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Prevalence of α_{s1}-casein genotypes in American dairy goats[1]

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ABSTRACT: Widespread genotyping of US dairy goat breeds for casein variants has not been reported, even though the genetic data could be of use in selective breeding programs. For instance, variability in the content of protein and solids in goat milk is attributed to allelic differences in the goat α_{s1}-casein gene. Concentrations of α_{s1}-casein in goat milk are positively correlated with milk components and coagulation properties. The alleles A and B are designated as strong alleles, resulting in the greatest amount of α_{s1}-casein in goat milk, whereas the E allele produces intermediate amounts and the weak allele F produces the least concentrations of α_{s1}-casein in goat milk. Here we report on one of the first surveys of the distribution of α_{s1}-casein genotypes in US dairy goats. The population surveyed, consisting of a total of 257 American dairy goats representing 7 main dairy breeds, contained a greater predominance of the weaker alleles, E and F, than the strong alleles, A and B. Allele distribution was related to breed, with Toggenburg, Alpine, Saanen, and Oberhasli containing the most E and F alleles and LaMancha, Nubian, and Nigerian Dwarf the fewest. Quantification of α_{s1}-casein production by 2-dimensional gel electrophoresis demonstrated that F/F animals had the least amount of α_{s1}-casein protein in their milk compared with all other genotypes. The results indicate that genetic improvement of dairy goats in the United States could be achieved if an α_{s1}-casein breeding scheme were adopted.

Key words: α_{s1}-casein, genotype, goat, milk production

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INTRODUCTION

The concentration of α_{s1}-casein in goat milk is an important variable and can be attributed to the α_{s1}-casein genotype of the goat. In turn, α_{s1}-casein concentrations have been positively correlated with the amount of total solids, total protein, and casein in goat milk and have been related to increases in cheese yield, coagulation times, and firmness of the curd (Ambrosoli et al., 1988; Pirisi et al., 1994; Clark and Sherbon, 2000).

The goat α_{s1}-casein gene (*CSN1S1*) is highly polymorphic and, to date, 17 different alleles have been identified that can be associated with different concentrations of α_{s1}-casein in the milk (Grosclaude and Martin, 1997). The high-expressing, or strong, and desirable alleles for cheese making (A, B_1, B_2, B_3, B_4, C, H, L, and M) produce 3.5 g/L of α_{s1}-casein per allele (Brignon et al., 1989; Chianese et al., 1997; Martin et al., 1999; Bevilacqua et al., 2002). The intermediate alleles (E and I) each produce 1.1 g/L of α_{s1}-casein (Martin et al., 1999). The low-expressing, or weak, and undesirable alleles for cheese making (F, D, and G) produce only 0.45 g/L of α_{s1}-casein (Martin et al., 1999), and the nonexpressing, or null, alleles (O_1, O_2, and N) produce no α_{s1}-casein (Cosenza et al., 2003; Ramunno et al., 2005). The H, I, L, and M variants are rare and have been identified in local southern Italian breeds (Chianese et al., 1997; Bevilacqua et al., 2002).

The dairy goat population in the United States has been growing steadily, increasing at a rate of 4 to 5% per year since 2006 (National Agricultural Statistics Service, 2008). Despite the increasing size of the dairy goat population, widespread genotyping of US dairy goat breeds for casein variants has not been reported, even though the genetic data could be of use in breeding

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programs to select for animals with greater milk components for cheese-making purposes. Here we report a genotyping scheme for the major α_{s1}-casein alleles and the frequency of α_{s1}-casein alleles in a sampling of 257 goats, and we relate genotypes to casein concentrations in milk.

MATERIALS AND METHODS

All animals were cared for and housed in conditions approved by the Association for Assessment and Accreditation of Laboratory Animal Care.

Animals

A total of 257 animals were typed for the α_{s1}-casein genotype. Included were goats from the University of California-Davis dairy goat herd (n = 91) of the Alpine (n = 19), Saanen (n = 17), Toggenburg (n = 26), Oberhasli (n = 1), LaMancha (n = 24), and Nubian (n = 4) breeds. An additional 166 goats were selected from the University of California-Davis Veterinary Genetics Laboratory archives of dairy goat hair samples submitted for parentage testing by the American Dairy Goat Association. Breeds included Alpine (n = 23), Saanen (n = 22), Toggenburg (n = 29), Oberhasli (n = 23), LaMancha (n = 24), Nubian (n = 22), and Nigerian Dwarf (n = 23). These breeds were chosen based on their recognition by the American Dairy Goat Association as the main breeds used for milk production in the United States. For the sampling procedures, pedigree records were used to avoid inclusion of first-degree relatives. The animals sampled included both males and females that represented both the older and current breeding stock, as well as young animals. Allele frequencies were calculated from this group of animals by using the Microsoft Excel-based Microsatellite Tool Kit program (Park, 2002).

