

ORIGINAL ARTICLE

QTL detection for milk production traits in goats using a longitudinal modelD.L. Roldán¹, A.E. Rabasa², S. Saldaño², F. Holgado³, M.A. Poli¹ & R.J.C. Cantet⁴

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Summary

Eight paternal half-sib families were used to identify chromosomal regions associated with variation in the lactation curves of dairy goats. DNA samples from 162 animals were amplified by PCR for 37 microsatellite markers, from *Capra hircus* autosomes CHI3, CHI6, CHI14 and CHI20. Milk samples were collected during 6 years, and there were 897 records for milk yield (MY) and 814 for fat (FP) and protein percentage (PP). The analysis was conducted in two stages. First, a random regression model with several fixed effects was fitted to describe the lactation function, using a scale (α) plus four shape parameters: β and γ , both associated with a decrease in the slope of the curve, and δ and ϕ that are related to the increase in slope. Predictions of α , β , γ , δ and ϕ were regressed using an interval mapping model, and *F*-tests were used to test for quantitative trait loci (QTL) effects. Significant ($p < 0.05$) QTLs were found for: (i) MY: CHI6 at 70–80 cM for all parameters; CHI14 at 14 cM for δ and ϕ ; (ii) FP: CHI14, at 63 cM was associated with β ; CHI20, at 72 cM, showed association with α ; (iii) PP: chromosomal regions associated with β were found at 59 cM in CHI3 and at 55 cM in CHI20 with α and γ . Analyses using more families and more animals will be useful to confirm or to reject these findings.

Introduction

Most studies of quantitative trait loci (QTL) detection for milk production traits have been carried out in cattle, using mostly aggregated data (Zhang *et al.* 1998; Heyen *et al.* 1999; Plante *et al.* 2001; Viitala *et al.* 2003; Ashwell *et al.* 2004). Genetic associations between molecular markers and economically important traits in goats have been reported by Cano *et al.* (2007) and Marrube *et al.* (2007). However, the only well-documented genetic association with dairy traits in goats is the one related with the highly variable alpha S1-casein polymorphisms (Grosclaude

et al. 1994; Adnoy *et al.* 2003; Manfredi 2003; Suárez 2004; Sacchi *et al.* 2005). Analyses on QTLs affecting milk traits of dairy goats are lacking.

In searching for QTLs in goats, one may look at those significant associations found between milk production traits and genetic markers in cattle (reviewed by Khatkar *et al.* 2004), and take advantage of the homology between the genetic maps of the cow and the goat. Moreover, Rodriguez-Zas *et al.* (2002) measured the association between chromosomal regions and the scale and shape that describe the lactation curve in dairy cattle using a two-stage procedure: a random regression model to predict the

elements of the lactation function on an animal basis, followed by a regression interval mapping using the predictions obtained in the first stage of the analysis. The goal of this research was to identify chromosomal regions associated with variation in the lactation function of goats using the two-stage procedure employed by Rodríguez-Zas *et al.* (2002).

Material and methods

Description of phenotypic data

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

Genotypic data

Eight paternal half-sib families composed of 87 young females and 75 older goats were used for QTL detection. Whereas six families were purebred Criollo goats, the two other families consisted of Saanen by Criollo crosses. The Criollo goat is a local dairy-like breed living in harsh environments. The breed has remained almost unselected since its introduction from Spain nearly 500 years ago (Rodero *et al.* 1992). The number of females recorded for MY and FP or PP, and the number of genotyped goats per family are displayed in Table 1.

DNA was extracted from whole blood using the technique by Madisen *et al.* (1987). PCR reactions were carried out using fluorescence or γ ^{32}P ATP-primers labels as previously described by Cano *et al.* (2007), and the PCR products were separated by electrophoresis in denaturing polyacrylamide gels, and visualized in an automatic sequencer or in autoradiography. We selected four *Capra hircus* auto-

Table 1 Breed composition, number of recorded goats, total number of records and number of genotyped goats per half-sib family

Families	Breed composition	Number of recorded goats	Total number of records		Number of genotyped goats
			MY	Contents	
1	Criollo	30	114	112	25
2	Criollo	22	92	83	16
3	Criollo	26	107	91	25
4	Criollo	23	99	93	18
5	Criollo	19	78	67	15
6	Criollo	16	46	34	7
7	Saanen cross	20	85	74	14
8	Saanen cross	56	276	260	42
Total	–	212	897	814	162

MY, milk yield.

somes (CHI), based on the homologies between the genetic maps of cattle and goats and the significant associations summarized by Khatkar *et al.* (2004) in *Bos taurus* autosome (BTA) 3, 6, 14 and 20.

