American Journal of Biochemistry and Biotechnology 9 (3): 300-306, 2013
ISSN: 1553-3468

doi:10.3844/ajbbsp.2013.300.306 Published Online 9 (3) 2013 (http://www.thescipub.com/ajbb.toc)

Polymorphism of Insulin-Like Growth Factor 1 Gene in Najdi Cattle Populations

[1]Ahmad Yazdanpanah, [1]Hedayatollah Roshanfekr, [1]Khalil Mirzadeh, [1]Morteza Mamouei and [2]Saber Khederzadeh

[1]Department of Animal Sciences, Faculty of Animal Sciences and Food Industries, Ramin Agricultural and Natural Resources University, Mollasani, P.O. Box 63417-73637, Iran
[2]Department of Genetic and Biotechnology, Faculty of Biological Sciences, Varamin-Pishva Branch, Islamic Azad University, Varamin, P.O. Box 33817-74895, Iran

Received 2012-08-08, Revised 2013-07-05; Accepted 2013-07-20

ABSTRACT

The Insulin-like Growth Factor 1 (IGF-1) system plays a critical endocrine role controlling nutrient metabolism in dairy cattle and it is a group of structurally-related polypeptides that regulate the growth of many types of mammalian cells. In liver, IGF-1 is dynamically regulated by lactation and energy balance. Less is known about the regulation of IGF-1 and IGF-binding protein mRNA in reproductive tissues and plays an important role in bovine follicular growth, acquisition of oocyte competence and embryo viability. The present study describes polymorphism of IGF-1 gene in Najdi cattle populations. In order to characterization polymorphism, blood sample were collected from 84 Najdi cattles from Shadegan, Mahshar cities and Shushtar station. DNA extraction was based on Boom method and exons 1 of the IGF-1 gene were amplified to produce a 249 bp fragment. The amplified fragment were digested with *Eco105*I (*SnaB*I) restriction endonuclease and then subjected to electrophoretic separation in ethidium bromide-stained 2% agarose gel. The results were revealed two alleles, A and B. Three genotypes were observed, Frequencies were 2.38, 14.28 and 83.33% for AA, AB and BB, respectively. This gives frequencies of 0/0952 and 0/9048 for A and B alleles. The populations were in hardy-weinberg equilibrium. It is possible that this gene has not exposed to selection. The heterozygosity is low and inbreeding is estimated high.

Keywords: Najdi Cattle, Polymorphism, IGF-1 Gene, Production Traits, PBR

1. INTRODUCTION

Quantitative traits are often controlled by a great number of genes. Localization of Quantitative Trait Loci (QTLs) can be done by linkage disequilibrium analysis or by candidate gene approach. Candidate genes have known biological functions related to the development or physiology of an important trait (Rothschild *et al*., 1997). Such genes can encode structural proteins or a member in a regulatory or biochemical pathway affecting the expression of the trait (Bryne and McMullen, 1996) and can be tested as putative QTLs (Yao *et al*., 1996). The Growth Hormone (GH) and Insulin-like Growth Factor 1 (IGF-1) genes are candidates for growth in bovine, since they play a key role in growth regulation and development (Breier, 1999). Genetic polymorphism in native breeds is a major concern considering the necessity of preserving genetic resources. It is very important to characterize genetically indigenous breeds (Bastos *et al*., 2001). Insulin-like Growth Factors 1 and 2 (somatomedins-IGF-1 and IGF-2) are structurally related proteins, playing a key role in cell differentiation, embryogenesis, growth and regulation of metabolism. IGF1 and IGF2 were first identified by Salmon and Daughaday (1956; 1957) and designated 'sulphationfactor' due to their ability to incorporate

