Scientific Annals of the Polish Society of Animal Production - Vol. 16 (2020), No 1, 17-26

DOI: 10.5604/01.3001.0014.0504

Association of selected polymorphic sites in the *IGF1R* gene with body weight and conformation of Hereford cattle

Małgorzata Anna Szewczuk[1#], Hanna Kulig[2]

West Pomeranian University of Technology in Szczecin,
Faculty of Biotechnology and Animal Husbandry,
[1]Department of Ruminant Science,
ul. Klemensa Janickiego 29, 71-270 Szczecin, Poland; [#]e-mail: malgorzata.szewczuk@zut.edu.pl
[2]Department of Genetics,
ul. Piastów 45, 70-310 Szczecin, Poland

The aim of this study was to determine the relationship between selected polymorphic sites located in various fragments of the *IGF1R* gene and the growth and development of Hereford cattle. Variation in the gene was identified using the PCR-RFLP and ACRS-PCR methods. The herd showed no variation at the *IGF1R/*i4*/Mph1103*I site (monomorphism), but in the case of *IGF1R/e7/Tai*I polymorphism, one heterozygous individual was observed, while the others had the *CC* genotype. In the case of *IGF1R/*e21*/Taq*I and *IGF1R/* i4*/Hinf*I, significant differences were only noted for birth weight ($P \leq 0.01$; ($P \leq 0.05$). In addition, in individuals with the rare genotype (*TT*), the lumbar spine was higher, overall body weight was greater, and calving took place earlier.

KEY WORDS: cows, *IGF1R*, body weight, daily gains

In livestock farming, it is important to know the molecular basis of variation in production traits. Because the processes involved are polygenically controlled (many genes having very minor effects), vast amounts of information are appearing about new QTL regions located in or in the vicinity of genes with high significance for specific features.

Body weight, daily gains, height at the withers and height at the lumbar spine are key indicators of the growth and development of young animals. They are influenced by both genetic and environmental factors. Many genes involved in the growth and development of young animals have been identified. Among genes considered most important in regulating these processes are those encoding elements of the somatotropic axis, and among these, genes encoding the system of insulin-like growth factors. One such element is insulin-like growth factor 1 (IGF-I), which is mainly synthesized in the liver in response

to growth hormone secretion (Kim, 2014). Its activity is closely linked to the presence of a specific receptor for insulin-like growth factor I – IGF-IR (Plath-Gabler et al., 2001; Macháčková, 2019).

IGF-IR is a heterotetrameric glycoprotein composed of 1367 amino acids, composed of two extracellular alpha subunits and two transmembrane beta subunits, which are connected by disulphide bridges. Built of 706 amino acids, the extracellular alpha subunits are a growth factor binding site, while the beta subunits, which consist of 627 amino acids each, initiate the intracellular signal transduction pathway through tyrosine kinase (Obrępalska-Stęplowska et al., 2005). Moody et al. (1996) mapped the *IGF1R* gene in bovine chromosome 21, which consists of 21 exons, sometimes separated by very long introns (up to 50-150 kb).

Because IGF-IR mediates IGF-I signal transduction, it seems worth investigating whether there is a relationship between selected polymorphic sites located in various *IGF1R* gene fragments and parameters of growth and development of Hereford cattle.

Material and methods

The study was conducted on 118 Hereford cows from a farm in the West Pomeranian Voivodeship. Cows with calves were kept in pens throughout the year. Only cows in late pregnancy, in the perinatal period, and one week after calving were kept indoors.

The summer diet, from May to November, was based on green pasture forage. In winter, the feed ration consisted of maize silage, grass silage, haylage and hay, supplemented with a mineral and vitamin preparation. Pregnant cows were additionally given a B-1 mix (produced in-house). The animals had continual access to water year round.

Peripheral blood was collected from the external jugular vein into tubes containing K3 EDTA as an anticoagulant. DNA was isolated using the MasterPure ™ Genomic DNA Purification Kit (Epicenter Technologies) as recommended by the manufacturer. Variation in the bovine insulin-like growth factor 1 receptor gene (*IGF1R*) was identified by PCR-RFLP (polymerase chain reaction – restriction fragment length polymorphism), and as there was no existing commercial restriction enzyme, the artificially created restriction site-PCR method (ACRS-PCR) was used.