Milk samples for casein quantification analysis were obtained from a total of 29 lactating does at the University of California-Davis Dairy Goat Facility. These animals were kept in dry lots and fed the same diet, consisting of alfalfa hay and 3.3 kg of concentrate (corn, oats, barley, cottonseed), at each milking. All does were milked twice daily by machine, and samples were taken from each half of the udder at the morning milking after discarding the first 3 streams of milk. Equal amounts of milk per udder half were combined to make a composite sample for analysis and then stored at −20°C until analysis.

Genotype Analysis

The characteristics of the various goat α_{s1}-casein variants and their relationships to each other have been well documented. Briefly, the high-expressing alleles (A, all forms of B, C, H, L, M) all have single AA substitutions that do not disrupt the mature form of the protein (Brignon et al., 1989; Chianese et al., 1997; Martin et al., 1999; Bevilacqua et al., 2002). The E allele has a 457-bp LINE insertion in noncoding exon 19 that results in decreased messenger RNA stability and the subsequent reduced concentrations of α_{s1}-casein in milk associated with this intermediate-expressing allele (Jansa Perez et al., 1994). The low-expressing alleles (F, D, G) have internal AA deletions resulting in the production of an altered protein. The F allele is characterized by a deletion of the 23rd nucleotide of exon 9 and an 11-bp insertion in intron 9 (Leroux et al., 1992; Ramunno et al., 2000). These changes result in the outsplicing of exons 9, 10, and 11, leading to the deletion of 37 AA from the mature protein, including a cluster of 5 phosphoseryl residues, an important determinant of micelle and curd formation. The null alleles are the result of either large deletions of the gene beginning in exon 12 (O_1 allele; Cosenza et al., 2003) or the deletion of a single cytosine at position 23 of exon 9 (N allele; Ramunno et al., 2005).

Based on this information, the α_{s1}-casein genotype was determined using allele-specific PCR. Two sets of primers were used in multiplexed PCR reactions to identify the 5 most common variants, *CSN1S1*-A, *CSN1S*-B, *CSN1S1*-F, *CSN1S1*-E, and *CSN1S1*-N. Primer set 1 amplified a region spanning the exon 9/intron 9 junction from position 9,791 (primer F-F 5′-GTA TGG AAG TGT GGA ATA GTT T-3′; Bevilacqua et al., 2002) to 10,046 (primer F-R 5′-TGG GGG TTG ATA GCC TTG TA-3′) of the goat α_{s1}-casein gene (accession number AJ504711). This region includes the 1-bp deletion in exon 9 and the 11-bp insertion in intron 9 characteristic of the F allele. Furthermore, insertions and deletions within this amplified region have been associated with the A, B, E (Ramunno et al., 2000), and N (Ramunno et al., 2005) alleles. Therefore, with primer set 1, animals carrying the A, F, N, and B or E alleles can be distinguished based on the size of the resulting PCR product. The correspondence between PCR product size and the presence of an individual allele was confirmed by sequencing each sized PCR product from a subset of animals and comparing it with known sequences for each α_{s1}-casein allele (data not shown). Polymerase chain reaction products of 244 bp resulted for the A allele, 254 bp resulted for the F allele, and 243 bp resulted for the N allele (deletion, no insert). A 255-bp product was indicative of either the B or E allele. To distinguish between the B and E alleles, a second set of 3 primers was used [primer E-F 5′-CTA TCA TGT CAA ACC ATT CTA TCC-3′ and primer E-R 5′-CAA TTT CAC TTA AGG ATG TTA CAC-3′, both from Amills et al., 1997) from position 754 to 1,343 (accession number X72221), and primer E-EF 5′-TCC CAT TCT CCC AAA TCA TC-3′ at position 1,119]. Primer E-EF was located within the 457-bp LINE insert characteristic of the E allele. These primers amplified a region in exon 19 that corresponded to a 133-bp product for the B allele (no insert in exon 19) and 225 bp for the E allele (presence of an insert in exon 19). Again, the identity of each sized product of primer set 2 was

confirmed by sequencing a subset of animals (data not shown).