Corresponding Author: Saber Khederzadeh, Department of Genetic and Biotechnology, Faculty of Biological Sciences, Varamin-Pishva Branch, Islamic Azad University, Varamin, P.O. Box 33817-74895, Iran

sulphate into ratcartilage in vitro. They were also known As Non-Suppressible Insulin-Like Activity (NSILA) I and II (Froesch *et al*., 1963). A decade later, the terms sulphation factor and NSILA were replaced by the term 'somatomedin' (Daughaday *et al*., 1972) and subsequently they were renamed 'IGFs 1 and 2' due to their structural similarity with insulin and their growth-promoting activities (Rinderknecht and Humbel, 1976a; 1976b). IGF1 is one of two ligands of the IGF family (Hwa *et al*., 1999; Spicer, 2004). The established components of the IGF system also include two receptors, six high-affinity IGF-Binding Proteins (IGFBPs) and IGFBP proteases (Giudice, 1995; Hwa *et al*., 1999; Spicer, 2004). Furthermore, another group of low-affinity binding proteins, known as IGFBP-related Proteins (IGFBP-rPs), belongs to the IGF family. However, no final nomenclature has been agreed for these proteins, as several research groups have identified the same protein and each group has used adifferent nomenclature (Hwa *et al*., 1999; Rosenfeld *et al*., 2001). Potential receptors for IGFBP(s) and IGFBP-rP(s) have also been reported to be part of the IGF family (Hwa *et al*., 1999) (**Table 1**). Due to similarities in structure and sharing intracellular signalling cascades with other members of the IGF system, insulin, its receptor and a hybrid insulin/IGF receptor are also considered to be part of the IGF superfamily (Jones and Clemmons, 1995; Monget and Martin, 1997; McCusker, 1998; Poretsky *et al*., 1999; Butler and Roith, 2001; Juul, 2003). Insulin-like Growth Factor I (IGF1) is known to play an important role in various aspects of muscle growth and development (Davis and Simmen, 2006). Due to the effect of IGF1 on the hypertrophy of muscle cells, muscle fiber diameter can be affected by IGF1. Since increasing muscle fiber diameter may decrease tenderness (Herring *et al*., 2009), it can be postulated that IGF1 may also affect tenderness by increasing the size of the muscle fibers (Koohmaraie *et al*., 1995). The aim of this study was to investigate relationship between DNA polymorphisms in the IGF1 gene and tenderness and muscle development. IGF-1 is a polypeptide of the molecular weight 7.5 kDa built of 70 amino acids (Daughaday and Rotwein, 1989). The amino acid sequence of IGF-1 is identical in humans, cattle, dogs and pigs (Nixon *et al*., 1999). In humans the IGF-1 gene contains 6 exons and is about 90 kbp-longs (Rotwein *et al*., 1986; Steenbergh *et al*., 1991). Due to an alternative splicing of exons 1 and 2, two different transcripts are formed: the one with exon 1 containing 1155 nucleotides (nt), while the other one, with exon 2, is shorter and contains 750 nt. Production of these transcripts is controlled by two different promoters both containing canonical regulatory sequences-TATA-box and CCAAT-box (Jansen *et al*., 1991). It was shown that transcripts of both classes are differentially expressed in various tissues, being, however, most abundant in liver (Wang *et al*., 2006). In vertebrates, the Insulin-Like Growth Factor 1 (IGF1) or somatomedin gene plays a key role in various physiological and metabolic processes, where IGF1 and growth hormone or somatotrophin is involved in the somatotropic axis. IGF1 is a mediator of many biological effects; for example, it increases the absorption of glucose, stimulates myogenesis, inhibits apoptosis, participates in the activation of cell cycle genes, increases the synthesis of lipids, stimulates the production of progesterone in granular cells and intervenes in the synthesis of DNA, protein, RNA and in cell proliferation (Etherton, 2004). The bovine IGF1 gene was mapped on chromosome 5, in the centimorgan 73.5 (Grosse *et al*., 1999). The provisional nucleotide sequence is approximately 72 kb (ID number 281239). In humans, pigs, goats, rats and chickens, the IGF1 nucleotide sequence is about 70-90 kb (Rose, 2002).

