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Effect of Single Nucleotide Polymorphisms in *IGF-1R* Gene on Growth Rate Traits in Makooei Sheep

Research Article

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ABSTRACT

Insulin-like growth factor 1 receptor (IGF-1R) is a main receptor of IGFs family which plays a critical role in the postnatal growth and skeletal growth in many species. However, there are few reports of *IGF-1R* gene structure and its effects on growth traits in sheep. The objectives of this study were detection of *IGF-1R* polymorphisms and assessment of their associations with growth traits in Iranian Makooei Sheep. Hence, 200 Makooei lambs were genotyped through polymerase chain reaction-single-strand conformation polymorphism (PCR-SSCP). The studied traits were birth weight (BW), weaning weight (WW), 6 months weight (6MW), average daily gains from birth to 3 months (ADG_{0-3}), from 3 months to 6 months (ADG_{3-6}), from birth to 6 months (ADG_{0-6}) and corresponding Kleiber ratios (KR_{0-3}, KR_{3-6}, KR_{0-6}). For this genetic position, three types of banding patterns (AA, AB and BB) were identified with the frequencies of 0.69, 0.16 and 0.15, respectively. In this study, *IGF-1R* genotypes indicated the significant associations with 6MW, ADG_{0-6}, KR_{0-3} ($P<0.05$) and ADG_{0-3} ($P<0.01$). In all of the significant traits, The AA genotype was linked to the highest values, while the BB genotype was linked to the lowest values. The results of this study indicated that single nucleotide polymorphism (SNP) variation in *IGF-1R* gene can be used as a molecular marker for improving of growth traits in marker assisted selection programs in sheep.

KEY WORDS growth rate traits, *IGF-1R*, Makooei sheep, PCR-SSCP.

INTRODUCTION

Lamb weight and average daily weight gains are regarded as the most important traits in sheep breeding programs. In Iran, the use of sheep meat is the most important source of red meat. So far, most improving programs of economic traits in sheep have been carried out through phenotypic and pedigree information. However, using of molecular genetics such as genotyping of candidate genes can lead to more accurate knowledge of quantitative traits and consequently more genetic gain in livestock population. The Makooei sheep is one of fat tailed native breeds in Iran used for multiple purposes including meat and wool production.

This breed has medium-sized body covering with white and black spots on the face and feet. These animals are distributed in the mountainous regions of the country, especially in west-Azerbaijan province (Saadat-Noori and Siah-Mansoor, 1992).

The insulin-like growth factor 1 receptor (IGF-1R) is a transmembrane receptor that belonging to the large group of tyrosine kinase receptors. It is activated by a hormone called insulin-like growth factor 1 (IGF-1) as well as mediates the effects of IGF-1 (Singh *et al.* 2014). The IGF-1 is one of the most important member of IGF family participating in the somatotrophic axis and plays an important role in carbohydrate and lipid metabolism in mammals

(Richardson *et al.* 2004). It has reported that IGF-1 can induce hypertrophy of skeletal muscle and other target tissues (O'Neill *et al.* 2015). In research of Epaud *et al.* (2012), mutant mice were generated with deletion of *IGF-1R* gene. The results showed that absence of *IGF-1R* in these mice significantly delayed the development and body mass as well as concluded that this receptor plays a vital role in promoting of growth. In sheep, *IGF-1R* gene is located on chromosome 18 and consists of 20 exons (Byun *et al.* 2012). IGF-1R encodes a protein containing 1367 amino acids that plays an important role in cell proliferation, growth regulation, protein synthesis and postnatal growth (Froesch *et al.* 1985).

There are numerous studies that indicate *IGF-1* gene affects muscle growth and meat production in sheep. A positive correlation was found between a SNP in *IGF-1* gene with body weight and height in Russian sheep (Trukhachev *et al.* 2016). Several studies have reported the effect of *IGF-1* gene variants on growth traits in different breeds of Iranian sheep (Tahmoorespur *et al.* 2009; Gholibeikifard *et al.* 2013; Hajihosseinlo *et al.* 2013; Negahdary *et al.* 2013).

