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Quantitative Trait Loci Mapping for Growth Curve Variables in Ghezel Sheep

Research Article

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ABSTRACT

Understanding the genomics aspect of curve variable allows for the combination of genomic regions of such model-based variables from multiple measurements into a few biologically meaningful variables. With this motivation, the aim of the current study was a model-based quantitative trait loci (QTL) detection for growth curve variables in Ghezel fat-tailed sheep. We tested the following items during research: 1) Determining the best nonlinear growth models using six nonlinear equations (Von Bertalanffy, Gompertz, Logistic, Richards, Weibull and Brody) according to 24905 obtained data sets collected from the Ghezel Sheep Breeding Center, Iran, during the 1994-2013 period; 2) Conducted partial genome scan to identify significant QTl controlling best growth model parameters in Ghezel sheep using three half-sib families (Family size=25-50) and 8 microsatellite markers distributed on ovine chromosome 1. In addition, QTL effects for two paternal half-sibs using two models, individual families and across families were calculated. Molecular data were analyzed using SAS and GridQTL programs. Observed results demonstrated the Brody model was the best growth model for growth data according to the lower values of RMSE, AIC and BIC and generally greater values of R^2adj than other models. Thus, Brody model parameters (A, B, and C) were subjected to further QTL analysis. Also, our observation identified one significant QTL between the markers INRA11-CSSM004 associated with Brody model A variable (maturity) located in 123 CM in chromosome 1 ($P<0.01$). Analyses using more families and advance massive genotyping tools will be useful to confirm or to reject these findings.

KEY WORDS Ghezel sheep, Half-sib, microsatellites, QTL mapping.

INTRODUCTION

Knowing growth curve parameters and the ability to control the growth curve in the investigated population may be an interesting aspect for breeders in the first step of breeding programs. Understanding the genetic architecture of the growth curve and its longitudinal data is an interesting biological scenario to simplify different stages of growth.

Also, related reports about growth curve parct selection that could improve curve parameters during the economic life of animals (Ghavi Hossein-Zadeh, 2015a). To determine the genetic flexibility of the shape of growth curves, QTL studies must be done for the underlying curve variables. Mapping QTL controlling growth model parameters highlight the rate of heritability and contribution of additive genetics, which reflect direth curve parameters has been

reported in different species: mice, pigs, sheep and dairy cattle in the overall growth pattern (Gebreselassie *et al.* 2020), and mapping of age-dependent QTL for growth curve parameters enables the animal to complete its life cycle under many different circumstances. Whereas, there are many reports of QTL for body weight and several for rate of growth at specific age, there is relatively limited information on QTL for growth curve parameters in sheep (Raadsma *et al.* 2009).

Recently, (Duan *et al.* 2021) highlighted the applicability of growth curve parameters for genome-wide association study (GWAS) in beef cattle and addressed that longitudinal data versus single data records can better describe the growth and production of livestock. Some studies have been performed for the identification of QTLs and markers related to growth traits. For example, GWAS analysis identified statistically significant SNPs on chromosome 1. That is associated with Hu sheep's body height and chest circumference (Jiang *et al.* 2021). Also, for body weight were identified QTLs on chromosome 1 for Suffolk (Walling *et al.* 2004), and Charollais (McRae *et al.* 2005) breeds. For birth body weight were identified 5 QTLs and the peak locations of that QTLs are 322.66 (cM), 299.22 (cM), 299.15 (cM), 48 (cM), and 9.37 (cM) on chromosome 1 (Haldar *et al.* 2014; Ghasemi *et al.* 2019). Also were identified 4 QTLs in related average dairy gain on chromosome1 in Awassi and Merino breeds (Raadsma *et al.* 2009). However, there is still a deficiency of scientific evidence related to QTL and the genome region responsible for growth curve variables and the different stages of growth, so further study is needed to solve this puzzle. With this motivation, the aim of the current study was a model-based QTL detection for growth curve variables in Ghezel fat-tailed sheep. We tested the following items during research: 1) determining the best nonlinear growth models using six nonlinear equations (Von Bertalanffy, Gompertz, Logistic, Richards, Weibull, and Brody), and 2) partial-genome scan was conducted to identify significant QTL-controlling best growth model parameters in Ghezel sheep using 8 microsatellite markers distributed on ovine chromosome 1.

MATERIALS AND METHODS

Animals and sampling

For the present study the data on 24905 Ghezel Sheep collected from Breeding Center, Iran, during the period 1994-2013. Controlled natural mating was applied to the herd, and ewes are routinely bred to rams following heat detection. Ear tags were used to identify newborn lambs as the offspring of its ram within 1-3 hours of birth. Pedigree information and fixed effects (birth year, sex, type of birth and parity) were also recorded at lambing (Table 1, Figure 1).