Three to 5 hair roots from each goat were incubated in 100 μL of hair lysis buffer [0.5% Tween 20, 1× PCR buffer (Applied Biosystems, Foster City, CA), 2.5 m*M* $MgCl_2$, and 0.1 mg/mL of Proteinase K) at 60°C for 45 min. The Proteinase K was then heat inactivated at 95°C for 45 min. Each PCR reaction of 25 μL total volume contained 2 μL of hair root solution as DNA template, 1× PCR buffer (Denville Scientific, Metuchen, NJ), 2 m*M* $MgCl_2$, 0.2 m*M* each deoxynucleotide 5′-triphosphate, 1 U of *Taq* polymerase (Denville Scientific), and dye-labeled primers at the following final concentrations: E-F(FAM) at 0.2 μ*M*, E-R at 0.4 μ*M*, E-EF(VIC) at 0.2 μ*M*, and F-F(FAM) and F-R at 0.16 μ*M* each. The PCR conditions consisted of 35 cycles of 93°C for 1 min, 56°C for 30 s, and 72°C for 45 s, with a final extension at 72°C for 30 min. The PCR products were first diluted 1:20 with water, and then 1 μL of each was combined with 10 μL of LIZ 500 size standard solution (Applied Biosystems) containing 5 μL of standard/mL of formamide. Amplicons were separated by capillary electrophoresis on ABI3730 instruments (Applied Biosystems). Fragment size analysis and genotyping were done with STRand software (Hughes, 2000).

Quantification of α_{s1}-Casein by SDS-PAGE and 2-Dimensional Gel Electrophoresis

Milk from at least 2 lactating does of each genotype was analyzed at 2 mo of lactation by using standard SDS-PAGE gels, followed by staining with Coomassie Blue. Total protein concentrations in milk were determined by a Bradford assay. Equal amounts of protein (200 μg) were loaded onto a 12% SDS-PAGE gel with the Precision Plus Protein Kaleidoscope prestained standard (Bio-Rad, Hercules, CA). Casein band intensities were measured using Alphaease FC software (AlphaInnotech Corporation, San Leandro, CA).

A total of 200 μg of protein was used for the 2-dimensional analysis of milk samples from does in their second month of lactation. Protein was precipitated from whole milk samples by the addition of 4 vol of ice-cold acetone, followed by incubation at −20°C for 30 min and centrifugation at 19,000 × *g* for 5 min at 4°C. Samples were resuspended in 200 μL of Immobiline DryStrip gels (**IPG**) rehydration buffer (0.5% ampholytes, pH 3 to 10, 15 m*M* dithioerythritol, and 8 *M* urea; GE Healthcare, Piscataway, NJ) and loaded onto 11-cm Immobiline DryStrips, pH 3 to 5.6 (GE Healthcare), by passive rehydration at room temperature. Proteins were separated by their isoelectric point in the first dimension by using a Protean IEF cell (Bio-Rad) at 65,000 Vh. For separation in the second dimension by size, the IPG strips were equilibrated twice for 10 min in IPG equilibration solutions (375 m*M* Tris-HCl, pH 8.8, 6 *M* urea, 30% glycerol, 2% SDS), first containing 65 m*M* dithiothreitol and then containing 135 m*M* iodoacetamide, after which the strips were loaded onto uniform 15% SDS-PAGE gels (Protean Xi, Bio-Rad) and run at 200 V for 1 h. Gels were then stained in Coomassie Blue (65 mL/gel) for 4 h with shaking, destained overnight in water, and scanned with an Epson 1680 Scanner (Epson, Long Beach, CA) to obtain an image of each gel. Proteins were quantified using the All-to-One warping strategy with Delta 2D gel analysis software (Decodon GmbH, Greifswald, Germany) as described previously (Valkova and Kültz, 2006). Individual spots were identified by extracting them from the gel for tryptic in-gel digestion and protein processing, using an Montage In-Gel Digest Zip Kit (Millipore, Billerica, MA), followed by matrix-assisted laser desorption ionization-time of flight/time of flight mass spectrometry as described by Valkova and Kültz (2006). Protein identification and annotation were carried out using GPS Explorer software with the Mascot search algorithm and DeNovo Explorer modules included in the 4700 Explorer software (Applied Biosystems). Differences in α_{s1}-casein concentrations between genotypes were analyzed by a Student *t*-test ($P < 0.05$; Microsoft Office Excel 2003, Microsoft Corporation, Redmond, WA).