Table 1. The insulin-like growth factor superfamily (Velazquez *et al*., 2009)

Ligands		Receptors
IGF1		Type 1 IGF receptor
IGF2		Type 2 IGF or IGF 2/mannose-6-phosphate (IGF2/M6P) receptor
Binding protein	**Binding protein proteases**	**Binding protein-related proteins**
IGFBP1	IGFBP2 proteases	IGFBP-rP1 a(IGFBP7/MAC25/TAF/PSF
IGFBP2	IGFBP3 proteases	IGFBP-rP2 a(CTGF
IGFBP3	IGFBP4 proteases	IGFBP-rP3 a(NovH)
IGFBP4	IGFBP5 proteases	IGFBP-rP4 a(CYR61)
IGFBP5		IGFBP-rP5 a(L56/HTRA1)
IGFBP6		IGFBP-rP6 a(ESM1
	Potential receptors	
	IGFBP(s)	IGFBP-rP7 a(rCOP-1/WISP2/CTGF-L)
	IGFBP-rP(s)	IGFBP-rP8 a(ELM1/WISP1)
		IGFBP-rP9 a(WISP3)

Exon number is different between species; for example, goats, pigs and sheep have 1-6 exons (Mikawa *et al*., 1995) and humans and rats 1-5 (Rotwein *et al*., 1986). The IGF-1 gene is extremely conserved among species and few polymorphisms are described. The presence of a microsatellite at the promoter region of this gene in bovine, human and horse allows to analyze genetic variations related to this locus (Kirkpatrick, 1992). Evidence of selection effects on allele frequencies at these two loci was found in the traditional lineage of Canchim (Regitano *et al*., 1999). Nucleotide sequence polymorphisms were identified in the bovine IGF-1 gene and their correlations with animals' growth rate and meat performance traits were found. The Short Tandem Repeat (STR) polymorphism in the 5'-flanking region and the Single Strand Conformation Polymorphism (SSCP) in intron 3 of the IGF-1 were reported by Kirkpatrick (1992). In Hereford cattle the STR polymorphism was shown to be associated with body weight at birth and at weaning and with the growth rate (Moody *et al*., 1996). Such associations were not found in other beef breeds (Curi *et al*., 2005). The SSCP in the 5'-flanking region of IGF-1 was found by Ge *et al*. (1997) in Angus cattle. This polymorphism was then identified as T/C transition, also recognizable as RFLP-SnaBI (Ge *et al*., 2001). Two alleles and three genotypes were found. Allele A (with nt T at position -472) appeared significantly more frequent than allele B (with nt C) in a group of animals selected for the high IGF-1 content of blood. However, the BB genotype (with nucleotides CC) was found to be associated with higher body weight at weaning (Li *et al*., 2004). No association was found between IGF-1 RFLP-SnaBI and dairy production traits in Holstein cattle (Hines *et al*., 1998). Two polymorphisms in the IGF-1 were reported by Lien *et al*. (2000) in Norwegian cattle: the TTTG Insertion/Deletion (InDel) in intron 4 and the RFLP-DpnI in intron 5. However, the effects of these polymorphisms on beef or milk production traits were not investigated. The objective of the present study was to Investigate of IGF-1 gene polymorphism in najdi cattle breed populations in khouzestan province of IRAN using PBR (PCR Based RFLP) technique.

2. MATERIALS AND METHODS

In current study, Random blood samples were collected from 84 Najdi Cattle from three populations involve: Shushtar station, Shadegan and Mahshar cities in Khuzestan province of Iran (**Fig. 1**). Approximately, 5 ml blood sample was gathered from venom in EDTA tube and was transferred to -20°C freezer. Genomic DNA was isolated by using DNA Extraction Kit (Diatom) and was based on Boom *et al*. (1989) method. Quantity was determined by measuring the absorbance at 260 nm and the concentration, purity and quality were determined by measuring the absorbance at 260/280 nm and 230/260 ratios using a NanoDropTM 1000 spectrophotometer (Thermo Scientific). DNA extractions were appropriately labeled and stored at -20°C for analysis. The study was concentrated on a 249 bp fragment of IGF-1 gene spanning over exon 1. Primer sequence for PCR were established by Ge *et al*. (2001); Li *et al*. (2004) and Laureano *et al*. (2009) (**Table 2**). The PCR reaction volume of 25 µL contained approximately 100 ng of genomic DNA, 1unit Taq DNA Polymerase, 1x PCR Buffer, 1.5 mM MgCl2, 200 µM dNTPs and 0.3 pMol of each primer. Amplification conditions included an initial denaturation at 95°C for 5 min, followed by 35 cycles at 94°C for 30 s, 63°C for 30 s and 72°C for 40 s, followed by a final extension at 72°C for 5 min. The amplified fragment was digested with *Eco105*I (*SnaB* I). The digestion reaction contained by 5 µL of PCR product, 2 µL Buffer 10X, 5 U of Eco105I (SnaB I) and H_2O up to a total volume of 20 µL then were incubated at 37°C for 12-16 h. The digestion products were electrophoresed on 2% agarose gel in 0.5X TBE and visualized by ethidium bromide staining for 40 min at 100 V. The frequencies of genotype, alleles, mean expected, observed and Nei's heterozygosities and Hardy-Wienberg equilibrium test were calculated using Popgene32 software (version 1.31).

