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The goat α_{s1}-casein gene:
A paradigm of the use of a major gene to improve milk quality?

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SUMMARY – Recent developments in molecular techniques have allowed for an easy identification of genotypes for major genes, with an important effect on quantitative traits, early in the life of candidates to selection. Using this genotypic information, together with performance values, may enhance the selection response. However, methods for combining genotypic and performance information should be designed specifically for each population and selection scheme. The case of the polymorphism of the major gene CSN1S1, coding for α_{s1}-casein, and its effects on casein content and renneting properties of milk is briefly reviewed, with particular reference to comparisons between French and Spanish breeds. Results of a simulation comparing different strategies for using CSN1S1 genotype information to improve selection response, under the specific conditions of main Spanish breeds, are given. Conclusions are drawn about the adequacy of different modes of using this information under different combinations of initial allele frequencies and average milk protein contents.

Key words: Goat, milk protein, α_{s1}-casein polymorphism, selection.

RESUME – *"Le gène de la caséine α_{s1} chez les caprins : Un paradigme de l'utilisation d'un gène majeur pour améliorer la qualité du lait ?". Les récents développements de la génétique moléculaire ont permis l'identification précoce et facile des génotypes des gènes majeurs, avec un effet important sur des caractéristiques quantitatives, dans les candidats à la sélection. L'utilisation de cette information génotypique, avec les valeurs des performances, peut améliorer la réponse de la sélection. Néanmoins, il faudra désigner les méthodes pour l'utilisation combinée de l'information génotypique et des performances des animaux spécifiquement pour chaque population et schéma de sélection. On fait une révision sommaire du cas du gène majeur CSN1S1, qui code pour la caséine α_{s1}, et ses effets sur le taux protéique et l'aptitude à la coagulation du lait, avec une référence particulière à la comparaison des races françaises et espagnoles. On présente aussi les résultats d'une simulation faite pour comparer différentes stratégies pour l'utilisation de ce polymorphisme sous les conditions spécifiques des races espagnoles. Des conclusions sont tirées sur l'adéquation de différents modes d'utilisation de cette information à différentes combinaisons des fréquences initiales des allèles et des valeurs moyennes du taux protéique.*

Mots-clés : *Chèvre, lait, protéine, caséine α_{s1}, polymorphisme, sélection.*

Introduction

The development of molecular techniques has generated methods for the identification of DNA markers (RFLP, RAPID, AFLP, SNP, etc.). These markers have been used to find regions of DNA closely linked to them with a quantitative effect on traits, the so-called Quantitative Trait Loci (QTL). Molecular techniques have also allowed finding major genes responsible for an important part of the genetic variance of some traits. Genotypes of animals (both males and females) for these QTL, or major genes, can be easily identified early in their lives. This has been proposed (in some cases they are already being used) as an aid to increase annual genetic gain through selection; what has been called Marker-Assisted Selection (MAS).

Potential results of MAS have been studied through simulation. Though not always comparable, due to differences between genetic structure of populations, selection schemes, selection intensities, QTL and major gene effects on the traits, some almost general conclusions can be derived from these works. One of these conclusions is that MAS renders higher genetic gains only when the QTL or the major gene has a large effect on performances (Fournet *et al.*, 1997; Larzul *et al.*, 1997; Manfredi *et al.*, 1998; Pong-Wong and Woolliams, 1998; Villanueva *et al.*, 1999). The other important conclusion is that standard selection leads to better long-term genetic gain due to the reduction of the selection intensity applied to polygenic background of the trait in MAS (Gibson, 1994; Ruane and Colleau, 1995; Fournet *et al.*, 1997; Larzul *et al.*, 1997; Pong-Wong and Woolliams, 1998). However, later studies by Dekkers and van Arendonk (1998), Manfredi *et al.* (1998) and Villanueva *et al.* (1999) showed that marker (QTL or major gene) and quantitative information can be optimally combined to obtain better response to both short and long term selection.

Milk protein polymorphisms have been thoroughly studied in the three domestic ruminant species. Their Mendelian inheritance has been proved and, in many cases, responsible genes have been mapped and sequenced. Methods for genotyping animals (both males and females) at a very early stage of their lives (even at born), using specific DNA probes, have been developed. Some of these polymorphisms have been proved to influence yield, composition, micelle organisation, renneting properties and cheese yields of milk (see reviews by Martin and Addeo, 1996; Barillet *et al.*, 1998; Moioli *et al.*, 1998; Trujillo *et al.*, 1998; Martin *et al.*, 1999) and they can be used in MAS programs.