Table 1 Summary of pedigree circumstance in the Ghezel

Items	values
Number of observations (N)	27537
Total and inbreeds in evaluated	93
Total sires	395
Progeny	5733
Total dams	10129
Progeny	17706
Individuals with progeny	10524
Individuals with no progeny	17013
Founders	9811
Progeny	13001
Sires	321
Progeny	4774
Dams	7427
Progeny	12222
With no progeny	2063
Non-founders	17726
Sires	74
Progeny	959
Dams	2702
Progeny	5484
Only with known sire	20
Only with known dam	11993
With known sire and dam	5713
Full-sib groups	574
Average family size	2.06794
Maximum	6
Minimum	2

Measurements

For present study the following traits were recorded: birth weight, adjusted weaning weight, and adjusted 6-month, 9-month, and yearling live body weight. These raw records plus fixed effect were subjected for statistical calculation to detect the best nonlinear growth models among six nonlinear mathematical equations (Von Bertalanffy, Gompertz, Logistic, Richards, Weibull, and Brody) according to the obtained data set. As a detail, a pedigree (number of animal per measurement class) summary of descriptive statistics was obtained: Male (13541), Female (10418), Single birth (20309), Twin birth (3577), Triple birth (73), a total of 34122 records, including BW (13282), WW (11080), 6W (7824), 9W (1936) and 12W (1114) were entered to the growth modeling process. The mathematic equations of the mentioned six non-linear growth curves are presented in Table 2.

PROC NLMIXED was run for weight records for all lambs, males, females, single and twin lambs; fitting of each model equation was done according to previous similar works for combinations of random effects; and the Gauss-Newton iterative method was applied using SAS version 9.6 software. The iterative process (Gauss-Newton iterative method in the present study) commences from starting values and applies derivatives or approximations to derivatives of the residual sum of squares with respect to the parameters to guide the search for the parameters producing the smallest residual sum of squares.

Figure 1 The image of Ghezel sheep

Table 2 Mathematical equations of six nonlinear mathematical models for growth curve modeling in sheep

Growth models	Equations	Parameters*			
Gompertz	$W_t = Ae^{(-Be^{-ct})}$	A	B	C	
Brody	$W_t = A(1 - Be^{-ct})$	A	B	C	
Logistic	$W_t = A(1 + Be^{-ct})^{-1}$	A	B	C	
Richards	$W_t = A(1 - Be^{-ct})^{M}$	A	B	C	M
Von Bertalanffy	$W_t = A(1 - Be^{-ct})^{3}$	A	B	C	
Weibull	$W_t = A - (Be^{-ct^{M}})$	A	B	C	M

W: body weight at age t (day); A: asymptotic weight, which is interpreted as mature weight; B: integration constant related to initial animal weight; C: parameter make the starting point be have as a relative value and M: parameter that gives shape to the curve by indicating where the inflection point occurs.
* The value of B is defined by the initial values for y and t.

The Gauss-Newton algorithm was chosen for iterations of nonlinear fit.

The maximum number of iterations used was 50 and the convergence criterion was: (Eq. (1)):

$$\{(SSE_{j-1}\text{-}SSE_j|SSE_j + 10^{-6}\} < 10^{-8}$$

Where:
SSE: residual sum of squares after fitting the function to the data.
j: round of iteration, as defaults for SAS.

To compare the suitability of the models, lower values of root mean square error (RMSE), Bayesian information criterion (BIC) and Akaike's information criterion (AIC) criteria and generally greater values of adjusted coefficient of determination (R^2_{adj}) were assumed as best model and goodness of fit for growth than other models, and parameter values for each model and their standard errors were derived from the iterative process.

Molecular analysis

Overall, 105 individuals from three half Sib families (size=25-50) were selected from the whole population and then the microsatellites located in chromosome one were used to determine the genotyping process. The marker spacing on the chromosomal map was between 5 to 40 cM. Figure 3 displays Pedigree diagram of three established half Sib families for QTL study.

DNA extraction, PCR reactions, and samples genotyping

DNA was extracted according to Shams *et al.* (2011) instruction. Assessment of purity and quality measurements for obtained DNA was done using a NanoDrop machine (Model: NanoDrop™ 2000/c, Thermo Fisher Scientific).

Overall, eight polymorphic microsatellites' loci located on chromosome 1 were used for preliminary screening of heterozygosity on candidate rams. Table 3 present summary of investigated microsatellite loci for QTL analysis.