RESULTS

Allele frequencies in the breeding population of the 257 selected animals were calculated (Table 1). Overall, the F allele was the most frequent (0.368), followed by the E and A alleles (0.257 and 0.235, respectively). The F allele was predominant in the Toggenburg breed (allele frequency of 0.927), and the E allele was predominant in the Saanen (0.705) and Oberhasli (0.542) breeds, whereas the A allele was more frequent in the LaMancha breed (0.583) and the B allele was more frequent in the Nubian breed (0.519). The E and F alleles were present in almost equal proportions in the Alpine breed (0.357 and 0.464, respectively), as were the A and B alleles in the Nigerian Dwarf breed (0.478 and 0.500, respectively). In terms of genotype distribution, Saanen goats were predominantly homozygous for the E allele and Toggenburg goats were homozygous for the F allele (Table 2). LaMancha and Alpine goats had the widest distribution of genotypes, consisting of mostly the strong A and B alleles and the weak E and F alleles, respectively. This distribution of the predominant alleles was the same in both subpopulations analyzed and across males and females (data not shown).

The effect of the α_{s1}-casein genotype on milk protein composition was analyzed. Differences in the amount of total casein present in milk could be visualized on Coomassie Blue-stained SDS-PAGE gels (Figure 1). Casein concentrations were greater when the strong alleles (A or B) were present. Compared with animals homozygous for the A allele, milk from F/F animals had 35% less casein and E/E animals had 25% less casein in their milk. The presence of an A or B allele in a heterozygote (with either the F or E allele) reduced the deficit in casein by only 5 to 7% compared with

Table 1. Frequency of the α_{s1}-casein allele by breed

Allele	Alpine (42)[1]	Saanen (39)	Toggenburg (55)	Oberhasli (24)	LaMancha (48)	Nubian (26)	Nigerian Dwarf (23)	All (257)
A	0.107	0	0.027	0.250	0.583	0.365	0.478	0.235
B	0.071	0	0	0	0.083	0.519	0.500	0.124
E	0.357	0.705	0.027	0.542	0.188	0	0	0.257
F	0.464	0.295	0.927	0.208	0.146	0	0.022	0.368
N	0	0	0.018	0	0	0.115	0	0.016

[1]Numbers of animals surveyed are shown in parentheses.

A/A does. Further analysis of milk samples using 2-dimensional gel electrophoresis allowed strong (A, B) and intermediate (E) alleles to be distinguished from the weak F allele by position on the gel, as well as by quantification of α_{s1}-casein concentrations (Figure 2). Goats of the F/F genotype made significantly less α_{s1}-casein than those of the F/E ($P = 0.009$) and E/E ($P = 0.029$) genotypes, and this amount approached significance for the 1 B/E goat ($P = 0.075$) analyzed.

DISCUSSION

The α_{s1}-casein genotype can have a profound effect on the milk production characteristics of dairy goats. Whereas α_{s1}-casein genotyping has been carried out in Europe since the early 1980s, application of this genetic test for dairy goats in the United States has been very limited. With the emergence of the dairy goat industry in the past few years, this type of analysis could be useful for producers and creameries. Here, we report the prevalence of the main α_{s1}-casein alleles and their correlation with casein concentrations in a sample of the main dairy goat breeds found in the United States.