The goat α_{s1}-casein polymorphism

The α_{s1}-casein was the first of protein polymorphism of goat milk to be studied. It was also the first for which an underlying genetic polymorphism was proved. The gene, CSN1S1, is the most polymorphic of all casein genes. The first 7 protein variants, described in the French Alpine and Saanen goats in the early nineteen eighties by Boulanger *et al.* (1984) on the bases of their different electrophoretic mobility, were classified into four groups, according to the average level of synthesis of the mature protein associated to each of them. First group was formed by the "strong" alleles, A, B and C, which were reported to have an average level of 3.6 g of α_{s1}-casein per kg of milk. Second group was constituted by only one "intermediate" allele, E, associated to an average level of 1.6 g/kg of this casein. The third group, with "weak" alleles D and F had an average effect of 0.6 g/kg. Fourth group is that of the "null" allele, which determines the absence of this casein in milk (Grosclaude *et al.*, 1987). More recent works, some of them carried out at field level (Barbieri *et al.*, 1995) and some other realised at a experimental station (Grosclaude and Martin, 1997; Martin *et al.*, 1999), have slightly modified these figures, maintaining the same relative ranking of variants.

Up to 15 additional alleles have been identified since the first works on this polymorphism were published (Martin and Addeo, 1996; Clark and Sherbon, 2000). Allele G, like alleles D and F, was associated with low average level of α_{s1}-casein synthesis. Allele B has been found to exist in three different forms, B1, B2 and B3, which became later B4 (Ricordeau *et al.*, 2000), all associated to a high synthesis of this protein. Other alleles have been found in very low frequency and can also be classified in one of the seven original groups.

The effects of this polymorphism on milk yield and composition, micelle structure, renneting properties and cheese yield have been thoroughly studied in French breeds (Remeuf, 1993; Grosclaude *et al.*, 1994; Mahé *et al.*, 1994; Vassal *et al.*, 1994; Barbieri *et al.*, 1995; Ricordeau *et al.*, 1996; Martin *et al.*, 1999; Ricordeau *et al.*, 2000). Results reported in these works can be summarised as followed: (i) no differences exist among genotypes with respect to milk yields; (ii) significant differences exist with respect to α_{s1}-casein, total casein and protein content; (iii) a significant effect of the polymorphism on fat content, not easy to explained, has been found in some of formerly cited works; (iv) milk from genotypes constituted wit "strong" alleles renders better renneting properties (faster coagulation and firmer curd) than "intermediate" genotypes, and these render better properties than "weak" genotypes; and (v) cheese yields of different genotypes are ranked in the same way as for renneting properties. A possible inconvenience of "strong" and "intermediate" genotypes has been found in relation with cheese flavour. Cheeses made with milk from these genotypes have less typical goat flavour than those from "weak" genotypes, due to different fatty acid profiles (Delacroix-Buchet *et al.*, 1996; Delacroix, 1998). It has, however, been discussed if this is really an effect of the CSN1S1 gene or a consequence of the lipolysis of fatty acids during cheese maturing.

The effects of this polymorphism have been studied also in Italian breeds (Pizzillo *et al.*, 1996; Marletta *et al.*, 2000; Meggiolaro *et al.*, 2000); Norwegian breeds (Vegarud *et al.*, 1999); and Spanish breeds (Díaz, 1993; Díaz *et al.*, 1994; Angulo *et al.*, 1996; Sánchez *et al.*, 1998; Analla *et al.*, 2000) and in a herd made with a mixture of breeds in USA (Clark and Sherbon, 2000). Results obtained in these breeds are qualitatively similar to those formerly described in French Alpine and Saanen, though they might quantitatively differ. In the case of the Spanish breeds, significant differences among CSN1S1 genotypes have been found for protein, casein and α_{s1}-casein contents and curd yield. Quantitative effects are slightly different than those observed in French breeds, but ranking of genotypes is the same (Table 1).

Table 1. Comparison of protein and casein contents (g/kg) of α_{s1}-casein genotypes in Malagueña and French Alpine goats

Genotypes	Protein		Casein	
	Malagueña†	Alpine††	Malagueña†	Alpine†††
AA	–	32.18	–	26.80
AB	34.70	–	26.40	–
BB	32.50	–	24.70	–
AE	29.50	30.26	22.42	–
BE	28.10	–	21.20	–
AF	–	29.81	–	–
BF	24.80	–	18.80	–
EE	27.40	28.80	20.60	22.80
EF	25.10	28.32	18.60	–
FF	–	27.63	–	20.70

†Angulo *et al.* (1996).
††Barbieri *et al.* (1995).
†††Remeuf (1993).