The amplification process of each microsatellite loci following PCR reactions and thermal cycle program was optimized and fixed: The final volume of PCR reactions was adjusted to 25 µL with: 50-100 ng of genomic DNA, 1X master mix kit (Ampliqon Company) and 0.5-1 µ forward and reverse primers and calculated residual ddH2O. T- gradient Thermo cycler (Germany) and touchdown program with initial 10 cycles (descending slope 68 to 58 per each

cycle) and followed initial denaturation 95 ˚C, 5 min and 25 cycles for 95 ˚C, 45s, 57 ˚C, 45s, 72 ˚C, 45s, and a final extension of 5 min at 72 ˚C. Finally, the PCR products were run through 6% MetaPhor gels at 65 V for 2 or 3 h, depending on the expected allele sizes, but the 25 bp ladder and those observed genotypes did not meet our expectation (polymorphism, Mendelian heredity and sharpness) were eliminated for further assessment within half Sib families.

Model-based QTL detection was estimated using individual families and across-families models (Knott *et al.* 1996). When the half-sib family is sufficiently large, it may be assumed that the offspring receives a random sample of the possible alleles at the marker locus from the dams. As there is no information about the genotype of the QTL, significant differences between the two phenotypes' mean of the two groups of offspring will be indicative of the presence of a QTL near the markers. The statistical analysis is based on a linear model developed by Soller and Genizi, (1978) displayed here in Eq. (2):

$$Y_{ijk} = \mu + S_i + M_{ij} + e_{ijk}$$

Where:
Y_{ijk}: phenotypic value for the k^{th} offspring of the i^{th} sire which receives the j^{th} marker allele.

μ: population mean of the trait.
S_i: effect of the i^{th} sire (1, 2).
M_{ij}: effect of the j^{th} marker allele of the i^{th} sire.
e_{ijkl}: residual effect.

Knott and Haley, (1992) suggested a regression model to find the QTL position in the chromosome, as shown in Eq. (3):

$$Y = \mu + aX_1 + \beta X_2 + e$$

Where:
y: observed phenotype.

$$X_1 = P(QQ/M_i) - p(qq/M_i)\ X_2 = P(Qq/M_i) \qquad (4)$$

In Eq. (4), X1 and X2 are probabilities for QTL genotypes conditional to the flanking marker genotypes. All suggestive and significant thresholds were calculated following the guidelines of (Lander and Kruglyak, 1995) using a permutation test (Churchill and Doerge, 1994) and all collected QTL data were analyzed using GridQTL software.

RESULTS AND DISCUSSION

Observed results demonstrated that the Brody model was the best growth model for growth data (and therefore highlighted in Table 4), according to the lower values of RMSE, AIC and BIC and generally greater values of R^2_{adj} than other models. Thus, Brody model parameters ((A, B and C) were subjected to further QTL analysis. Statistically, the effect of factors such as year and season of birth, sex, litter size, parity, and family number (fixed effect) on Brody growth model question parameters (A, B and C) was significant (P<0.05). Also, can be seen from the data in Table 1 that some graphical growth model fitness for Ghezel population.

Table 3 shows polymorphism and allelic size at the 8 microsatellite loci for the three half Sib families within the MetaPhor agarose gel. All microsatellite loci were amplified and produced a minimum of 2 and a maximum of 10 alleles ranging from 120 to 220 bp in size. Loci INRA11 and CSSM11 produced the highest and the lowest observed number of alleles, respectively. Figure 2 illustrated a graphical description of investigated growth data fitted with four different models. The pedigree diagram of three established half Sib families for the QTL study is displayed in Figure 3. Figure 4 compares the quality of genotyping process per investigated locus using horizontal electrophoresis and metaphor agarose visualization. Also, as shown in Table 5 summary of molecular diversity criteria for six microsatellites across families. Figure 5 shows an overview of molecular genetic descriptive statistics for investigated microsatellite loci across all families. It illustrated that information of content (CI) and F-statistic curves resulted from the joint analysis of half-sib families on chr. 1 of sheep.

Our observation identified one significant QTL between the markers INRA11-CSSM004 associated with Brody model A variable (maturity), located in 123 CM in chr. 1 (P<0.01). In this study, we investigated the growth curve pattern and variability of model-based parameters for the identification of QTL controlling growth in sheep.