Fig. 1. Geographical location of the populations studied

Table 2. Primer used in the amplification in the bovine IGF1 gene

Locus/Primer	Primer sequence
IGF-1-F	ATT ACA AAG CTG CCT GCC CC
IGF-1-R	ACC TTA CCC GTA TGA AAG GAA TAT ACG T

3. RESULTS

The amplified Insulin-like Growth Factor 1 (IGF-1) resulted in a DNA fragment with 249 bp including the sequences of spanning over exon 1 regions with PCR technique (**Fig. 2**). From the analysis, two alleles (A and B) were observed, resulting in three genotypes. The *Eco105*I (*SnaB* I) digestion of the PCR products produced digestion fragments of 226 and 23 bp. The animals with both alleles were assigned with AB genotype, whereas those possessing only A or B alleles were assigned with AA or BB genotypes, respectively. Genotype AA showed the two band pattern (bands of approximately 226 and 23 bp). Genotype BB showed one band pattern (approximately 249 bp), while AB animals displayed a pattern with all three bands (249, 226 and 23) (**Fig. 3**). The genotypes of all animals were used to determine the allele frequencies. A and B allele frequencies were 0.0952 and 0.9048, respectively and were similar to the 0.98 and 0.02 (Laureano *et al*., 2009), to the 0.7 and 0.3 (Kim *et al*., 2004) and to the 0.97 and 0.03 (Reyna *et al*., 2010) previously reported. The high frequency of the B allele suggests that this allele Variant might have been favored by selection for production traits. The observed genotype frequencies were 0.023 for AA, 0.142 for BB and 0.833 for AB (**Table 3**). najdi population was in Hardy-Weinberg equilibrium ($p<0.05$). The observed and expected heterozygosity were 0.1429 and 0.1734, respectively. Effective allele and true allele estimates were 1.20 and 2.00, respectively. This difference between effective all and true allele number and low diversity is due to more frequency of allele B compare to allele A, that reduced frequency in any locus. This number is larger, if there are more loci with same combination of alleles. In Shadegan and Mahshar cities, A and B allele frequencies were 0.1538 and 0.8462, respectively but in shushtar station, A and B allele frequencies were 0.0000 and 1.0000, respectively. In Shadegan city, the observed genotype frequencies were 0.051 for AA, 0.743 for BB and 0.205 for AB. In Mahshar city, the observed genotype frequencies were 0.000 for AA, 0.692 for BB and 0.307 for AB and In Shushtar station, the observed genotype frequencies were 0.000 for AA, 1.000 for BB and 0.000 for AB (**Table 4**).

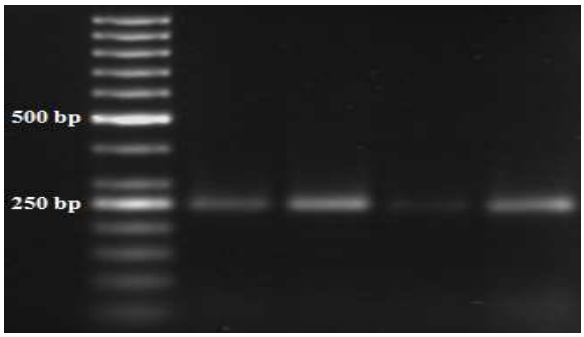

Fig. 2. Gel electrophoresis of PCR products of IGF-1 (Size obtained: 249 bp)