A total of 37 microsatellite markers (MS) were selected from the web genetic map resources (<http://locus.jouy.inra.fr/cgi-bin/lgbc/mapping/common/intro2.pl?BASE=goat>, <http://locus.jouy.inra.fr/cgi-bin/lgbc/mapping/common/intro2.pl?BASE=cattle>, <http://www.animalgenome.org/cattle/maps/db.html> and <http://bioinformatics.roslin.ac.uk>). The linkage maps were used as a guide for intermarker distance, and the microsatellites were positioned and ordered on the chromosomes with the CRI-MAP 2.4 program (Green *et al.* 1990). A summary of the informative markers used in the study across the four chromosomes are shown in Table 2. The average number of informative markers by autosome was 6 (ranging from 4 to 8), with an average spacing of 19.22 cM. The highest proportion of heterozygous sires averaged over all markers by chromosome was in CHI6. The average heterozygosity was 60.72%, and the average number of alleles by marker across families was 6.7. The markers showing the highest polymorphic information content (PIC) were microsatellites BM4621, BM143 and CSN, with PIC values of 0.798, 0.789 and 0.763, respectively, and located in CHI6.

Statistical analysis

The analysis was conducted in two stages. We first calculated the predictions of the random regression coefficients, and then we tested the effects of the chromosome regions on those predictions. The random regression model used in the first stage included the goat-specific parameters plus the predictions of

Table 2 A summary of the informative markers used across chromosomes

CHI	Number of markers	PIC	Proportion of heterozygous sires ^a	Marker distances (cM)
3	4	0.604	0.50	INRA006 (0.0), McM58 (23.4), INRA023 (29.7), HUJ177 (17.5)
6	5	0.665	0.62	BM1329 (0.0), BM143 (31.7), BM4621 (34.4), BM415 (23.3), CSN (42.3)
14	8	0.511	0.58	ETH225 (0.0), ILSTS011 (9.4), RM011 (26.8), CSSM66 (17.8), CSSM36 (9.1), BMC1207 (20.4), BM302 (36.5), BM4513 (38.8)
20	7	0.516	0.43	TGLA304 (0.0), TGLA443 (6.4), BM4107 (17.2), INRA036 (17.6), OarHH62 (13.2), ILSTS072 (10.9), BMS1719 (7.1)

CHI, *Capra hircus* autosome; PIC, polymorphic information content.

^aProportion of heterozygous sires averaged over all markers by chromosome.

individual breeding values and permanent environmental effects. The model equation was as follows:

$$\begin{aligned}
 y_{ijlnrs} = & c_l + b_n + d_r + p_s + \sum_{m=1}^5 \kappa_{nsm} \varphi(t)_m \\
 & + \sum_{m=1}^5 \psi_{imm} \varphi(t)_m + \sum_{m=1}^5 \tau_{im} \varphi(t)_m \\
 & + \sum_{m=1}^5 \pi_{im} \varphi(t)_m + \varepsilon_{ijlnrs} \quad (1)
 \end{aligned}$$

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

$$\begin{aligned}
 \sum_{m=1}^5 \lambda_{ijm} \varphi(t_{ij}) = & \alpha_i + \beta_i \left(\frac{t_{ij}}{280} \right) + \gamma_i \left(\frac{t_{ij}}{280} \right)^2 + \delta_i \ln \left(\frac{280}{t_{ij}} \right) \\
 & + \phi_i \left[\ln \left(\frac{280}{t_{ij}} \right) \right]^2
 \end{aligned}$$

where λ_{ijm} is either τ_{ijm} or π_{ijm} , and t_{ij} is the j th test-day for animal i . The scale parameter that character-

izes the overall level of the trait (MY, FP or PP) for the curve of individual i is α_i . The remaining parameters are responsible for the shape of the curve, and represent the rate of change of the trait at different stages of the lactation: β_i and γ_i are associated with a decreasing slope of the curve, and δ_i and ϕ_i with increasing slope. The lactation length was taken to be 280 days. The variance and covariance functions in the random regression model (1) were estimated by Restricted Maximum Likelihood using the program VCE5 (Kovac & Groeneveld 2003). The permanent environmental matrix (E) was estimated with a submodel of (1) in which the fifth and sixth terms were left out. To fit (1), E was split into 'across lactations' (E_B) and 'within lactation' (E_W) components, such that $E_W = 0.4 E$ and $E_B = (1-0.4) E$. The value 0.4 corresponds to the correlation between permanent environmental effects of first and second lactations. The estimates of the fixed effects, as well as of the additive genetic and permanent environmental effects were calculated by solving the mixed model equations using a program written in PROC IML (SAS Institute Inc 2005).

In the second stage, we performed a QTL analysis using the half-sib regression interval mapping method of Knott *et al.* (1996), with the software QTL Express (Seaton *et al.* 2002). The test statistics were computed every centiMorgan over the mapped chromosome. F -statistic thresholds for chromosome-wise level were calculated from 10 000 permutations (Churchill & Doerge 1994). Families that displayed the highest evidence for a QTL at the location in the across-family analysis were taken from the QTL-express output (Knott *et al.* 1996).