The A, B, E, and F alleles account for the majority of the α_{s1}-casein alleles present in European milking breeds (Grosclaude et al., 1994). In our analysis, we found a predominance of the intermediate-expressing (E) and weak-expressing (F) alleles in Swiss-derived breeds, whereas Spanish- and African-derived breeds contained a predominance of the strong A and B alleles. The prevalence of the A and B alleles in our sample of Nigerian Dwarf goats was similar to that found by Caroli et al. (2007). Before selection for the α_{s1}-casein genotype in France, the E and F alleles were predominant in the French Alpine and Saanen breeds (Grosclaude et al., 1987; Mahe and Grosclaude, 1989). Alpine goats in France had frequencies of 0.41 and 0.34 for the F and E alleles, respectively, similar to our estimates of 0.46 and 0.36. Our findings with Saanen goats were different, with frequencies in our herd of 0.30 and 0.70 for the F and E alleles, respectively, compared with 0.43 and 0.41 for French Saanen goats. Strong alleles (A, B, C) in France accounted for frequencies of 0.2 in Alpine goats and 0.13 in Saanen goats, whereas we found a combined strong allele frequency of 0.18 for Alpine goats, and the Saanen goats sampled contained none of these alleles. These differences could be due to population variation but also to sample size because not as many animals were analyzed in our study. In France, frequencies of strong alleles (A, B, and C) were increased and the intermediate and weak alleles (E and F) were decreased over a 7-yr period when using AI with genotyped bucks (Grosclaude et al., 1994). In Alpine goats, the proportion of animals carrying strong alleles increased from 70 to 93%, and in Saanen goats, this proportion increased from 11 to 50%. If the allele frequencies estimated in our study are truly representative of American dairy goat herds, there is a clear indication that selective breeding programs are needed to improve the cheese-making quality of goat milk.

Table 2. Distribution of the α_{s1}-casein genotype by breed

Genotype	Alpine	Saanen	Toggenburg	Oberhasli	LaMancha	Nubian	Nigerian Dwarf	All
A/A	1[1]	—[2]	—	2	17	3	7	30
A/B	1	—	—	—	5	11	7	24
A/E	3	—	—	3	7	—	—	13
A/F	3	—	3	5	10	—	1	22
A/N	—	—	—	—	—	2	—	2
B/B	—	—	—	—	—	6	8	14
B/E	4	—	—	—	3	—	—	7
B/F	1	—	—	—	—	—	—	1
B/N	—	—	—	—	—	4	—	4
E/E	4	21	1	10	3	—	—	39
F/E	15	13	1	3	2	—	—	34
F/F	10	5	48	1	1	—	—	65
F/N	—	—	2	—	—	—	—	2

[1]Numbers of animals of each genotype.
[2]A dash (—) indicates that no animals of that genotype were found.

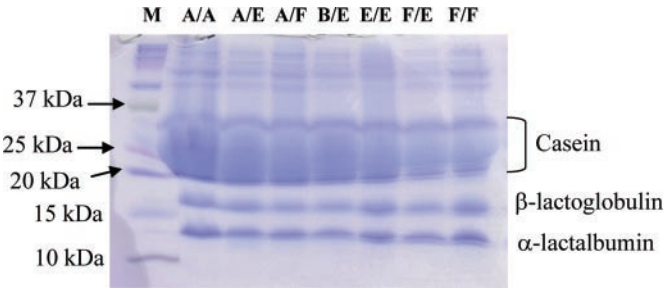

Figure 1. Sodium dodecyl sulfate-PAGE results of milk samples from goats with various α_{s1}-casein genotypes. Standardized amounts of milk protein from goats containing strong (A and B), intermediate (E), and weak (F) α_{s1}-casein alleles were run on a 12% SDS-PAGE gel and stained with Coomassie Blue. The genotype of the goat is indicated above each lane. Lane M contains a protein standard. Figure 1 is available in color online (http://jas.fass.org/content/vol87/issue11/).

The presence of the E and F alleles is associated with reduced α_{s1}-casein concentrations, milk protein content, and cheese yield (Grosclaude et al., 1987; Remeuf, 1993; Barbieri et al., 1995; Clark and Sherbon, 2000). Hence, selection for the strong alleles could be beneficial. In this work, we also demonstrated a correlation between α_{s1}-casein genotype and milk composition. Differences in casein concentrations and variants were evident on SDS-PAGE and 2-dimensional gels, with those containing the strong alleles having more α_{s1}- and total casein. Clark and Sherbon (2000) reported a positive correlation between milk components and α_{s1}-casein concentrations, without any genotype information. Interestingly, they found greater concentrations of α_{s1}-casein and milk components in the Nubian and LaMancha breeds than in the Swiss breeds, indicating a distribution of alleles similar to that found in our study.