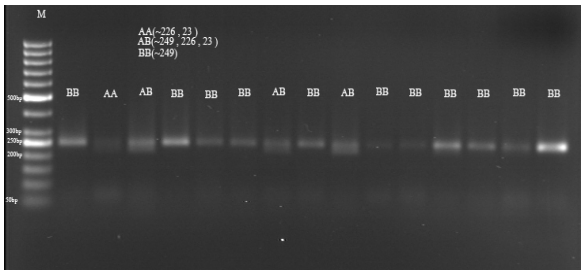

Fig. 3. IGF-1genotyping by PBR method (2% agaros gel)

Table 3. Genotype and Allele frequencies of Najdi Cattle Population

Genotype frequencies			Allele frequencies	
AA	AB	BB	A	B
0.023	0.833	0.142	0.0952	0.9048

Table 4. Genotype and Allele frequencies of Najdi cattle in different regions

	Genotype frequencies			Allele frequencies	
Regions	AA	AB	BB	A	B
Shadegan	0.051	0.205	0.743	0.1538	0.8462
Mahshar	0.000	0.307	0.692	0.1538	0.8462
Shushtar	0.000	0.000	1.000	0.0000	1.0000

Two Populations of Najdi Cattle (Shadegan and Mahshahr cities) were in Hardy-Weinberg equilibrium but Shushtar station was in hardy-weinberg disequilibrium ($p<0.05$). In Shadegan city, the observed and expected heterozygosity were 0.2000 and 0.2600, respectively. In Mahshar city, the observed and expected heterozygosity were 0.3000 and 0.2700 and In Shushtar station, the observed and expected heterozygosity were 0.0000 and 0.0000, respectively (**Table 5**).

Table 5. The observed and expected heterozygosity in different regions

Regions	Observed heterozygosity	Expected heterozygosity
Shadegan	0.2	0.26
Mahshar	0.3	0.27
Shushtar	0.0	0.00

4. DISCUSSION

Candidate genes have known biological functions related to the development or physiology of an important trait. Such genes can encode structural proteins or a member in a regulatory or biochemical pathway affecting the expression of the trait (Bryne and McMullen, 1996) and can be tested as putative QTLs (Yao *et al*., 1996). The study by Ge *et al*. (2001) characterizes a G→A transition polymorphism within an *Eco130*I site of intron 3 of the IGF1 gene. Polymorphisms in the bovine IGF-I gene are associated with circulating IGF-I concentrations and growth traits. Growth in animals is controlled by a complex system, in which the somatotropic axis plays a key role. Genes that operate in the somatotropic axis are responsible for the postnatal growth, mainly GH that acts on the growth of bones and muscles mediated by IGF-1.

5. CONCLUSION

Najdi cattle breed showed a low degree of genetic diversity for the IGF-1 locus. Although we observed the low variability for this locus, in the other hand, this data provide evidence that Iranian najdi cattle populations have a good polymorphism for IGF-1 gene, which opens interesting prospects for future selection programs, especially marker assistant selection between different genotypes of different locus and milk, gain and meat traits. Present results showed that PCR-RFLP (PBR) is appropriate tools for evaluating genetic variability.

6. ACKNOWLEDGMENT

The current study was supported by Faculty of Animal Sciences and Food Industries, Ramin Agricultural and Natural Resources universities and Department of Genetic and Biotechnology in the Varamin Pishva branch of Islamic Azad University in the Iran.

7. REFERENCES

Bastos, E., A. Cravador, J. Azevedo and H. Guedes, 2001. Single strand conformation polymorphism (SSCP) detection in six genes in the Portuguese indigenous sheep breed “Churra da Terra Quente”. Biochtechnol. Agron. Soc. Environ., 5: 7-15.

Boom, R., C.J. Sol, M.M. Salimans, C.L. Jansen and P.M. Wertheim-van Dillen *et al*., 1989. Rapid and simple method for purification of nucleic acids. J. Clin. Microbiol., 28: 495-503. PMID: 1691208

Breier, B.H., 1999. Regulation of protein and energy metabolism by the somatotropic axis. Domest. Anim. Endocrinol., 17: 209-218. DOI: 10.1016/S0739-7240(99)00038-7

Bryne, P.F. and M.D. McMullen, 1996. Defining genes for agricultural traits: QTL analyses and the candidate gene approach. Probe, 7: 24-27.