In this report, the best non-linear growth models using six non-linear equations (Van Breittalenfy, Gompertz, Logistic, Richards, Weibull, and Brody) were done. The study results provided some interesting findings regarding the Brody model as the best nonlinear growth model for growth data according to the lower values of RMSE, AIC, and BIC and generally greater values of R2adj than other models. Thus, Brody model parameters (A, B, and C) were subjected for further QTL analysis, like our study. Most prior research has applied Van Breittalenfy, Gompertz, Logistic, Richards, Weibull, and Brody models for fitting initial growth records to produce the shape of the curve in small ruminants. A similar conclusion was reached byaboutKordi sheep; Sonadi sheep (Gautam *et al*. 2018); Mehraban sheep (Hojjati and Hossein-Zadeh, 2018); Deccani sheep (Nimase *et al.* 2017) and Guilan sheep (Ghavi Hossein-Zadeh, 2015a).

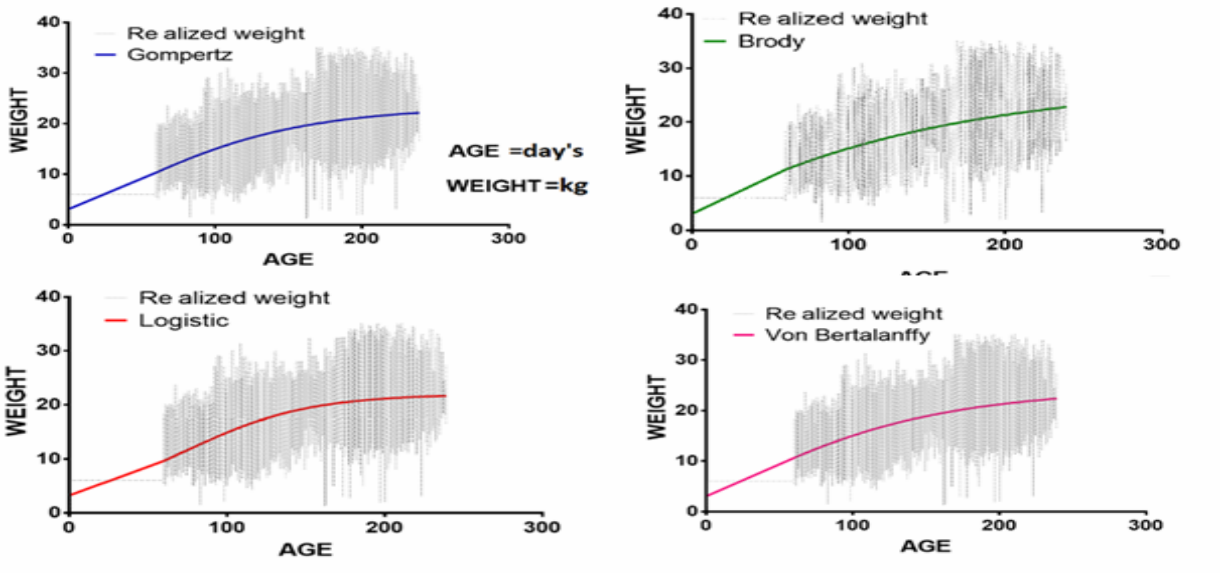

Figure 2 Some fitted graphical based growth model for ghezel population

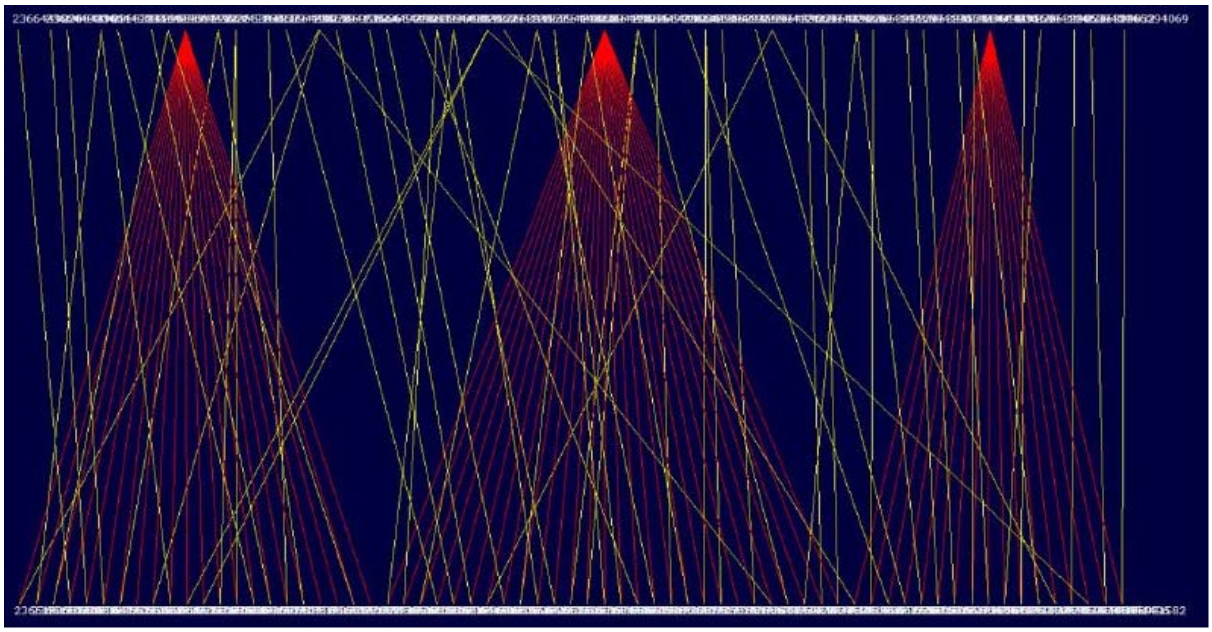

Figure 3 Pedigree diagram of three established half sib families for QTL study (family size: 25-50) with pre assumption of heterozygous ram per each investigated SSR locus. Red lines representative of Rams with their candidate half-sib progenies for QTL mapping

Overall these findings are in accordance with findings reported in the present study. Several other research studies with highlighted Logistic (Verhulst, 1845, 1847) growth model showed that it was the best and most suitable fitted model for Spanish Merino, Fleischschaf, and crossbred (Fleischschaf×Merino) lambs (López *et al.* 2018), as was the Richard model for Shall sheep (Ghavi Hossein-Zadeh, 2015b) and Van Breittalenfy mathematical equations for Kermani sheep (Mokhtari *et al.* 2019). Their findings were inconsistent with this work.

