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Effects of SNP within Exon 7 of the Insulin-like Growth Factor Receptor Type 1 (*IGF1R*) Gene on Growth Traits in Angus Cows

Małgorzata SZEWCZUK^a

^aThe West Pomeranian University of Technology, Department of Ruminant Science, Laboratory of Biostatistics, Judyma 10, 71-460, Szczecin, POLAND

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Corresponding Author: Małgorzata SZEWCZUK, E-mail: malgorzata.szewczuk@zut.edu.pl, Tel: +48 (91) 449 68 07

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ABSTRACT

Insulin-like growth factor 1 receptor (*IGF1R*) signaling pathway plays a key role in the postnatal growth and development. The tyrosine kinase receptor *IGF1R* forms homodimers that is activated by *IGF-I* which trigger autophosphorylation of *IGF1R* and subsequent downstream signal transduction. The objectives of this study were to identify, characterize and the examination of the association between silent SNP (rs41961336; C→T) within exon 7 of bovine *IGF1R* gene and growth traits. A total of 672 cows of four breeds was genotyped using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) method. A *TaiI* restriction endonuclease was used. Among all breeds under study (Polish Holstein Friesian, Angus, Hereford, Limousine), the presence of all three genotypes was observed only for the Angus breed. The *CC* genotype was the most frequent in all investigated breeds (0.7987-0.9904) followed by *CT* (0.0096-0.1946). Only Angus cows were selected for association analysis. At weaning weight adjusted to 210 days of age (WWT_{210}), statistically significant differences ($P \leq 0.05$) were shown-female calves with the *CC* genotype were heavier (+5.5 kg) than the individuals with the *CT* genotype. However, individuals carrying the *CT* genotype had significantly higher body weight at first calving (+10.62 kg; $P \leq 0.05$). The present work failed to show association between genotypes of the *IGF1R/TaiI* polymorphism and BWT, ADG or age at first calving.

Keywords: Beef; Genetic markers; Tyrosine kinase; Quantitative trait loci

İnsülin-benzeri Büyüme Faktörü Reseptör Tip 1 (*IGF1R*) Geninin Ekson 7 İçindeki Tek Nükleotid Polimorfizminin (SNP) Angus İneklerinin Büyüme Ölçütleri Üzerine Olan Etkileri

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Araştırma Makalesi

Sorumlu Yazar: Małgorzata SZEWCZUK, E-posta: malgorzata.szewczuk@zut.edu.pl, Tel: +48 (91) 449 68 07

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ÖZET

İnsülin benzeri büyüme faktörü-1 reseptör (IGF1R) sinyal yolu, doğum sonrası büyüme ve gelişmede önemli bir rol oynar. IGF1R tirozin kinaz reseptörü, IGF1R'nin otofosforilasyonunu tetikleyen IGF-I tarafından aktive edilen homodimerleri ve sonrasında meydana gelen aşağı sinyal transdüksiyonu oluşturmaktadır. Bu çalışmanın amacı, sığır *IGF1R* geni içinde bulunan ekzon 7 içindeki sessiz SNP (rs41961336; C→T) ile büyüme özellikleri arasındaki ilişkinin tanımlanması, karakterize edilmesi ve incelenmesidir. Dört farklı ırktan toplam 672 adet inek polimeraz zincir reaksiyonu-restriksiyon parça uzunluk polimorfizmi (PCR-RFLP) metodu kullanılarak genotiplenmiştir. Çalışılan tüm ırklar (Polonya Holstein Friesian, Angus, Hereford, Limousine) içinde, her üç genotip varlığı sadece Angus ırkında gözlenmiştir. *CC* genotipi araştırılan tüm ırklarda en sık gözlenen genotip olmuş (0.7987-0.9904) ve bunu *CT* genotipi takip etmiştir (0.0096-0.1946). Sadece Angus inekleri ilişkilendirme analizleri için seçilmiştir. 210 günlük yaşa (WWT_{210}) düzeltilmiş süttten kesim ağırlığında, *CC* genotipli dişi buzağuların, *CT* genotipli bireylerden istatistiki olarak daha ağır oldukları (+5.5 kg) bulunmuştur ($P \leq 0.05$). Buna karşılık, *CT* genotipini taşıyan bireyler, ilk buzağılamada daha yüksek canlı ağırlık kazanmıştır (+10.62 kg; $P \leq 0.05$). Bu çalışma, *IGF1R/Tail* polimorfizminin genotipleri ile doğum ağırlığı, günlük canlı ağırlık kazancı veya ilk buzağılama yaşı arasındaki ilişkiyi göstermede başarısız olmuştur.