A fragment of exon 7 was amplified using primer sequences (IGF1Re7F 5'-acagtgtttgggtccttagtgg-3′ and IGF1Re7R 5'-aggtgatgatgattcggttctt-3') and reaction conditions proposed by Szewczuk (2016a). Within the 236 bp fragment there are three DNA sequences recognized by the *Tai*I restriction enzyme (A**C**GT↓; MBI Fermentas/ABO, Gdańsk, Poland), with a silent polymorphic site in the third letter of the codon for aspartic acid (D^{491}; GA**C** → GA**T**), hereafter referred to as *IGF1R*/e7/*Tai*I.

A fragment of exon 21 of the *IGF1R* gene was amplified using the methodology described by Szewczuk et al. (2013). The *IGF1R*/e21/*Taq*I site refers to mutations in the 3′ UTR region of *IGF1R*. The primer sequences (IGF1Re21F: 5′-gccggtcaccataggtct**C**g-3′; IGF1Re21R: 5′-agtgggggttttggcagaat-3′) flanked a 163 bp fragment, introducing an artificial restriction site for the *Taq*I enzyme (T↓CG**A**; MBI Fermentas/ABO, Gdansk, Polska).

The last two polymorphic sites (*IGF1R*/i4/*Hinf*I and *IGF1R*/i4/*Mph*1103I) are located outside the coding sequence. A pair of primers (IGF1Ri4F: 5'-ctggatatgtccgccttagc-3′ and IGF1Ri4R: 5'-acagctcttgtgtccctggt -3′) was used to amplify a 231 bp gene fragment (Szewczuk et al., 2013). Two restriction enzymes, *Hinf*I (G↓ANT**C**) and *Mph*1103I (A**T**GCA↓T), were used to identify two polymorphic sites on intron 4.

We evaluated the body weight of calves at birth, standardized body weight of calves at 210 days of age, average daily gains of calves from birth to 210 days, and then their body weight at first calving, height at the lumbar spine, chest girth, and age at first calving. The cows in the herd were inseminated. The mating criteria adopted by the breeder were the cow's age, body weight and body condition.

Data on the performance of cows were obtained from breeding documentation kept on the farm and by the Polish Association of Beef Cattle Breeders and Producers.

A statistical analysis of the relationship between the genotypes of the *IGF1R*/e21/*Taq*I and *GF1R*/i4/*Hinf*I sites and cattle performance parameters was performed. The statistical calculations were performed using the general linear model (GLM) included in the Statistica® 12.0 PL software package. The following statistical model was used:

$$Y_{ijkl} = \mu + G_i + S_j + YS_k + e_{ijkl}$$

where:
Y_{ijkl} – analysed trait
μ – grand mean
G_i – effect of *IGF1R* genotype (i = 1, 2 or 1,..., 3)
S_j – random effect of sire (j = 1,…, 29)
YS_k – fixed effect of year/season (k = 1,…, 18)
e_{ijkl} – sampling error

The significance of differences between means was calculated using Duncan's multiple range test.

Results and discussion

In the herd of 118 Hereford beef cows, no variation was found at the *IGF1R*/i4/*Mph*1103I site (monomorphism; only the C allele). One individual with the heterozygous *CT* genotype for the *IGF1R*/e7/*Tai*I site was noted, while the remaining individuals were monomorphic (*CC* genotype).

Variation was observed within the next two polymorphic sites. In the case of the SNP located in the 3'UTR part, about 17% of cows had a heterozygous genotype, while the rest

had the homozygous *AA* genotype (the A allele dominated, with 0.915 frequency). The highest variation was found for the site located in intron 4, identified by the *Hinf*I enzyme. Over half of the individuals in the herd were heterozygous (52.1%). A high frequency (0.375) was noted for the *CC* genotype, while cows with the *TT* genotype were the least common (10% of the population; Table 1).

Table 1
Genotype and allele frequencies for four polymorphisms in the herd

SNP	Genotype	n	f	Allele
IGF1R/e7/*Tai*I	CC	105	0.991	C = 0.995 T = 0.005
	CT	1	0.009	
	TT	0	0.000	
	Total	106	1.000	
IGF1R/e21/*Taq*I	AA	98	0.831	A = 0.915 G = 0.085
	AG	20	0.169	
	GG	0	0.000	
	.Total	118	1.000	
IGF1R/i4/*Hinf*I	CC	36	0.375	C = 0.635 T = 0.365
	CT	50	0.521	
	TT	10	0.104	
	Total	96	1.000	
IGF1R/i4/*Mph*1103I	CC	96	1.000	C = 1.000 T = 0.000
	CT	0	0.000	
	TT	0	0.000	
	Total	96	1.000	

n – number, f – frequency

Due to the lack of variation at the first two sites, they were not included in further statistical analysis. The results for the other sites (*IGF1R*/e21/*Taq*I and *IGF1R*/i4/*Hinf*I) are presented in Table 2.