When translated to gross milk composition, previous studies have found the protein and fat content of milk from F/F animals to be significantly less than those from A/A and E/E animals (Remeuf, 1993; Barbieri et al., 1995; Martin et al., 1999; Schmidely et al., 2002). Work by Hayes et al. (2006) using a multigene haplotype approach in Norwegian dairy goats resulted in significant effects of the α_{s1}-casein locus on the production traits of protein and fat percentages and fat yield, but not milk yield. This, along with other work using the haplotype approach (Caroli et al., 2006), suggests that the other casein genes play a role in the nutritional qualities of goat milk, and analysis of the whole haplotype (α_{s1}-, β-, α_{s2}-, and κ-casein) should be considered when selecting animals for breeding to obtain the desired milk qualities.

Overall, selection of animals for the strong α_{s1}-casein alleles could lead to improvements in milk composition and quality, particularly in protein content. It has been estimated that the substitution of a weak allele (F) with a strong allele (A) could increase the protein content of goat milk by 2.5 g of protein/kg of milk (Schmidely et al., 2002). This could be of great benefit for cheese production in the United States. In addition, goat milk with reduced α_{s1}-casein concentrations (null and weak alleles) has been associated with reduced milk sensitivity in some people with cow milk intolerance (Bevilacqua et al., 2001; El-Agamy, 2007), thereby providing another selection basis for fluid milk production based on human nutrition. In simulations, it was estimated

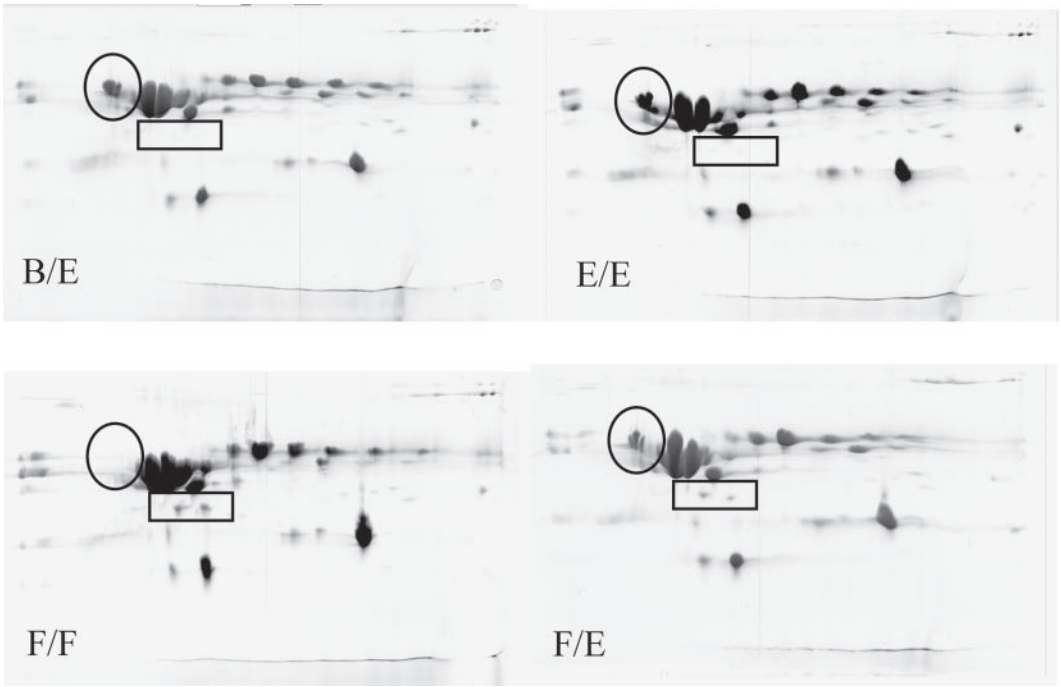

Figure 2. Two-dimensional gel analysis of milk from does with strong and weak α_{s1}-casein alleles. Different α_{s1}-casein variants were identified by 2-dimensional gel electrophoresis, followed by mass spectrometry. Circles represent the location of strong (B) and intermediate alleles (E), and squares represent the location of the weak (F) allele. The α_{s1}-casein genotype of each sample is indicated in the lower left corner of each gel.

that the best genetic gain in protein content would be achieved by using α_{s1}-casein genotype information for both sires and dams in selective breeding programs (Sanchez et al., 2005). Because of the low prevalence of strong alleles in the animals sampled in this study, genotyping for α_{s1}-casein could lead to genetic improvements in the American dairy goat population.

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