Gene and genotype frequencies vary between breeds. There seem to be two groups of breeds, those evolved from the Alpine lineage, with a higher frequency of "intermediate" and "weak alleles" and other breeds of other origins, where "strong" alleles prevail. Table 2 shows a comparison between gene frequencies observed in French Alpine and the most important Spanish breeds.

Table 2. Mean allelic frequencies of CSN1S1 locus in four Spanish dairy goats breeds and French Alpine (source: Jordana *et al.*, 1996)

Breeds	Sample size	Alleles					
		A	B	C	E	F	D + O
Murciano-Granadina	109	0.08	0.23	–	0.59	0.08	0.02
Malagueña	373	0.09	0.09	–	0.65	0.04	0.13
Payoya	111	0.05	0.19	–	0.76	–	–
Canaria	74	0.28	0.32	–	0.20	–	0.20
Palmera	22	0.68	0.23	–	0.09	–	–
Majorera	21	0.07	0.38	–	0.24	–	0.31
Tinerfeña	31	0.15	0.35	–	0.32	–	0.18
Alpine	213	0.14	0.05	0.01	0.34	0.41	0.05

Some research has been also done on other casein polymorphisms, particularly on the genes of α_{s2}-casein (CSN1S2) and β-casein (CSN2). With a null variant each of them (Persuy *et al.*, 1999; Ramunno *et al.*, 2001) which have an important effect on milk casein content. Nothing is known so far on the effect of the κ-casein polymorphism. Molecular genotyping of this gene (CSN3) has been recently described (Yahyaoui *et al.*, 2001). Neither is known the effect of haplotypes of these genes on milk composition and renneting properties.

Using goat α_{s1}-casein polymorphism to improve selection response

As it has been shown in previous paragraph, variation at the CSN1S1 locus is associated to an important influence on protein content in goat milk and to a smaller influence on protein yield. Genotype for this locus can, therefore, be used as an early (at birth if needed) selection criteria for both males and females. Manfredi *et al.* (1995) showed, in a retrospective study, that CSN1S1 genotypes of AI bucks are partial predictors of future progeny test results for protein traits. This information is presently used for pre-selecting Alpine and Saanen young males to be progeny tested in France (Manfredi *et al.*, 2000). However, the major gene variation only accounts for 48% of the additive variance of protein content and only 5% of the additive variance of protein yield. Therefore, specific methods should be developed in order to combine the genotypic information at the mayor locus with quantitative performance information on the trait. These methods will depend on the effect of the major gene on the selected trait, the selection scheme, selection intensities and the structure of the population being selected.

A simulation study was carried out to test three modes of combining these two sources of information under the specific population structure and the plausible selection schemes of the Spanish dairy goats. Twenty cycles of selection (one year per cycle) were independently simulated for each of two traits: Protein Yield (PY) and Protein Content (PC). Demographic, phenotypic and genetic parameters, as well as the effect of the "strong" and "weak" alleles on the traits, used in the simulation were estimated in the Malagueña breed. The latter were 0.6 and 2.2 phenotypic standard deviations for PY and PC traits, respectively. Details on these parameters and on the simulation procedures were described by Sánchez-Palma *et al.* (1998). Three modes of using CSN1S1 genotype information were simulated: (i) after indexing sires and dams (BLUP values obtained with an animal model) the best CSN1S1 genotypes among male kids, issued from the best indexed sires and dams, were selected (method S_1); (ii) genotype information was included only as a fixed effect in the animal model used for obtaining BLUP values for sires and dams (method S_2); and (iii) a combination of former modes of selection, using genotype information both in the genetic evaluation of sires and dams and for selecting male kids issued from coupling these high indexed sires and dams (method S_3).

The case where genotype information is not used at all was taken as reference (method S_0).

Results of these simulations are summarised in Table 3, where responses to selection, expressed as increments of polygenic and total genetic values between 1st and 20th selection cycles, as well as the rates of fixation of favourable are given for each of the methods and each of the traits considered.