There are several possible explanations for inconsistent results, including different environmental conditions influencing animals during measurement and recording, for instance, differing feeding regime of different sheep breed; and the variation in the determination of the most appropriate model, which can be due to genetic background and also the method of weighing animals (traditional scale and modern digital scale) and adjustment methods for the body weight of animals in age after birth weight.

Table 3 Microsatellites' loci characteristics, motifs, and expected allele sizes in this study

Locus	Primer sequence	Motif sequence	Annealing	Allelic size (bp)	NCBI probe ID[2]
MAF64	F:AATAGACCATTCAGAGAAACGTTGAC R:CTCATGGAATCAGACAAAAGGTAGG	(GT)13	63	109-141	9715826
ILST004	F:CTTAAAATCTGTCTTTCTTCC R:TAGTGTGTATTAGGTTTCTC	(CA)16	50	90-106 100	9715827
INRA11	F:CGATTTCTTTCCTCGTGGTAGGC R:GCTCGGCACATCTTCCTTAGCAAC	-	55	183-186 196-220	9715833
CSSM04	F:ATGCGTCCTAGAAACTTGAGATTG R:GAAATCATCTGGTCATTATCAGTG	(GT)10(T)5	61	173-197	9715830
CSSM011	F: GCCTGGAAAACTCCTTGAACAGAG R: AACACAGGGAAGTTTGTCATACTC	(CA)3.CG.(CA)12	65	157-195	9715830
MAF109	F:GGAAGATTAGAACTTTCATATATCTTTAAACTC R:AATTGAATTTGAAGTGTATATGCCTAAATGC	(CT)7,TT,CT)14(AT)6,GT,(AT)8	58	137-155 143-159	9715846
CSSM32	F:TTATTTTCAGTGTTTCTAGAAAAC R:TATAATATTGCTATCTGGAAATCC	(CA)19	55	206-220 226	9715845
CSSM19	F:TGTTTTAAGCCACCCAATTATTTG R:TTGTCAGCAACTTCTTGTATCTTT	(TG)18	58	203-215	9715850

Table 4 Determining the best nonlinear growth models

Models	AIC	AICC	BIC	S^2e	-2 loglLkli-hood	R^2	r
Gompertz	158456	158456	158489	2626.29	158448	0.6515	0.8071
Brody	**156435**	**158435**	**156427**	**27.0312**	**156427**	**0.8688**	**0.9321**
Logistic	160899	160899	160931	32.2020	160891	0.8453	0.9194
Richards	155853	155853	155893	26.4388	155843	0.8214	0.8971
Von Bertalanffy	157665	157665	15768	28.3673	157657	0.8624	0.9287
Weibull	177812	177812	177852	62.5072	177802	0.6967	0.8347

AIC: akaic information index; AICC: AIC corrected; BIC: bayesian information index; S^2e: mean square error; -2 loglLklihood: negative logarithm likelihood; R2: recognition coefficient and r: correlation coefficient.
Bold font numbers representative of significant suitable model.