In comparison to *IGF-1* gene, there are few investigations for the association of *IGF-1R* gene variants with growth traits in sheep. A study indicated a significant association between a SNP in *IGF-1R* gene with body weight and average daily weight gain in Polish sheep (Proskura and Szewczuk, 2014). We did not find any studies for associations of the *IGF-1R* gene with growth traits in Iranian sheep.

Because of the fact that growth is a continuous function during life of animal, the average daily gain (ADG) in weight is a better criterion for measuring growth than weight in end of period (Nkrumah *et al.* 2007). On the other hand, selection for mass or growth may lead to undesirable consequences such as greater deposit of fat and lower fertility in animal (Scholtz and Roux, 1988). Kleiber ratio (KR) is a ratio of growth rate to metabolic mass ($W^{0.75}$) introduced as a criterion for measuring efficiency of feed conversion (Kleiber, 1947).

Kleiber ratio has a positive correlation to ADG as well as does not lead to undesirable correlated responses for longevity and fertility traits (Kleiber, 1947). The objectives of this study were to detect polymorphisms in *IGF-1R* gene and survey of effects of *IGF-1R* variants on body weight in different ages as well as ADG and KR in different periods of age in Makooei sheep.

MATERIALS AND METHODS

Ethical statement

This study has been performed with the approval of Makooei Sheep Breeding Station of west-Azerbaijan province, Iran. All institutional and national guidelines for the care and use of laboratory animals were followed.

Animal resources and measurement of traits

The used data in this study was obtained from 200 Makooei lambs (included both male and female sexes) collected from Makooei Sheep Breeding Station, west-Azerbaijan province, Iran. The Makooei sheep were kept with conventional industry practices. In this system, the animals were kept on pasture during spring and summer and kept indoors in winter. The mating period started from early October to mid-November consequently, lambing occurred from mid-February to late-March. The studied traits were: birth weight (BW), weaning weight (WW), 6 months weight (6MW), average daily gain from birth to 3 months (ADG_{0-3}), from 3 months to 6 months (ADG_{3-6}), from birth to 6 months (ADG_{0-6}) and corresponding Kleiber ratios (KR_{0-3}, KR_{3-6}, KR_{0-6}, respectively). Average daily gain and Kleiber ratio for each period were calculated as follow:

ADG= (end weight–first weight) / (number of days in period)

KR= (ADG for each period) / (end weight)$^{0.75}$

Sampling and genotyping

The blood samples (approximately 2 to 3 mL) were collected from sheep venous jugular and stored in ethylene diamine tetracetic acid (EDTA)-coated tubes. Genomic DNA was extracted from blood samples using a modified salting out protocol following Miller *et al.* (1988). After the DNA extraction, a 364 bp fragment of *IGF-1R* gene containing part of intron 2 and exon 3 was amplified using the primers designed by Byun *et al.* (2008). The amplification of genomic DNA was performed in 20 µL of reaction volume, which included 100 ng of genomic DNA, 0.6 pm of each primer, 0.2 m*M* of each dNTP, 2 µL of 10 × PCR buffer, 2 m*M* of $MgCl_2$, and 1.5 units of Taq DNA polymerase. The temperature cycles for amplification of DNA were as follows: the initial denaturation at 95 ˚C for 5 min; 33 cycles were included: denaturation at 95 ˚C for 45 s, annealing at 60 ˚C for 45 s, extension at 72 ˚C for 45 s; and a final extension at 72 ˚C for 5 min. The PCR products of *IGF-1R* gene were analyzed by polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) method. The PCR products (8 mL) were mixed with an equal volume of sample buffer. The mixture was denatured at 95 ˚C for 5 minutes and was snap chilled on ice (Pipalla *et al.* 2004). The samples were resolved on vertical electrophoresis at 37 ˚C for 4 hours using polyacrylamide gel 12%. The gels were stained with 0.1% silver nitrate and visualized through 2% NaOH solution (containing 0.1% formaldehyde).