Anahtar Kelimeler: Sığır; Genetik markörler; Tirozin kinaz; Kantitatif özellik lokusu

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1. Introduction

The insulin-like growth factor (IGF) signaling pathway has many important roles in normal cell growth and development. In mammals, insulin regulates cell metabolism, whereas insulin-like growth factor I (IGF-I) is an important regulator of cell growth (Humbel 1990). Remarkably, all of the components of this system (IGFs, receptors, and binding proteins) are also expressed in bovine mammary gland (Plath-Gabler et al 2001) and skeletal muscle (Blum et al 2007; Micke et al 2011) where development, nutrient uptake and utilization is largely coordinated by growth hormone (GH) and its main downstream effector, IGF-I. In laboratory animals, several studies have shown that GH treatment increases IGF-I mRNA in skeletal muscle through STAT5 molecules (Udy et al 1997; Teglund et al 1998; Woelfle et al 2003). IGF-I signals via the type 1 of IGF-I receptor (IGF-IR), which is a widely expressed cell surface $\alpha_2\beta_2$ heterotetramer held together by disulfide bridges, highly similar to the IR (Ullrich et al 1986). The importance of the IGF-IR in normal mammalian development is clear from studies in mice lacking functional receptors. Liu et al (1993) demonstrated that *igf1r* null mice were 45% of the size of wild-type individuals at birth, and died shortly due to severe organ hypoplasia

while mouse embryonic fibroblasts cultured from *igf1r* null mice grew more slowly than wild-type fibroblasts, and were unable to proliferate under anchorage-independent conditions (Sell et al 1994).

The bovine IGF-IR, similar to human homologue, is synthesized as a single chain precursor composed of 1367 amino acids. The pre-receptor monomer of human IGF-IR includes a 30 residue signal peptide (residues 1 to 30) and an Arg-Lys-Arg-Arg furin protease cleavage site at residues 737-740, divided into one α -chain and one β -chain. The α -chain (residues 31-736) and 195 residues of β -chain comprise the extracellular portion of the IGF-IR and contain eleven and five potential N-linked glycosylation sites, respectively (Ullrich et al 1986). Subsequently, there is also a single transmembrane sequence (residues 936-959) and a 408 residue cytoplasmic domain (residues 960-1337) possessing intrinsic kinase activity (Favelyukis et al 2001). Free IGF-I molecule bind to the cysteine-rich domain of the α -subunits, leading to the transmission of a specific signal through the transmembrane domain to the β -subunit. Conformational change of the transmembrane domain causes stimulation of tyrosine kinase activity, followed by autophosphorylation of a cluster of tyrosine residues of the IGF-IR (Keyhanfar

et al 2007). It is known, that IGF-I induces skeletal muscle hypertrophy by activating the IGF-IR/IRS1/PI3K/Akt pathway (Shi et al 2011).

Human *IGF1R* gene is greater than 300 kbp in size and contain 21 exons, ten in the α -chain and eleven in the β -chain (Ullrich et al 1986). Bovine *IGF1R* homolog has been mapped to chromosome 21 (Moody et al 1996). More than 200 single nucleotide polymorphisms (SNPs) were identified in *Bos taurus* and submitted to the National Center for Biotechnology Information (NCBI) website (NCBI reference sequence: AC_000178.1; alternate assembly UMD 3.1 WGS) but most of them are located in non-coding regions. Several of these SNPs are silent mutation or localized within 3'UTR.

The objectives of this study were to identify, characterize and the examination of the association between SNP within exon 7 of bovine *IGF1R* and performance traits.