We hypothesized this research platform may create several advantages, such as a significantly reduced dependency of QTL analysis to volume of phenotypic data, reducing computation time, particularly during permutation to meet the significance thresholds level; and increased accuracy of outputs with unbalanced phenotype data and finally opening new avenues to understand clear biological meanings of growth curve variables. Many good alternative methods for targeting breeding traits need repeated measurement over the animal's lifetime.

QTL mapping in half-sib families in growth model – based variables have been used to search for the possibility of transmission from heterozygote genome segment originated from rams to their offspring through a pedigree (Seyedsharifi *et al.* 2020).

Our results demonstrated that one significant QTL between the markers INRA11-CSSM004 is associated with Brody model A variable (maturity) when located in 123 CM in chr 1 (P<0.01).

When comparing our results to the Animal QTL database and older studies, it must be recognized that from more than 3,562 QTL extracted from 186 scientific had already been reported, related to 270 different traits for sheep species and in details. Only chr. 1 carries 256 QTLs for different health traits, wool traits, meat and carcass traits, production traits, reproduction traits, milk traits, and exterior traits.

The present study showed QTLs for growth and body weight on chromosome 1, agreeing with earlier reports. The QTL for birth weight was significant when the family analysis was conducted for chromosome 1 in families one and two. Individual family analysis showed a significant QTL (P<0.051) for BW90 on chromosome 1 segregating in family one.

Most literature describes and highlights the important role of genomic regions located in sheep chr 1 for controlling growth traits, for example, QTL for birth weight in the Brahman breed (Lien *et al.* 2000), conformation traits in Japanese Black cattle (Malau-Aduli *et al.* 2005). Reviewed from literature, approximately 3430 genes and coding genome regions were identified only in chr 1 on sheep transcriptome and most of the identified QTL related to growth and body weight in flanking regions and map position of the *POU1F1* gene, a strong candidate gene for growth traits (Gebreselassie *et al.* 2020; Woollard *et al.* 2000) as well as on the SLC9A9 gene located in ovine chromosome 1 physical map.