Statistical analyses

The pop gene software (Yeh *et al.* 1999) was used to estimate the allele and genotype frequency. The standard error of allele frequency was calculated by the following formula (Falconer and Mackay, 1996):

$$SEM = \sqrt{p(1-p)} / 2n$$

Where:
n: sample size.
p: frequency of the A allele.

The normality of the distribution of phenotypic data was examined using SAS software (SAS, 2002). The errors of studied traits follow a normal distribution. The fixed effects for considering in final model were tested using the general linear model (GLM) procedure of SAS. The significant fixed effects included in the final statistical model were sex, type of birth and age of dam at lambing. The association of *IGF-1R* genotypes with growth traits was analyzed using the least square method of GLM procedure of SAS. The significant differences between means were assessed by Tukey's test. The full model was as follows:

$$y_{ijkl} = \mu + SNP_i + sex_j + \text{type of birth}_k + \text{age of dam}_l + e_{ijkl}$$

Where:
y_{ijkl}: vector of the observed traits.
μ: overall mean.
SNP_i: SNP genotype.
Sex_j: fixed effect of sex (male or female).
Type of $birth_k$: fixed effect of type of birth (single or twin lamb in birth).
Age of dam_l: 2 to 7 years.
e_{ijkl}: residual effect to each observation.

The total variance explained by each significant SNP σ^2_{QTL} was estimated as the sum of its additive $\sigma^2_{QTL\text{-}a}$ and dominance $\sigma^2_{QTL\text{-}d}$ variances, which were estimated as follows (Falconer and Mackay, 1996):

$$\hat{a} = (BB - AA)/2$$
$$\hat{d} = AB - (BB + AA)/2$$
$$\alpha = \hat{a} + (q - p)\hat{d}$$
$$\delta = 2pq\hat{d}$$
$$\sigma^2_{QTL\text{-}a} = 2pq\,(\alpha)^2$$
$$\sigma^2_{QTL\text{-}d} = (\delta)^2$$
$$\sigma^2_{QTL} = \sigma^2_{QTL\text{-}a} + \sigma^2_{QTL\text{-}d}$$

Where:
p and q: allele frequencies.
$\hat{a}$: additive.
$\hat{d}$: dominance effects estimated from the genotype effects (AA, AB and BB) of the significant SNP.
α: allele substitution effect.
δ: dominance deviation.

The QTL variance (σ^2_{QTL}) was expressed as a fraction of the total phenotypic variance (V_P) which was estimated based on model without SNP effect. The genetic variance of traits was estimated in a model without SNP effect using WOMBAT software (Meyer, 2006).

RESULTS AND DISCUSSION

Population phenotypic and genetic information

The descriptive statistics for phenotypic data of growth traits are presented in Table 1. According to the results of PCR-SSCP analysis, a total of three genotypic patterns were observed for 364 bp amplified fragment of *IGF-1R* gene (Figure 1). In the examined group of 200 sheep, the genotypic patterns 138 AA, 32 AB and 30 BB were identified. The allelic and genotypic frequencies, standard error of means and result of fisher's exact test are shown in Table 2. The fisher's exact test was revealed that there is a significant difference between the observed genotypic patterns ($P<0.05$). The highest and least frequencies of genotypic patterns were AA and BB, respectively.

The results of polymorphisms in this study are consistent with previous researches in sheep (Proskura and Szewczuk, 2014), yak (Liang *et al.* 2010), Turkish cattle breeds (Akis *et al.* 2010), Japanese quail (Moe *et al.* 2007) and pig (Wang *et al.* 2006) that reported two alleles for *IGF-1R* gene. On the other hand, the findings of this study are not similar to performed studies in Egyptian buffalo (El-Magd *et al.* 2013), sheep (Byun *et al.* 2008) and chicken (Lei *et al.* 2008) that identified more than two alleles for *IGF-1R* gene. The variations in polymorphisms of *IGF-1R* gene might be due to the difference of the studied species or breeds, the studied genetic position of gene and discrepancy in sample size.