Table 2
Performance parameters of Hereford cows (standard errors in brackets)

SNP	Genotype	n	BWT (kg)	ADG (g)	WWT_{210} (kg)	Height of lumbar spine (cm)	Chest girth (cm)	BW-FC (kg)	Age at first calving (days)
IGF1R/e21/*TaqI*	AA	98	33.5^{A} (0.4)	1045.3 (13.0)	260.0 (3.5)	135.7 (0.3)	194.6 (0.8)	570.9 (3.9)	1071.6 (33.6)
	AG	20	35.7^{A} (0.9)	1047.0 (35.6)	257.5 (6.4)	135.4 (0.9)	213.7 (18.3)	566.9 (10.7)	1167.6 (110.6)
IGF1R/i4/*HinfI*	CC	36	34.3 (0.7)	1008.0 (17.9)	250.4 (4.0)	135.5^{Ab} (0.7)	211.9 (14.3)	567.9^{a} (4.9)	1036.4^{A} (42.6)
	CT	50	35.2^{a} (0.6)	1037.8 (24.5)	254.2 (5.3)	137.2^{ab} (0.6)	194.2 (0.8)	573.2 (8.3)	955.7^{b} (30.4)
	TT	10	33.6^{a} (1.4)	1066.2 (32.2)	257.5 (7.2)	139.2^{Aa} (1.3)	192.2 (1.4)	586.4^{a} (13.9)	819.4^{Ab} (41.7)

n – number of animals in the group; BWT – birth weight; ADG – average daily gains between birth and weaning; WWT_{210} – weaning weight adjusted to 210 days of age; BW-FC – body weight of cows
a, b – values in columns with lowercase letters differ significantly at P≤0.05
A – values in columns with a capital letter differ significantly at P≤0.01

In the case of the SNP located in the 3'UTR part of the bovine *IGF1R* gene, significant differences ($P \leq 0.01$) were noted only for birth weight. Individuals with the heterozygous genotype weighed 2.24 kg more at birth than calves with the *AA* genotype. Due to the absence of individuals with the *GG* genotype, a thorough assessment of the effect of this polymorphism on this feature is not possible.

Differences in birth weight were also found for the site in the non-coding part of the gene, as heterozygous calves were born 1.6 kg heavier than calves with the rare *TT* genotype ($P \leq 0.05$). There were no statistically significant differences between individuals with different genotypes and daily gains, standardized body weight at 210 days of age, or chest girth. Individuals with the rare genotype (*TT*) were significantly taller at the lumbar spine than homozygotes with the *CC* genotype (+3.7 cm; $P < 0.01$) and heterozygotes (+2 cm; $P \leq 0.05$), and later in life they had higher body weight ($P \leq 0.05$) and calved earlier ($P \leq 0.01$) than cows with the *CC* genotype (differences of +18.5 kg and 217 days). There was also a difference in age at first calving between individuals with the *TT* and heterozygous genotypes (80.7 days; $P \leq 0.05$). Although heterozygotes had a higher birth weight (non-additive effect), later in life the individuals with the lowest birth weight (*TT*) were

found to have a faster growth rate (which allowed them to reach the highest target weight) and to calve earlier than other animals, especially those with the *CC* genotype (potential additive effect).

To date, little information has appeared in the Polish or world literature regarding polymorphism in the bovine *IGF1R* gene and the meat production parameters analysed in this study. The most commonly identified polymorphic site is *IGF1R*/*Taq*I, described for the first time by Moody et al. (1996), which does not occur in *B. taurus*. This site does not correspond with the *IGF1R*/e21/*Taq*I site presented in this paper. Zhang and Li (2011), Akis et al. (2010), and Curi et al. (2005) showed significant differences between *IGF1R*/*Taq*I genotypes and cattle growth traits.

Szewczuk et al. (2013), in a study on 310 Angus calves, showed no significant differences in birth weight, daily gains or body weight at 210 days for the *IGF1R*/e21/*Taq*I site. However, significant differences in body weight at 210 days were noted for another site in exon 12 (*IGF1R*/e12/*Msp*I), where calves with the *GG* genotype were 5.06 kg heavier than heterozygotes. Analysis of combined genotypes also confirmed these observations. At another site, described by Arnim et al. (2018) as *IGF1R*/*Msp*I, associated with an SNP located in intron 12, no significant relationships with daily gains or body conformation were found.

