, Chianese L. 2000. Molecular characterisation of the goat α_{s2}-casein E allele and its detection in goat breeds of Italy. 7th International Conference on Goats, Tours, France, pp. 727.

Weekes TL, Luimes PH, Cant JP. 2006. Responses to amino acid imbalances and deficiencies in lactating dairy cows. J Dairy Sci. 89:2177-2187.

Weikard R, Kühn C, Goldammer T, Freyer G, Schwerin M. 2005. The bovine PPARGC1A gene: molecular characterization and association of an SNP with variation of milk fat synthesis. Physiol Genomics 21:1-13.

Winter A, Kramer W, Werner FAO, Kollers S, Kata S, Durstewitz G, Buitkamp J, Womack JE, Thaller G, Fries R. 2002. Association of a lysine-232/alanine olymorphism in a bovine gene encoding acyl-CoA:diacylglycerol acyltransferase (*DGAT1*) with variation at a quantitative trait locus for milk fat content. Proc Natl Acad Sci USA 99:9300-9305.

Yahyaoui MH, Pena RN, Sánchez A, Folch JM. 2000. Rapid communication: polymorphism in the goat β-lactoglobulin proximal promoter region. J Anim Sci. 78:1100-1101.

Yahyaoui MH, Angiolillo A, Pilla F, Sànchez A, Folch JM. 2003. Characterization and genotyping of the caprine κ-casein variants. J Dairy Sci. 86:2715-2720.

Zidi A, Fernández-Cabanás VM, Urrutia B, Carrizosa J, Polvillo O, González-Redondo P, Jordana J, Gallardo D, Amills M, Serradilla JM. 2010[a]. Association between the polymorphism of the goat stearoyl-coA desaturase 1 (*SCD1*) gene and milk fatty acid composition in Murciano-Granadina goats. J Dairy Sci. 93:4332-4339.

Zidi A, Serradilla JM, Jordana J, Carrizosa J, Urrutia B, Polvillo O, González-Redondo P, Gallardo D, Amills M, Fernández-Cabanás VM. 2010[b]. Association analysis between goat malic enzyme 1 (*ME1*) genotype and dairy traits. Animal 4: 1953-1957.

Zidi A, Fernández-Cabanás VM, Carrizosa J, Jordana J, Urrutia B, Polvillo O, González-Redondo P, Gallardo D, Amills M, Serradilla JM. 2010[c]. Genetic variation at the goat hormone-sensitive lipase (*LIPE*) gene and its association with milk yield and composition. J Dairy Res. 77:190-198.

Zidi A, Serradilla JM, Jordana J, Carrizosa J, Urrutia B, Polvillo O, González-Redondo P, Gallardo D, Amills M, Fernández-Cabanás VM. 2010[d]. Pleiotropic effects of the goat prolactin receptor genotype on milk fatty acid composition. Domest Anim Endocrinol.39: 85-89.

Zygoyiannis D. 1994. A study of genetic and phenotypic parameters for milk yield and milk characteristics in indigenous and crossbred goats in Greece. Wld Rev Anim Prod. 29:29-37.