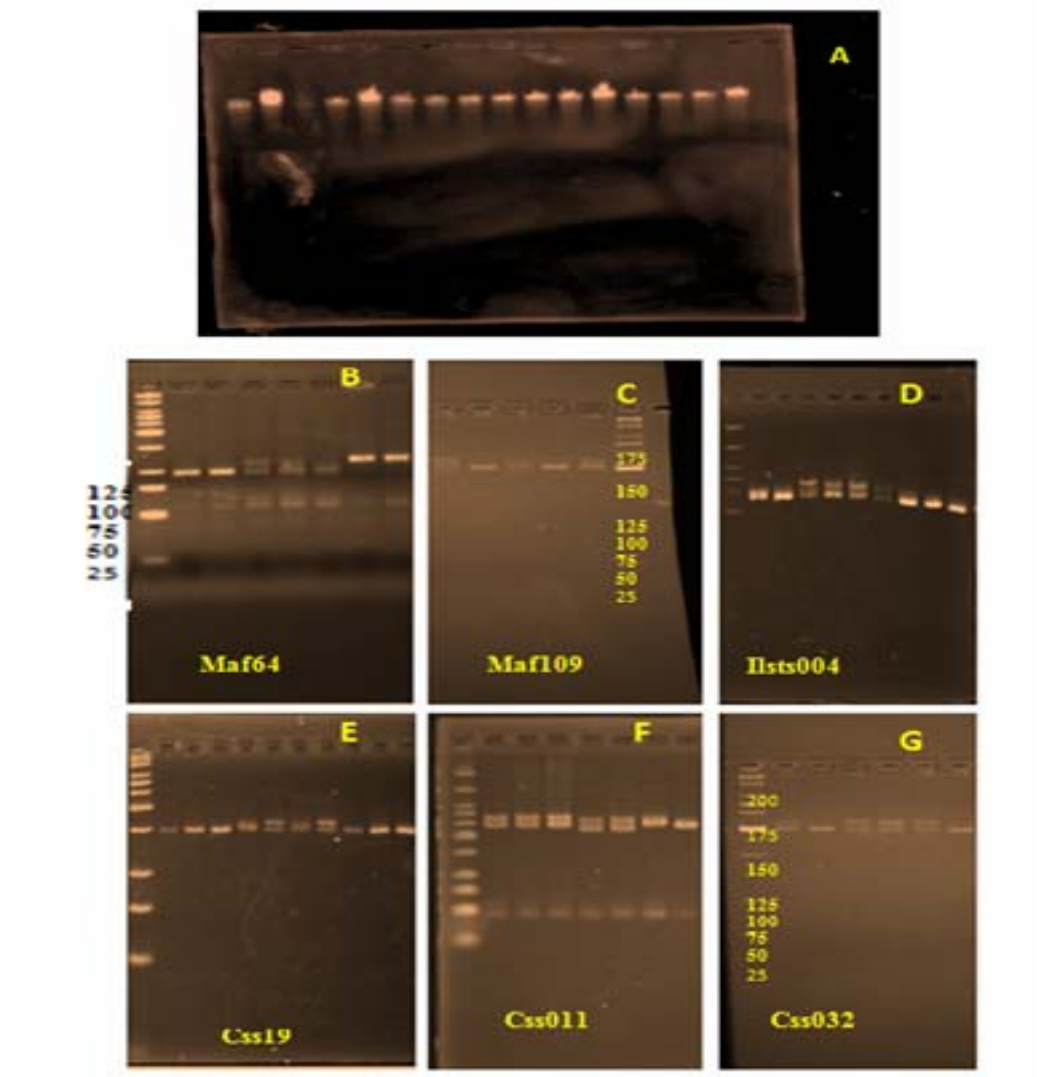

Figure 4 Quality of genotyping process per investigated locus using horizontal electrophoresis and MetaPhor agarose visualization
A: quality and quantity of extracted genomic DNA; B: Maf64 genotype; C: Maf109; D: ILsts004; E: Css19 and F: Css011 and G: Css032 microsatellite genotype
One band are homozygote and two bands are heterozygote genotype for each microsatellites locu

Table 5 Molecular diversity criteria for six microsatellites across families

Locus	Na	Ne	I	Ho	He
MAF64	6.000	4.720	1.637	0.787	0.788
ILST004	8.000	3.889	1.585	0.813	0.743
INRA11	9.000	4.910	1.806	0.796	0.796
CSSM04	6.000	4.148	1.562	0.787	0.759
CSSM011	2.000	2.000	0.693	0.000	0.500
MAF109	10.000	4.205	1.719	0.840	0.762
CSSM32	6.000	3.599	1.465	0.755	0.722
CSSM19	7.000	4.477	1.660	0.863	0.777

Na: observed allele; Ne: expected allele; I: Shannon index; Ho: observed heterozygosity and He: expected heterozygosity.

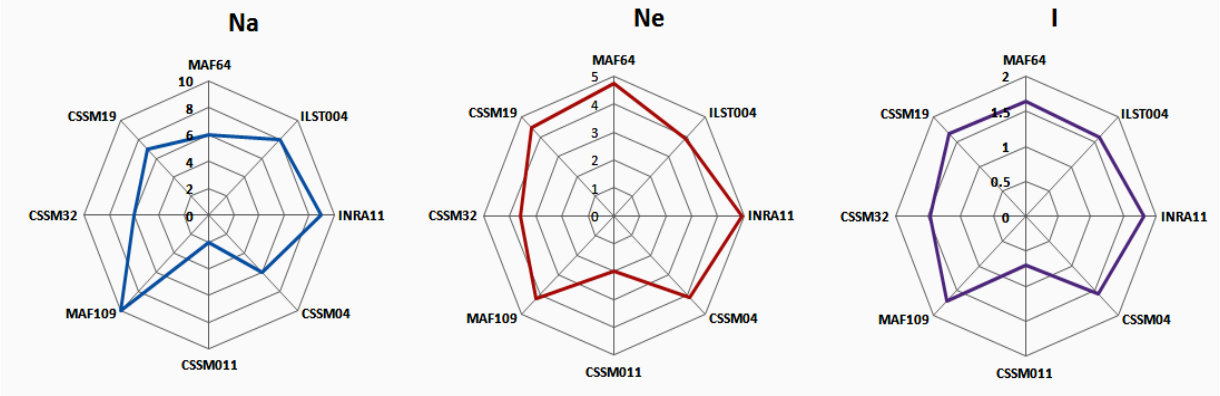

Figure 5 Overview of molecular genetic descriptive statistics for investigated microsatellite loci across all families
Na: observed allele number; Ne: expected allele number and I: Shandon index

Table 6 Summary of related literature about QTL identification for growth in chr 1 in livestock