With regard to the *IGF1R*/e7/*Tai*I site, which in the present study was nearly monomorphic in the Hereford cow population, individuals with the *CC* genotype (about 80% of the population) had significantly higher standardized body weight at 210 days of age, by 5.5 kg ($P \leq 0.05$), but their weight at first calving was 10.6 kg lower than the average weight of individuals with the *CT* genotype ($P < 0.05$) (Szewczuk, 2016a).

The *IGF1R*/e12/*Msp*I site was also the subject of research by Szewczuk et al. (2017) conducted on 141 Hereford individuals and 161 Limousin individuals. Variation in exon 12 had no effect on birth weight, but a relationship was demonstrated between daily weight gains and standardized body weight at 210 days of age, also in favour of the *GG* genotype, as in the Angus breed. This observation was independent of breed.

All three of the above-mentioned sites were also analysed by Szewczuk (2016b) in the context of milk yield traits in Montbéliarde cattle. The study found a higher frequency of heterozygotes (about 10%) at the *IGF1R*/e7/*Tai*I site (there were no individuals with the *TT* genotype) and dominance of the G allele at the *IGF1R*/e21/*Taq*I site instead of the A allele, as is the case in beef cattle.

The only references to the two analysed SNPs located in intron 4 concern Holstein-Friesian dairy cattle. In dairy cattle, the presence of the T allele at the *IGF1R*/i4/*Hinf*I site appears to be more common than in meat breeds, in which the C allele is dominant. In the case of the *IGF1R*/i4/*Mph*1103I polymorphism, the T allele is extremely rare, irrespective of the cattle breed and use type (Szewczuk et al., 2011).

Yi-Lei et al. (2019) analysed parameters characterizing the conformation and body weight of beef cattle in relation to copy number variation (CNV). This is a relatively recently described form of genetic variation, defined as an insertion or deletion of more than 50 bp at

the genome level between individuals of the same species. The authors suggest that CNVs may affect phenotype features in cattle, particularly those associated with height ($P \leq 0.01$) and body weight ($P \leq 0.05$).

Regarding polygenic control of meat traits in cattle, the somatotropic axis contains a number of promising candidate genes, whose main core is genes encoding growth hormone together with a specific receptor (*GH*/*GHR*) and insulin-like growth factor 1, also with its receptor (*IGF1*/*IGF1R*). Casas et al. (2003) and Morris et al. (2003) indicate the presence of significant QTL (quantitative trait loci) regions for calf birth weight on chromosome 21 (BTA21), specifically in the centromeric region on a 1-10 cM segment. This is the area corresponding to the location of the *IGF1R* gene. In the present study, it was primarily the birth weight of calves that significantly differed depending on the genotype.

Silent mutations in exons, such as the *IGF1R*/e7/*Tai*I site chosen in this study, have no direct impact on the mature amino acid chain of the receptor. Aspartic acid (D^{491+30}), within which this mutation is located in the codon corresponding to this amino acid, is located in one of three domains of type III fibronectin (amino acids 461-897) (Ullrich et al., 1986), which are not directly linked to attachment of the IGF-I ligand to the extracellular IGF-IR subunit. However, even silent mutations can affect both the speed and precision of translation (Drummond and Wilke, 2008) and determine how 'raw' mRNA is assembled and ultimately organized (Parmley et al., 2006). In contrast, point mutations within the 3'UTR region, like the *IGF1R*/e21/*Taq*I polymorphism analysed in this study, in connection with the activity of microRNAs may have an indirect role in determining the stability or instability of an mRNA molecule, e.g. of the *IGF1R* gene, and 'silencing' of the information stored on it. They may sometimes even lead to the formation of new disease entities (Huntzinger and Izaurralde, 2011).

The least attention is focused on polymorphic sites located in the non-coding part (introns), until recently considered to play no significant role. An example in the present study is the two sites *IGF1R*/i4/*Hinf*I and *IGF1R*/i4/*Mph*1103I. Introns, however, in which incomparably more SNPs are detected than in exons, may include sequences for many enhancers or silencers that regulate transcription of genetic information or control alternative gene splicing (Cooper, 2010). Nevertheless, neither polymorphic site occurs within regions of known human and mouse enhancers deposited in the VISTA, FANTOM5 and dbSUPER databases (Visel, 2007; Andersson et al., 2014; Khan and Zhang, 2016).