IGF-1R association analyses

The IGF-1R protein is a main receptor of IGFs family and mediates in many physiological processes such as cell proliferation, bone growth, protein synthesis and increasing of muscle mass (Delafontaine *et al.* 2004; Charge and Rudnicki, 2004). Also, several studies have reported that *IGF-1R* gene has an important effect on growth, carcass and meat quality traits in many species (Moe *et al.* 2007; Lei *et al.* 2008; Liang *et al.* 2010; El-Magd *et al.* 2013). However, there are few reports about association of *IGF-1R* gene variants with growth traits in sheep.

Table 1 Descriptive statistics of examined traits in Makooei sheep

Traits	Mean	Standard deviation	Minimum	Maximum	Coefficient of variation (%)
BW (kg)	4.15	0.43	3.2	5	10.55
WW (kg)	21.98	2.47	17	28	11.27
6MW (kg)	29.72	2.61	22.5	38	8.79
ADG_{0-3} (g/day)	198.10	26.49	137.77	266.66	13.37
ADG_{3-6} (g/day)	85.96	24.39	22.22	177.77	28.37
ADG_{0-6} (g/day)	142.01	14.32	101.11	187.22	10.08
KR_{0-3}	19.45	1.03	16.41	21.90	5.30
KR_{3-6}	6.69	1.81	0	12.91	27.07
KR_{0-6}	11.14	0.41	9.78	12.37	3.74

BW: birth weight; WW: weaning weight; 6MW: 6 month weight; ADG_{0-3}: average daily gains from birth to 3 months; ADG_{3-6}: average daily gains from 3 months to 6 months and ADG_{0-6}: average daily gains from birth to 6 months; KR_{0-3}: kleiber ratios from birth to 3 months; KR_{3-6}: kleiber ratios from 3 months to 6 months and KR_{0-6}: kleiber ratios from birth to 6 months.

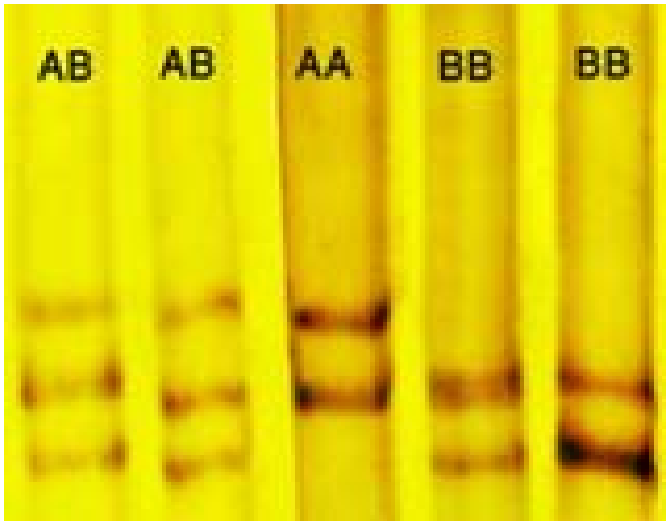

Figure 1 Single strand conformation polymorphism (SSCP) patterns observed for *IGF-1R* gene in Makooei sheep

Table 2 Summary of population genetic information for *IGF-1R* gene in Makooei sheep

Loci	Genotypic frequency			P-value	Allelic frequency		SEM
	AA	AB	BB		A	B	
IGF-IR	0.69^{a}	0.16^{b}	0.15^{b}	0.01	0.77	0.23	0.02

SEM: standard error of the means.

Thus in present research, *IGF-1R* gene was chosen for an association study with growth traits in Makooei sheep.