Results and discussion

The estimated heritability for MY ranged from 0.142 to 0.593, and the average estimated over the whole lactation period was 0.343. These values were in

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

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

For the QTL analysis, all significant *F*-statistics and their *p*-values for the three traits obtained from the regression interval mapping method of Knott *et al.* (1996) are displayed in Table 3.

Milk yield

Seven tests were significant for at least one parameter. In CHI6, we detected a significant effect for all parameters in the interval flanked for the MS

Table 3 *F*-statistics and *p*-values for the significant marker associations in at least one parameter of the lactation function for each milk production trait

Autosome	Traits	λ^a	Map position (cM)	<i>F</i> -statistics (p-values)	Family
3	PP	β	59	2.99 (0.01205)	5/7
6	MY	α	75	4.35 (0.00016)	7
6	MY	β	78	4.89 (0.00004)	7
6	MY	γ	75	4.38 (0.00016)	7
6	MY	δ	71	3.48 (0.00146)	7
6	MY	ϕ	70	3.20 (0.00293)	7
14	MY	δ	14	2.35 (0.04062)	7
14	MY	ϕ	14	2.42 (0.03559)	7
14	FP	β	63	2.63 (0.01300)	6
20	PP	α	55	4.49 (0.00056)	5
20	PP	γ	55	4.56 (0.00049)	5
20	FP	α	72	4.71 (0.00034)	5

MY, milk yield; FP, fat percentage; PP, protein percentage.

^aParameters of the lactation function. α , scale parameter; β and γ , decreasing slope; δ and ϕ , increasing slope.

BM4621 and BM415 (from 70 to 78 cM). One chromosomal region was associated with δ and ϕ on CHI14. Several studies based on cumulative single records in dairy cattle detected the presence of QTL at the genome-wise and suggestive thresholds on BTA3, in the interval from 16 to 32 cM (Heyen *et al.* 1999), at 39 cM (Plante *et al.* 2001), and at 40 cM (Vandervoort & Jansen 2002). On the other hand, neither Viitala *et al.* (2003) nor Ashwell *et al.* (2004), reported evidence of a QTL for MY on BTA3. Rodriguez-Zas *et al.* (2002) using test-day milk records reported a significant association between marker MS BL41 (32 cM) and the parameter that describes the shape of the function at the beginning of the lactation. Additionally, these workers reported significant associations between the scale parameter and two chromosomal regions of BTA3 that were located in the centromere from 0 to 36 cM and in the telomere from 91 to 113 cM (close to MS HUJ177 at 100 cM and MS BR4502 at 113 cM).

An association with increasing slope parameters δ and ϕ was found at 70 and 71 cM, respectively, on CHI6. Also at 75 cM, the scale parameter (α) and the descriptor of the shape at the end of the lactation (γ) were found to be significant. Another association with the remained descriptor of the decreasing slope (β) was detected at 78 cM. The correlation between the estimates of α , γ , δ and ϕ was high (0.922–0.998). Similarly, the correlation between β and the other parameters ranged from 0.652 to 0.758. Such correlations may suggest a QTL with pleiotropic effects on these parameters. Rodriguez-Zas *et al.* (2002) detected a putative QTL between 0 and 21 cM in dairy cattle that affected the scale parameter for MY. They also reported the finding of another QTL affecting the shape parameters for MY, which is located in the region from 108 to 129 cM. In dairy cattle, Zhang *et al.* (1998) reported a putative QTL in the interval between 30 to 50 cM on BTA6 (between MS BM1329 and BM143).

In the goat, the casein gene cluster has been mapped to the distal region of CHI6 (Grosclaude *et al.* 1994), and is composed of four genes (α S1-casein, α S2-casein, β -casein, and κ -casein). Moioli *et al.* (2007) reviewed the several associations between casein genes, and dairy traits of goats have been reported in the literature. This is especially so for the α S1 gene, which displays a higher level of polymorphism than the one observed in the bovine, and has been related to fat and protein contents (Grosclaude *et al.* 1994; Adnoy *et al.* 2003; Manfredi 2003; Sacchi *et al.* 2005). However, the effect of α S1 casein alleles on MY does not seem to be important

(Moioli *et al.* 2007). In the current research, we used α S1 casein gene as a marker gene (MS CSN) and did not find association to MY. A QTL on chromosome 6 of cattle located closer to the casein gene cluster was reported by Khatkar *et al.* (2004).