Butler, A.A. and D.L. Roith, 2001. Control of growth by the somatropic axis: Growth hormone and the insulin-like growth factors have related and independent roles. Annual Rev. Physiol., 63: 141-164. DOI: 10.1146/annurev.physiol.63.1.141

Curi, R.A., H.N.D. Oliveira, A.C. Silveira and C.R. Lopes, 2005. Effects of polymorphic microsatellites in the regulatory region of IGF1 and GHR on growth and carcass traits in beef cattle. Anim. Genet., 36: 58-62. DOI: 10.1111/j.1365-2052.2004.01226.x

Daughaday, W.H. and P. Rotwein, 1989. Insulin-like growth factors I and II. peptide, messenger ribonucleic acid and gene structures, serum and tissue concentrations. Endocrinol. Rev., 10: 68-91. DOI: 10.1210/edrv-10-1-68

Daughaday, W.H., K. Hall, M.S. Raben, W.D. Jr. Salmon and J.L.V.D. Brande *et al*., 1972. Somatomedin: Proposed designation for sulphationfactor. Nature, 235: 107-107. DOI: 10.1038/235107a0

Davis, M.E. and R.C.M. Simmen, 2006. Genetic parameter estimates for serum insulin-like growth factor I concentrations and body weight and weight gains in Angus beef cattle divergently selected for serum insulin-like growth factor I concentration. J. Anim. Sci., 84: 2299-2299. DOI: 10.2527/jas.2005-567

Etherton, T.D., 2004. Somatotropic function: The somatomedin hypothesis revisited. J. Anim. Sci., 82: E239-E244.

Froesch, E.R., H. Burgi, E.B. Ramseier, P. Bally and A. Labhart, 1963. Antibody-suppressible and non-suppressible insulin-like activities in human serum and their physiologic significance. An insulin assay with adipose tissue of increased precision and specificity. J. Clin. Investigat., 42: 1816-1834. DOI: 10.1172/JCI104866

Ge, W., M.E. Davis and H.C. Hines, 1997. Two SSCP alleles detected in the 5'-flanking region of the bovine IGF-1 gene. Anim. Genetics, 28: 155-156. PMID: 9172322

Ge, W., M.E. Davis, H.C. Hines, K.M. Irvin and R.C.M. Simmen, 2001. Associations of a genetic marker with blood serum insulin-like growth factor-1 concentration and growth traits in angus cattle. J. Anim. Sci., 79: 1757-1762. PMID: 11465363

Giudice, L.C., 1995. The insulin-like growth factor system in normal and abnormal human ovarian follicle development. Am. J. Med., 98: 48S-54S. DOI: 10.1016/S0002-9343(99)80059-X

Grosse, W.M., S.M. Kappes, W.W. Laegreid and J.W. Keele, 1999. Single Nucleotide Polymorphism (SNP) discovery and linkage mapping of bovine cytokine genes. Mamm. Genome, 10: 1062-1069. DOI: 10.1007/s003359901162

Herring, H.K., R.G. Cassens, G.G. Suess, V.H. Brungardt and E.J. Briskey, 2009. Tenderness and associated characteristics of stretched and contracted bovine muscles. J. Food Sci., 32: 317-323. DOI: 10.1111/j.1365-2621.1967.tb01321_32_3.x

Hines, H.C., W. Ge, Q. Zhao and M.E. Davis, 1998. Association of genetic markers in growth hormone and insulin-like growth factor I loci with lactation traits in Holsteins. Anim. Genetics.