The significant fixed effects included in the final statistical model were sex, type of birth and age of dam at lambing. It is obvious that male lambs and single born lambs were heavier and faster growing rate than other individuals. Furthermore, differences in dams for maternal behavior and mothering ability at different ages as well as limited uterine space (especially in young dams) significantly affect lamb weight.

Table 3 shows the effect of the *IGF-1R* genotypes on growth traits in Makooei sheep. The results showed that the AA genotype is associated with more 6MW, ADG_{0-6}, KR_{0-3} ($P<0.05$) and ADG_{0-3} ($P<0.01$) if compared to other genotypes.

Also, for 6MW, ADG_{0-3} and ADG_{0-6} traits, AA genotype was similar to AB genotype but for KR_{0-3} trait, AA genotype was similar to BB genotype. The results of the present study are consistent with those of other researches that have shown the significant association of *IGF-1R* gene with growth traits and ADG (Wang *et al.* 2006; Moe *et al.* 2007; Lei *et al.* 2008; Liang *et al.* 2010; El-Magd *et al.* 2013; Proskura and Szewczuk, 2014).

Proskura and Szewczuk (2014) reported that g.195C > T SNP in intron 12 of *IGF-1R* gene was significantly associated with body weight at day 1, 33 and 90 of age and ADG at 1-33, 33-90 and 1-90 days of age in Polish ewes. They showed that sheep with the TT and CC genotypes, respectively, had highest and lowest values of the all analyzed traits.

Table 3 Effect of genotypes of *IGF-1R* gene on growth traits in Makooei sheep (Least-square means±standard errors)

Traits	*IGF-1R* genotypes			P-value
	AA	AB	BB	
BW (kg)	4.17±0.43	4.02±0.39	4.10±0.52	0.734
WW (kg)	22.33±2.35	21.98±2.76	21.62±2.27	0.061
6MW (kg)	30.10±2.67^{a}	2.30^{a}±29.98	28.10±3.29^{b}	0.034
ADG_{0-3} (g/day)	201.83±25.14^{a}	195.31±30.24^{a}	183.55±23.51^{b}	0.008
ADG_{3-6} (g/day)	84.96±24.07	94.30±21.48	83±27.90	0.071
ADG_{0-6} (g/day)	143.39±12.65^{a}	140.53±14.77^{a}	133.27±18.01^{b}	0.027
KR_{0-3}	19.59±0.97^{a}	18.71±1.07^{b}	18.92±0.99^{ab}	0.014
KR_{3-6}	6.61±1.74	7.35±2.01	6.72±1.90	0.065
KR_{0-6}	11.18±0.36	11±0.41	10.89±0.54	0.055

BW: birth weight; WW: weaning weight; 6MW: 6 month weight; ADG_{0-3}: average daily gains from birth to 3 months; ADG_{3-6}: average daily gains from 3 months to 6 months and ADG_{0-6}: average daily gains from birth to 6 months; KR_{0-3}: kleiber ratios from birth to 3 months; KR_{3-6}: kleiber ratios from 3 months to 6 months and KR_{0-6}: kleiber ratios from birth to 6 months.
The means within the same row with at least one common letter, do not have significant difference (P>0.05).

Table 4 Variances of *IGF-1R* gene for significant traits in Makooei sheep

Traits	σ^2_{OTL-a}	σ^2_{OTL-d}	σ^2_{OTL}	SNP variance (% of V_P)
6MW (kg)	0.138	0.052	0.190	0.008
ADG_{0-3} (g/day)	21.582	0.825	22.407	0.008
ADG_{0-6} (g/day)	3.966	1.498	5.464	0.045
KR_{0-3}	0.033	0	0.033	0.022

SNP: single nucleotide polymorphism; 6MW: 6 month weight; ADG_{0-3}: average daily gains from birth to 3 months; ADG_{3-6}: average daily gains from 3 months to 6 months and KR_{0-3}: kleiber ratios from birth to 3 months.