In many cases, identified SNPs may be located adjacent to functional but as yet undescribed SNPs of potentially great practical importance. These SNPs can be used as genetic markers in genome-wide association studies (GWAS) (Hay and Roberts, 2018). According to Fortes et al. (2013), variation within the genes encoding the IGF-I signalling pathway (especially *IGF1R*) may be linked to earlier sexual maturation in cows, especially if the analysis takes into account *IGF1R* haplotypes. The location of intron 4, which is directly associated with the two polymorphisms studied here, may determine its functionality, as

the main IGF-IR amino acid chain is not coded until exon 3, and subsequent gene fragments and their regulation on the exon-intron plane affect the final α subunit of the receptor, which interacts directly with IGF-I.

Conclusions

The results presented above indicate that polymorphism in the *IGF1R* gene can be used to improve meat traits in cattle. The study showed for the first time a relationship between the *IGF1R*/i4/*Hinf*I polymorphism and the analysed growth and development parameters of Hereford cattle, in favour of the T allele. The observations should, however, be supported by further studies conducted in other, larger herds and with more uniform frequency of individual genotypes, as well as in other breeds of beef cattle.

REFERENCES

Akis I., Oztabak K., Gonulalp I., Mengi A., Un C. (2010). IGF-1 and IGF-1R gene polymorphisms in east anatolian red and South Anatolian red cattle breeds. Russian Journal of Genetics, 46 (4): 497–501 (DOI: 10.1134/S1022795410040083).

Andersson R., Gebhard C., Miguel-Escalada I., Hoof I, Bornholdt J., Boyd M. (2014). An atlas of active enhancers across human cell types and tissues. Nature, 507: 455–461 (DOI:10.1038/nature12787).

Arnim Y., Afriani T., Putra D.E. (2018). Association of GH, IGF1R, and PIT1 genes polymorphism with average daily gain and body measurement in Pesisir cattle. Nusantara Bioscience, 10: 221-225 (DOI: doi.org/10.13057/nusbiosci/n100404).

Casas E., Shackelford S.D, Keele J.W., Koohmaraie M., Smith T.P., Stone R.T. (2003). Detection of quantitative trait loci for growth and carcass composition in cattle. Journal of Animal Science, 81: 2976-2983 (DOI: 10.2527/2003.81122976x).

Cooper D.N. (2010). Functional intronic polymorphisms: Buried treasure awaiting discovery within our genes. Human Genomics, 4 (5): 284–288 (DOI:10.1186/1479-7364-4-5-284).

Curi R.A., Oliveira H.N., Silveira A.C., Lopes C.R. (2005). Association between IGF-I, IGF-IR and GHRH gene polymorphisms and growth and carcass traits in beef cattle. Livestock Production Science, 94: 159–167.

Drummond D.A., Wilke C.O. (2008). Mistranslation-induced protein misfolding as a dominant constraint on coding-sequence evolution. Cell, 134: 341-352 (DOI: 10.1016/j.cell.2008.05.042).

Fortes M.R., Li Y., Collis E., Zhang Y., Hawken R.J. (2013). The IGF1 pathway genes and their association with age of pubertyin cattle. Animal Genetics, 44: 91–95 (DOI: 10.1111/j.1365-2052.2012.02367.x).

Hay E.H., Roberts A. (2018). Genome-wide association study for carcass traits in a composite beef cattle breed. Livestock Science, 213: 35–43 (DOI: 10.1016/j.livsci.2018.04.018).

Huntzinger E., Izaurralde E. (2011). Gene silencing by microRNAs:contributions of translational repression and mRNA decay. Nature Reviews Genetics, 12: 99–110 (DOI: 10.1038/nrg2936).

Kim J.W. (2014). Modulation of the somatotropic axis in periparturient dairy cows. Asian-Australasian Journal of Animal Sciences, 27 (1): 147-154 (DOI: https://doi.org/10.5713/ajas.2013.13139).

Khan A., Zhang X. (2016). dbSUPER: a database of super-enhancers in mouse and human genome. Nucleic Acids Research, 44: D164–71 (DOI: 10.1093/nar/gkv1002).

Macháčková K., Mlčochová K., Potalitsyn P., Hanková K., Socha O., Buděšínský M., Muždalo A., Lepšík M., Černeková M., Radosavljević J., Fábry M., Mitrová K., Chrudinová M., Lin J., Yurenko Y., Hobza P., Selicharová I., Žáková L., Jiráček J. (2019). Mutations at hypothetical binding site 2 in insulin and insulin-like growth factors 1 and 2 result in receptor- and hormone-specific responses. Journal of Biological Chemistry, 294 (46): 17371–17382 (DOI: 10.1074/jbc.RA119.010072).