Hwa, V., Y. Oh and R.G. Rosenfeld, 1999. The Insulin-like Growth Factor-Binding Protein (IGFBP) superfamily. Endocrine Rev., 20: 761-787. DOI: 10.1210/er.20.6.761

Jansen, E., P.H. Steenbergh, D. Leroith, C.T. Roberts Jr. and J.S. Sussenbach, 1991. Identication of multiple transcription start sites in the human insulin-like growth factor I gene. Mol. Cellular Endocrinol., 78: 115-125. DOI: 10.1016/0303-7207(91)90192-U

Jones, J.I. and D.R. Clemmons, 1995. Insulin-like growth factors and their binding proteins: Biological actions. Endocrine Rev., 16: 3-34. PMID: 7758431

Juul, A., 2003. Serum levels of insulin-like growth factor I and its binding proteins in health and disease. Growth Hormone IGF Res., 13: 113-170. DOI: 10.1016/S1096-6374(03)00038-8

Kim, M.H., D.S. Seo and Y. Ko, 2004. Relationship between Egg Productivity and Insulin-Like Growth Factor-I Genotypes in Korean Native Ogol Chickens. Poultry Sci., 83: 1203-1208. PMID: 15285513

Kirkpatrick, B.W., 1992. Identification of a conserved microsatellite site in the porcine and bovine insulin-like growth factor-I gene 5' flank. Anim. Genet., 23: 543-548. DOI: 10.1111/j.1365-2052.1992.tb00176.x

Koohmaraie, M., S.D. Shackelford, T.L. Wheeler, S.M. Lonergan and M.E. Doumit, 1995. A muscle hypertrophy condition in lamb (callipyge): Characterization of effects on muscle growth and meat quality traits. J. Anim. Sci., 73: 3596-3607. PMID: 8655433

Laureano, M.M.M., A.R. Otaviano, A.L.F. Lima, R.B. Costa and A.K.D. Salman *et al*., 2009. Characterization and polymorphism screening of IGF-I and prolactin genes in Nelore heifers. Ital. J. Anim. Sci., 8: 277-283.

Li, C., J. Basarab, W.M. Snelling, B. Benkel and B. Murdoch *et al*., 2004. Assessment of positional candidate genes myf5 and IGF1 for growth on bovine chromosome 5 in commercial lines of Bos taurus. Anim. Sci., 82: 1-7.

Lien, S., A. Karlsen, G. Klemetsdal, D.I. Vage and I. Olsaker *et al*., 2000. A primary screen of the bovine genome for quantitative trait loci affecting twinning rate. Mammalian Genome, 11: 877-882. DOI: 10.1007/s003350010180

McCusker, R.H., 1998. Controlling insulin-like growth factor activity and the modulation of insulin-like growth factor binding protein and receptor binding. J. Dairy Sci., 81: 1790-1800. DOI: 10.3168/jds.S0022-0302(98)75748-0

Mikawa, S., G. Yoshikawa, H. Aoki, Y. Yamano and H. Sakai *et al*., 1995. Dynamic aspects in the expression of the goat Insulin-like Growth Factor-I (IGF-I)Gene: Diversity in transcription and post-transcription. Biosci. Biotechnol. Biochem., 59: 87-92. DOI: 10.1271/bbb.59.87

Monget, P. and G.B. Martin, 1997. Involvement of insulin-like growth factors in the interactions between nutrition and reproduction in female mammals. Hum. Reproduct., 12: 33-52. DOI: 10.1093/humrep/12.suppl_1.33

Moody, D.E., D. Pomp, S. Newman and M.D. Macneil, 1996. Characterization of DNA polymorphisms in three populations of Hereford cattle and their associations with growth and maternal EPD in line 1 Herefords. J. Anim. Sci., 74: 1784-1793. PMID: 8856432

Nixon, A.J., B.D. Brower-Toland and L.J. Sandell, 1999. Primary nucleotide structure of predominant and alternate splice forms of equine insulin-like growth factor I and their gene expression patterns in tissues. Am. J. Vet. Res., 60: 1234-1241. PMID: 10791936

Poretsky, L., N.A. Cataldo, Z. Rosenwaks and L.C. Giudice, 1999. The insulin-related ovarian regulatory system in health and disease. Endocrine Rev., 20: 535-582. DOI: 10.1210/er.20.4.535

Regitano, L.C.A., J.L. Azevedo, R. Vencovsky, I.U. Packer and P.F. Barbosa *et al*., 1999. Selection for breed-specific growth hormone and IGF-1 alleles in a synthetic beef cattle cross, Canchim. Genet. Mol. Biol., 22: 531-537. DOI: 10.1590/S1415-47571999000400011