Table 3. Polygenic (sub-indexed *p*) and genetic (sub-indexed *g*) response to selection[†] for the traits protein yield (sub-indexed *py*) and protein content (sub-indexed *pc*), expressed as phenotypic standard deviation units, and change of the favourable allele (A) frequency

Selection methods[††]	g_{ppy}	g_{gpy}	$\Delta f\ (A_{py})$	g_{ppc}	g_{gpc}	$\Delta f\ (A_{pc})$[†††]
S_0	3.11 ± 0.06^a	3.46 ± 0.06^a	+54.90	1.87 ± 0.05^b	3.63 ± 0.05^b	+80.00 (11)
S_1	2.99 ± 0.04^a	3.49 ± 0.04^a	+79.85 (13)	2.10 ± 0.04^a	3.86 ± 0.04^a	+79.70 (9)
S_2	3.08 ± 0.05^a	3.53 ± 0.05^a	+72.00	2.02 ± 0.06^a	3.79 ± 0.06^a	+79.80 (9)
S_3	2.88 ± 0.07^a	3.39 ± 0.07^a	+79.91 (12)	2.05 ± 0.04^a	3.83 ± 0.04^a	+80.30 (8)

[†] Response to selection expressed as increments of polygenic and genetic values between 1st and 20th selection cycles.

[††] See text for explanations on the different methods.

[†††] Change of frequency of favourable allele (A) between 1st cycle of selection and that of the year (in parenthesis) in which this frequency $f\ (A_{pc})$ is higher than 95%, or the 20th cycle of selection if the 95% is not reached.

[a,b] Values with different letters are significantly different at $p \leq 0.05$.

Evolution of the frequencies of favourable allele A in the cases of selection of traits PY and PC are shown in Figs 1 and 2, respectively.

This simulation shows, as it was expected, that using major gene CSN1S1 information yields higher genetic gains only when the major gene has a large effect on performances (more than 2 vs. less than 1 phenotypic standard deviations). Rates of fixation of favourable allele A are also much slower in the first case than in the second case. However, under the specific conditions of the population and selection scheme simulated, which are those which can be realistically developed for Spanish breeds, a decline of polygenic values and genetic gain in a long term is not observed.

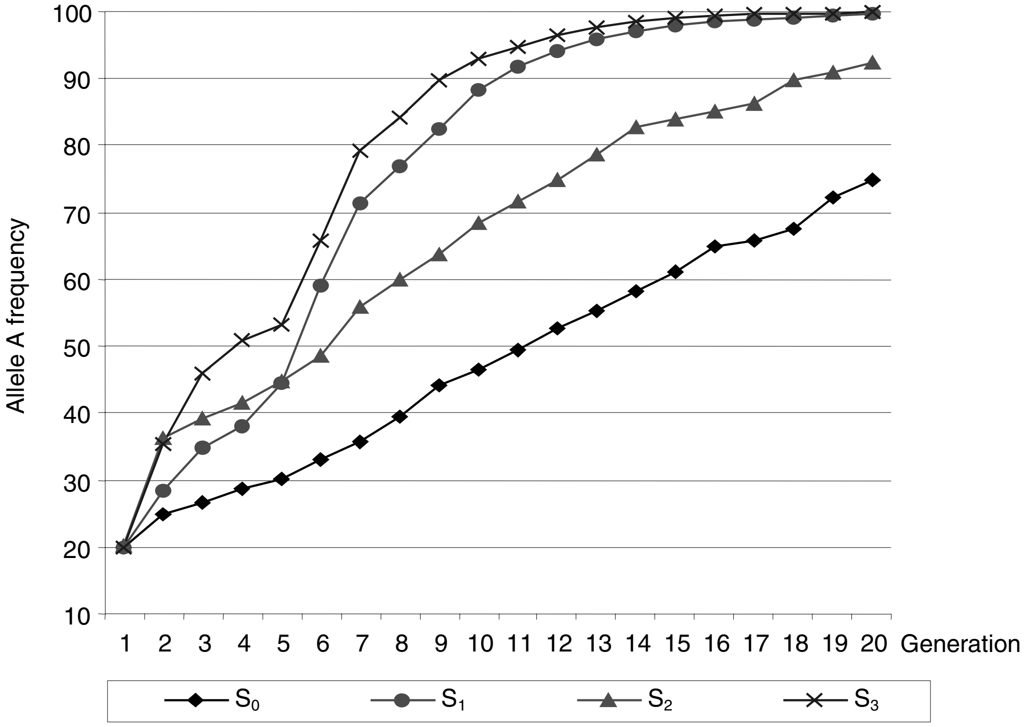

Fig. 1. Evolution of the frequencies of the favourable allele A when selecting for protein yield (source: Sánchez-Palma *et al.*, 1998).