Wang *et al.* (2006) reported that AA-genotype pigs exhibited greater body weights at birth, 2 and 6 months of age. An association study for *IGF-1R* on yak indicated that animals with AA genotype had more body weight and height than the other individuals (Liang *et al.* 2010). A study showed that AA genotype of *IGF-1R* gene was significantly associated with growth traits and ADG in chicken (Lei *et al.* 2008). Moe *et al.* (2007) reported a significant effect of *IGF-1R* gene on 10-week body weight and ADG in Japanese quail. A research on Egyptian buffalo confirmed that the heterozygous animals had higher ADG_{0-6} than the homozygous animals (El-Magd *et al.* 2013). We did not find any studies about the effects of *IGF-1R* on Kleiber ratio in sheep.

The results of this study did not show a significant effect of *IGF-1R* on birth weight and weaning weight but confirmed the significant associations between this gene and ADG and KR in period (0-3). These findings prove the importance of evaluating the growth rate traits as well as a difference between weight at a stage of animal life with weight gain in different periods of age. Because, growth is a continuous function during life of animal, the growth gain traits may be more suitable breeding objectives to use in sheep breeding programs to achieve more meat production. Also, our findings confirmed the significant effect of *IGF-1R* gene on ADG_{0-6}, but no significant association was observed for KR in this period. This result shows that there is a difference between growth gain and Kleiber ratio. Because, KR is based on efficiency of feed conversion, selection for KR does not lead to undesirable results such as increasing of fat deposit in animal and consequently decreasing of longevity and fertility. We found discrepancy in effects of *IGF-1R* gene on ADG and KR traits in different periods of age. The records related to ADG and KR traits are repeated data over time; thus, the level of gene expression as well as heritability and genetic correlation between repeated measurements vary in different periods of age (Mrode, 2014). A genome wide association study on Baluchi sheep reported that SNP markers affecting KR were not necessarily the same with corresponding ADG (Pasandideh *et al.* 2018). These evidences prove that our results are reasonable and acceptable.

The *IGF-1R* variances for significant traits are shown in Table 4. The variance of *IGF-1R* gene for ADG_{0-6} trait was obtained 0.045 as a fraction of the total phenotypic that was the highest variance of this gene on studied traits. The value of dominance variance for KR_{0-3} trait was so nominal (0.0001) mentioned zero in Table 4. For all of significant traits, the values of additive variances were higher compared to the dominance variances. Although, these percentages were probably overestimated according to the Beavis effect (Beavis, 1998), these results confirmed that dominance plays a role in the genetic architecture of growth traits but specially, the additive effects are involved in genetic variance of studied traits more than dominance effects. In this regard, the results of this study are consistent with previous studies. Two GWA studies in Baluchi sheep showed that the additive effects are more involved than dominance in genetic variance of reproductive and growth rate traits (Pasandideh *et al.* 2017; Pasandideh *et al.* 2018).

Su *et al*. (2012) reported that the additive genetic variance of daily gain in pigs was 3.73 fold higher than the dominance genetic variance. The additive variance is the most important component of genetic variance because it determines most of the correlation of relatives and the opportunities for genetic change by natural or artificial selection, consequently, effects on response to selection (Falconer and Mackay, 1996).

CONCLUSION

The present study showed the significant associations of *IGF-1R* variants with some of growth traits in Makooei sheep. The animals with AA genotype were higher than other individuals for 6MW, ADG_{0-3}, ADG_{0-6}, KR_{0-3} traits. Also, AA genotype was similar to AB genotype for 6MW, ADG_{0-3} and ADG_{0-6} traits but for KR_{0-3} trait, AA genotype was similar to BB genotype. We suggest to perform further studies in different breeds of sheep to verify the IGF-1R effects on growth traits. Finally, IGF-1R marker can be used in sheep breeding programs through marker-assisted selection (MAS) in order to increasing and improving of meat production.

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