Reyna, X.F., H.M. Montoya, V.V. Castrelln, A.M.S. Rincn and M.P. Bracamonte *et al*., 2010. Polymorphisms in the IGF1 gene and their effect on growth traits in Mexican beef cattle. Genet. Mol. Res., 9: 875-883. DOI: 10.4238/vol9-2gmr745

Rinderknecht, E. and R.E. Humbel, 1976a. Polypeptides with nonsuppressible insulin-like and cell-growth-promoting activities in human serum: Isolation, chemical characterization and some biological properties of forms I and II. PNAS, 73: 2365-2369. DOI: 10.1073/pnas.73.7.2365

Rinderknecht, E. and R.E. Humbel, 1976b. Amino-terminal sequences of two polypeptides from human serum with nonsuppressible insulin-like and cell-growth-promoting activities: Evidence for structural homology withinsulin B chain. PNAS, 73: 4379-4381. DOI: 10.1073/pnas.73.12.4379

Rose, M.T., 2002. The somatotropic axis of the dairy cow revisited. Anim. Sci. J., 73: 13-19. DOI: 10.1046/j.1344-3941.2002.00002.x

Rosenfeld, R.G., V. Hwa and O. Youngman, 2001. Nomenclature of the insulin-like growth factor-binding protein superfamily. J. Clin. Endocrinol. Metab., 86: 946-946. DOI: 10.1210/jc.86.2.946

Rothschild, M.F., L.A. Messer and A. Vincent, 1997. Molecular approaches to improved pig fertility. J. Reprod. Fertil., 52: 227-236. PMID: 9602731

Rotwein, P., K.M. Pollock, D.K. Didier and G.G. Krivi, 1986. Organization and sequence of the human insulin-like growth factor I gene. Alternative RNA processing produces two insulin-like growth factor I precursor peptides. J. Biol. Chem., 261: 4828-4832. PMID: 2937782

Salmon, W.D. Jr. and W.H. Daughaday, 1957. A hormonally controlled serum factor which stimulates sulfate incorporation by cartilage *in vitro*. J. Laboratory Clin. Med., 149: 825-836. PMID: 13429201

Salmon, W.D.J. and W.H. Daughaday, 1956. Sulfation factor, a serum component mediating the action of growth hormone in stimulating incorporation of sulfate into cartilage. Journal of Clinical Investigation 35 733 (abstract).

Spicer, L.J., 2004. Proteolytic degradation of insulin-like growth factor bindingproteins by ovarian follicles: A control mechanism for selection of dominant follicles. Biol. Reproduct., 70: 1223-1230. DOI: 10.1095/biolreprod.103.021006

Steenbergh, P.H., A.M.C.B. Koonen-Reemst, C.B.J.M. Cleutjens and J.S. Sussenbach, 1991. Complete nucleotide sequence of the high molecular weight human IGF-1 mRNA. Biochem. Biophys. Res. Commun., 175: 507-514. DOI: 10.1016/0006-291X(91)91593-2

Velazquez, M.A., J. Zaraza, A. Oropeza, R. Webb and H. Niemann, 2009. The role of IGF1 in the in vivo production of bovine embryos from superovulated donors. Reproduction, 137: 161-180. DOI: 10.1530/REP-08-0362

Wang, T.H., C.L. Chang, H.M. Wu, Y.M. Chiu and C.K. Chen *et al*., 2006. Insulin-like Growth Factor-II (IGF-II), IGF-Binding Proteins-3 (IGFBP-3) and IGFBP-4 in follicular fluid are associated with oocyte maturation andembryo development. Fertility Sterility, 86: 1392-1401. DOI: 10.1016/j.fertnstert.2006.03.064

Yao, J., S.E. Aggrey, D. Zadworny, J.F. Hayes and U. Kvhnlein, 1996. Sequence variations in the bovine growth hormone gene characterized by Single-Strand Conformation Polymorphism (SSCP) analyses and their association with milk production traits in Holstein. Genetics, 144: 1809-1816. PMID: 8978066