Moving to CHI14, there was evidence for a QTL at 14 cM (the interval flanked by ILSTS011 and RM011) related to δ and ϕ . This result suggests that there may be a QTL with pleiotropic effects on both parameters. It may also be the case that, due to the high correlation (0.996) between the estimates of those parameters, one of the associations observed may be a false positive. Similarly, Rodriguez-Zas *et al.* (2002) reported an association between the chromosomal region at about 13 cM on BTA14 (marker CSSM66), and the shape parameters that describe the changes in milk yield during mid and late lactation. However, in dairy cattle a QTL affecting MY was seemingly associated with BTA14 by Khatkar *et al.* (2004). Several studies in cattle reported QTLs for MY on BTA20. The chromosomal regions in the bovine were at 21 cM (Plante *et al.* 2001), 82 cM (Viitala *et al.* 2003) and 68 cM (Ashwell *et al.* 2004). In the current study, no microsatellite marker on CHI20 was associated with some lactation descriptors.

Fat percentage

Although several studies in dairy cattle reported a putative QTL on BTA3 and BTA6 affecting FP (Khatkar *et al.* 2004), we did not find evidence for the effects of a chromosomal region in either CHI3 or CHI6, at the chromosomal-wise threshold. However, for FP we detected significant effects from CHI14 and CHI20.

When analyzing CHI14, one chromosomal region at 63 cM (between CSSM66 and CSSM36) associated with variation of the parameter β was found significant. Conversely, analyses with dairy cattle found strong evidence for a putative QTL affecting FP near the centromere of BTA14, being the MS CSSM66 the nearest marker (Coppieters *et al.* 1998; Zhang *et al.* 1998; Heyen *et al.* 1999; Ashwell *et al.* 2004). A QTL proximal to the centromere on BTA14 with an effect on FP has consistently been reported (Grisart *et al.* 2002 and Winter *et al.* 2002), and the mutation underlying this QTL has been identified (Winter *et al.* 2002) as the K232A substitution in exon VIII of acylCoA/diacylglycerol acyltransferase 1 enzyme (*DGAT1*). This enzyme is considered to be of importance in controlling the synthesis rate of triglycerides in adipocytes. Nevertheless, no associations with several microsatellite markers on BTA14 were

found by Rodriguez-Zas *et al.* (2002) using a longitudinal mapping model. Comparing the goat and bovine linkage maps, CHI14 shows a partial homology with BTA14 from MS CSSM66 to the telomere. The centromeric region of CHI14 flanked between MS ETH225 and MS BM757, corresponds to the same region of chromosome 9 in cattle. Therefore, it is likely that an association with FP could be found near the centromeric end of CHI9.

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

Protein percentage

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

We did not find significant associations among chromosomal regions of CHI6 and any parameter when looking at PP. Nevertheless, many studies in dairy cattle have detected the presence of a QTL close to MS BM143 in BTA6 that is related to PP, and the marker position agrees in all these studies (Spelman *et al.* 1996; Zhang *et al.* 1998; Ron *et al.* 2001; Viitala *et al.* 2003). Using longitudinal phenotypic data, Rodriguez-Zas *et al.* (2002) found significant association between MS BM143 and the scale and the shape parameters at middle and late lactation for PP in dairy cows. Recently, Schnabel *et al.* (2005) performed a fine-mapping study of BTA6 of dairy cattle and identified the osteopontin (*OPN*) gene as an ideal functional candidate gene for a QTL very close to BM143. The *OPN* is a secreted glycoprotein and its expression in the murine mammary gland depends on the stage of postnatal development, which in turn suggests a role for *OPN* in mammary involution.

Lactation patterns

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

Although breeders do not usually breed for lactation shape, some traits such as persistence that are described by lactation curve parameters are economically relevant. We have looked at MY persistency. However, we did not find any significant association with any of the markers studied here.

General

Although the function of Ali & Schaeffer (1987) may suffer from high correlations among the five predicted parameters, Macciota *et al.* (2005) observed that certain combinations in the signs of the parameters were more prone to a high correlation than others. For the correlation patterns observed among the five predicted parameters ranged from 0.658 (correlation between β and ϕ) to 0.998 (correlation between α and γ). The function of Ali & Schaeffer (1987) is flexible as it allows accounting for differences in the rate of change in milk along the entire lactation, thus displaying a large number of different curves as described by Macciota *et al.* (2005).

A limitation of this study is the less number of animals involved in the analysis, which was coupled with a limited size of the half-sib families involved. Clearly, these results have low statistical power. Even if the results are not conclusive, they provide, nevertheless, a general idea of potential QTL locations in Criollo and Creole cross goats. Analyses using more families and more animals will be useful to confirm or to reject our findings.

To our knowledge, this is the first report in goats searching for chromosomal regions associated with variation in the lactation curve. Nine map positions were identified as affecting any parameter of the lactation function of dairy goats: one in CHI3, four in CHI6, two in CHI14 and two in CHI20. Some of these results were consistent with QTLs found in dairy cattle while using either aggregate lactation records, or longitudinal-linkage analysis.

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