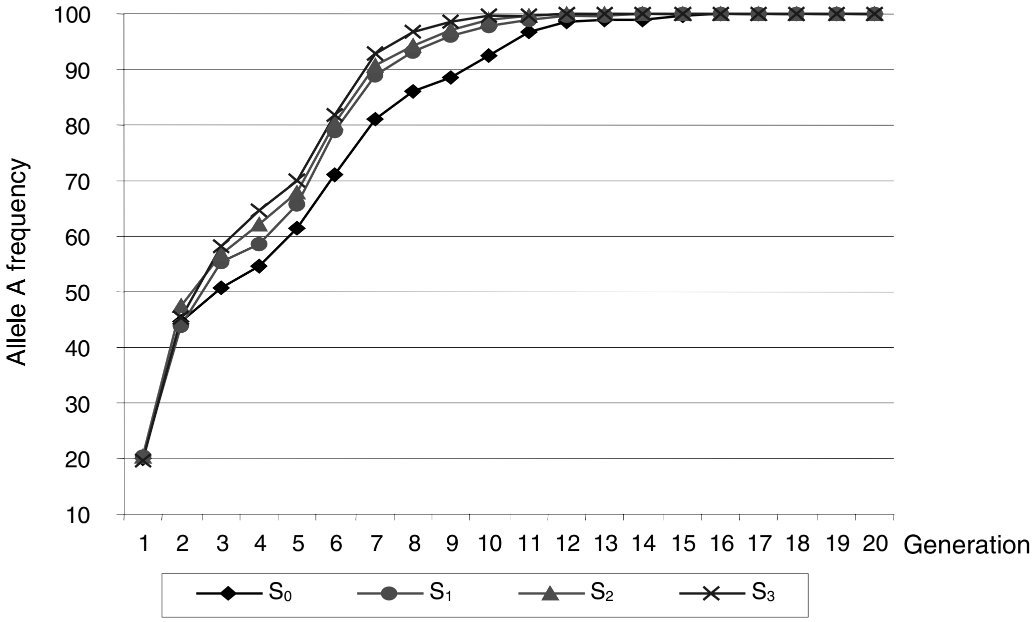

Fig. 2. Evolution of the frequencies of the favourable allele A when selecting for protein content (source: Sánchez Palma *et al.*, 1998).

No significant differences were found between the three methods which use genotypic information. Only slight differences were observed between them with respect to the rates of fixation. This has economic and organisational implications since second and third methods require genotyping all animals, while first method only requires genotyping young males issued from the best-indexed sires and dams. However, some authors (Dekkers and van Arendonk, 1998; Manfredi *et al.*, 1998) have proposed the use of indexes combining optimally performances and major genotype information, changing their relative weight over time according to the change of allele frequencies at the major locus. This is expected to enhance the selection response obtained in the long term. Moreover, using CSN1S1 genotype information to optimise matings, as suggested by Manfredi *et al.* (1998) may also improve long term response. Another reason to genotype all animals would be to discard as dams and sires those animals with null alleles for CSN1S2 and CSN2 loci.

Conclusions

Whether to use the CSN1S1 genotype information or not and the method to use it will depend on selection objectives and allele frequencies in the population. If the breed being selected has a low frequency of "strong" alleles and low protein and casein contents, genotyping all animals and applying the optimum combination of genotype and performance information to plan matings and to select male and female replacement will be meaningful. In the case of breeds with a relatively high frequency of "strong" alleles and high protein and casein contents, as some of the Spanish breeds, like Canaria-Palmera, and some other Mediterranean breeds, like Garganica and Maltese, using CSN1S1 genotype information does not seem very sound. It remains the case of some other breeds, like Murciano-Granadina and Malagueña in Spain, with not a very low frequency of "strong alleles", a relatively high frequency of "intermediate" alleles, relatively high protein and casein contents and low milk yields, for which the main selection objective will be to increase milk yield, maintaining present levels of protein contents. In these cases, according to the results of our simulations, using the major gene information only for selecting young males to be progeny tested seems a reasonable strategy, oriented mainly to maintain present levels of protein contents while increasing milk yields.

Further studies on the other casein polymorphisms and, particularly, on the effects of different haplotypes might modify these conclusions and encourage new research on the methods to use these major genes for selection.

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