Author	Country	Breed	Marker	QTL location	QTL peak	confidence level(cM)	Closest marker(s)	Trait
(Raadsma *et al.* 2009)	Australia	Awassi, Merino sheep	Microsatellite	87.3 (cM)	81.03-81.23 (cM) 62.9-63.0 (Mbp)	< 0.05	BM4129	Body weight and growth
(Visser *et al.* 2013)	South Africa	Angora goat	Microsatellite	-	-	None	-	Pre-weaning growth
(Seyedsharifi *et al.* 2021)	Iran	Sanjabi lambs	Microsatellite	235(cM) 225-238(cM)	-	None	MCM130 MCM137	Growth trait
(Walling *et al.* 2004)	UK	Suffolk sheep Texel sheep	Microsatellite	BMS2321 BMS1789	227(cM)	< 0.05 < 0.01	BM8246 and McM130	Growth trait
Our study	Iran	Ghezel sheep	Microsatellite	591(cM) 689(cM)	591(cM) 689(cM)	< 0.05 < 0.01	Cssm019 Cssm032	Pre-weaning growth

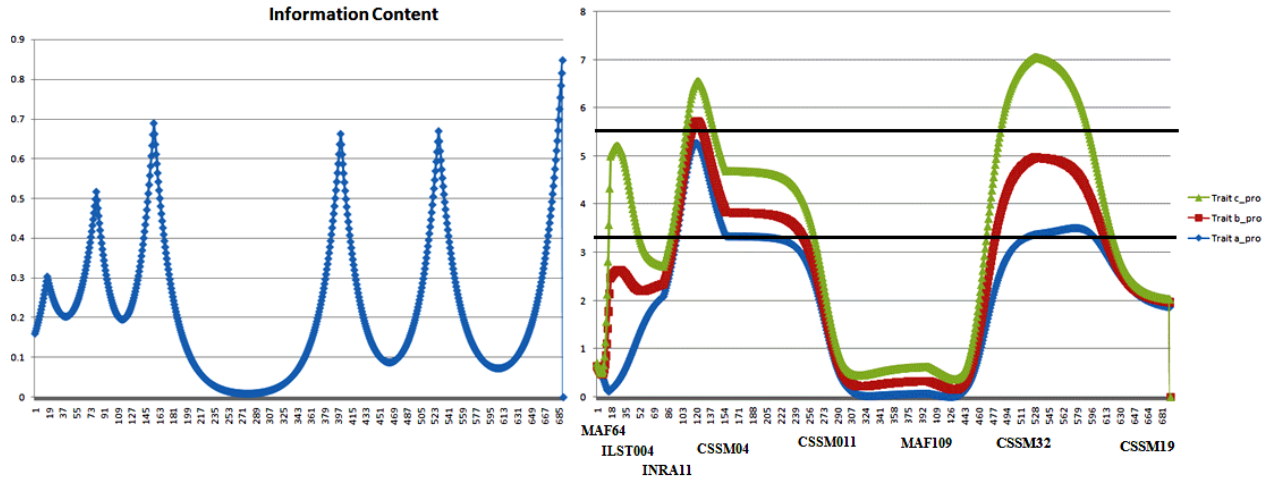

Figure 6 Graph for information of content (CI) and F-statistic curves resulted from the joint analysis of half-sib families on chromosome 1 of sheep
The lower and upper horizontal lines represent five and 1% chromosome-wide significant levels of linkage, respectively

Table 6 provides some related literature about QTL identification for growth in chr 1 in livestock.

As logical justification, the reason for a difference in the present result with other findings seems mainly due to different sheep breeds and geographical, chromosomal regions, investigated microsatellite loci, genotyping technique and, which may influence the output of analysis and interpretation of raw data.

There are limitations in this study: natural service was a routine breeding program for Ghazel sheep breeding station and several different HF families and offspring within each paternal HF families were affected due to this natural barrier. Only two sires exhibited heterozygote patterns for most of the investigating loci and analyses; using more families and more animals will be useful to confirm these findings.

There are limitations in this study: natural service was a routine breeding program for Ghazel sheep breeding station and a number of different HF families and offspring within each paternal HF families affected due to this natural barrier. Only two sires exhibited heterozygote patterns for most of investigating loci and analyses using more families and more animals will be helpful to confirm these findings.

CONCLUSION

Based on our results, we conclude that the Brody model is the best growth model for growth data given its lower values of RMSE, AIC and BIC and generally greater values of R2adj than other models. Thus, Brody model parameters (A, B and C) were subjected to further QTL analysis. Our observation identified one significant QTL between the markers INRA11- CSSM004 associated with Brody model A variable (maturity) located in 123 cM in chr 1 ($P<0.01$). To our knowledge, this is the first report of growth model–based QTL analysis in Ghezel fat-tailed sheep. Future GWAS and variant calling–based evidence in whole genome sequencing / next-generation sequencing investigations are necessary to validate the kinds of conclusions that can be drawn from this study.

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