Moody D.E., Pomp D., Barendse W. (1996). Linkage mapping of the bovine insulin-like growth factor-1 receptor gene. Mammalian Genome, 7: 168–169 (DOI: doi.org/10.1007/s003359900046).

Morris C.A., Cullen N.G., Pitchford W.S., Hickey S.M., Hyndman D.L., Crawford A.M., Bottema C.D. (2003). QTL for birth weight in Bos taurus cattle. Association for the Advancement of Animal Breeding and Genetics Proceedings, 15: 400–403.

Obrępalska-Stęplowska A., Durzyński Ł., Goździcka-Józefiak A. (2005). Insulinopodobny czynnik wzrostu i białka z nim współdziałające. Insulin-like growth factor and interacting proteins. Postępy Biochemii, 51 (1): 70–79 (in Polish).

Parmley J.L., Chamary J.V., Hurst L.D. (2006). Evidence for purifying selection against synonymous mutations in mammalian exonic splicing enhancers. Molecular Biology and Evolution, 23: 301–309 (DOI: 10.1093/molbev/msj035).

Plath-Gabler A., Gabler C., Sinowatz F., Berisha B., Schams D. (2001). The expression of the IGF family and GH receptor in the bovine mammary gland. Journal of Endocrinology, 168: 39–48.

STATSOFT INC. (2013). STATISTICA® (data analysis software system), version 12. (www.statsoft.com).

Szewczuk M. (2016a). Effects of SNP within Exon 7 of the Insulin-like Growth Factor Receptor Type 1 (IGF1R) Gene on Growth Traits in Angus Cows. Tarim Bilimleridergisi – Journal of Agricultural Sciences, 22: 492–499.

Szewczuk M. (2016b). Association of single nucleotide polymorphisms in genes coding insulin-like growth factor 1 system and milk production traits in Montbeliarde cows. South African Journal of Animal Science, 46: 191–195 (DOI: dx.doi.org/10.4314/sajas.v46i2.10).

Szewczuk M., Sablik P., Kulig H. (2017). The effect of polymorphism within exon 12 of IGF1R gene on meat production traits in Limousin and Hereford cattle. Acta Scientiarum Polonorum Zootechnica, 16 (4): 53–56 (DOI: 10.21005/asp.2017.16.4.08).

Szewczuk M., Wilkowiecki P., Zych S., Czerniawska-Piątkowska E., Wójcik J. (2011). Asso-ciation between two polymorphisms within intron 4 of insulin-like growth factor receptor type 1 gene (IGF1R/HinfI and IGF1R/Mph1103I) and milk traits of Polish Holstein-Friesian cows. Acta Scientiarum Polonorum Zootechnica, 10 (4): 133–140.

Szewczuk M., Zych S., Wójcik J., Czerniawska-Piątkowska E. (2013). Association of two SNPs in the coding region of the insulin-like growth factor 1 receptor (IGF1R) gene with growth-related traits in Angus cattle. Journal of Applied Genetics, 54: 305–308 (DOI: 10.1007/s13353-013-0155-z).

Ullrich A., Gray A., Tam W., Yang-Feng T., Tsubokawa M., Collins C., Henzel W., Le Bon T., Kathuria S., Chen E. (1986). Insulin-like growth factor I receptor primary structure: comparison with insulin receptor suggests structural determinants that define functional specificity. The EMBO Journal, 5: 2503–2512.

Visel A., Minovitsky S., Dubchak I., Pennacchio L.A. (2007). VISTA Enhancer Browser—a database of tissue-specifc human enhancers. Nucleic Acids Research, 35: D88–92.

Yi-Lei M., Yi-Fan W., Xiu-Kai C., Jie Ch., Yong-Zhen H., Yun M., Lin-Yong H., Chu-Zhao L., Xing-Lei Q., Hui C., Hong Ch. (2019). Copy number variation (CNV) in the IGF1R gene across four cattle breeds and its association with economic traits. Archives Animal Breeding, 62 (1): 171–179 (DOI: 10.5194/aab-62-171-2019).

Zhang R., Li X. (2011). Association between IGF-IR, m-calpain and UCP-3 gene polymorphisms and growth traits in Nanyang cattle. Molecular Biology Reports, 38: 2179–2184 (DOI: 10.1007/s11033-010-0346-1).