2. Material and Methods

The study involved a total of 672 female individuals including Angus (n= 298), Limousine (n= 141), Polish Holstein Friesian (n= 129) and Hereford (n= 104) cows kept on four different farms (one for each breed) belonging to the largest co-operative firm located in the West Pomeranian province, Poland.

Dairy cows were kept in an intensive system in free stalls with access to the feed. A complete Total Mixed Ration (TMR) feeding system was used and cows had continuous access to water from automatic drinkers. Milking took place twice a day in the milking parlor, "side by side", using the ALPRO system.

Beef cows were kept in a chamber system. Only calving cows were driven to the barn, where they stayed with their calves for one week after calving. After this time, dams with their offspring were moved to the outside run. Summer feeding was entirely based on the good pasture. In winter, the diet consisted of grass silage and maize, haylage and hay supplemented with minerals and vitamins. Calving cows were additionally fed the B-1 concentrate

mixture. The animals had permanent access to water. Data on the beef performance were collected based on the breeding documentation ("heifer-beef cow" charts) and the information from the farm according to the guidelines of The Polish Association of Beef Cattle Breeders and Producers.

Peripheral blood was taken from animals from the external jugular vein into test tubes containing the EDTA anticoagulant. The DNA was isolated using MasterPure™ DNA Purification Kit (Epicentre Technologies) according to the manufacturer's instructions.

A silent transition at the third nucleotide of the codon encoding for aspartic acid (D⁴⁹¹; GAC → GAT) is localized within exon 7 of the *Bos taurus IGF1R* gene and submitted as rs41961336 (NCBI 2015).

Genotyping of the selected *IGF1R* SNP marker was carried out using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) method. A *TaiI* restriction endonuclease (neoschizomer of *MaeII*) is able to recognize cytosine at this position. To genotype the *IGF1R/e7/TaiI* polymorphism, a pair of primers (IGF1Re7F 5' acagtgttggtccttagtg 3' and IGF1Re7R 5' aggtgatgatgattcggtctt 3') were designed based on the sequence of the *IGF1R* gene (GenBank Accession No. JQ715681) and then used to amplify a 236-bp DNA fragment.

The PCR reaction volume of 20 μ L contained approximately 30-50 ng of genomic DNA, 0.5 units of *Taq* DNA polymerase (FERMENTAS, Lithuania), 1 \times PCR buffer with (NH₄)₂SO₄ (FERMENTAS, Lithuania), 2 mM MgCl₂, 10 pmol of each primer (IBB PAS, Poland), 200 μ M of each dNTP (FERMENTAS, Lithuania) and nuclease-free deionized water (Epicentre Technologies, Madison, USA). Thermal cycling conditions were as follows: 5 min at 94 °C, 30 cycles of 94 °C for 30 s, annealing temperature (60 °C) for 30 s, and 72 °C for 40 s, followed by a final step of 72 °C for 5 min in the Biometra thermal cycler. Amplified fragments were digested for 3 hours at 65 °C with 5 units of *TaiI* restriction enzyme (10 U μ L⁻¹, ACGT↓;

FERMENTAS, Lithuania), and next subjected to electrophoretic separation in 2% ethidium bromide-stained Agarose gel (Basica LE GQT, Prona, Spain). The length of the obtained products was compared with the pUC19/*MspI* molecular mass marker (FERMENTAS, Lithuania). To confirmation, selected samples for a particular genotypes were additionally sequenced (IBB PAS, Poland).

Association analyses between genotype and birth weight (BWT), weaning weight adjusted to 210 days of age (WWT_{210}) as well as average daily gains between birth and weaning (ADG) following by age and body weight at first calving was analyzed based on the data obtained from the official recordings.

The differences between particular genotypes were evaluated with Duncan’s test and Bonferroni’s test (STATISTICA 10.0 PL software package, Statsoft Inc. 2009). Statistical calculations were performed using a General Linear Model (GLM). As the statistical models Equation 1 and Equation 2 were used.

$$BWT, ADG, WWT_{210}, Y_{ijkl} = \mu + G_i + s_j + BYS_k + e_{ijkl} \quad (1)$$

Where; Y_{ijkl} , analyzed trait; μ , overall mean; G_i , fixed effect of *IGF1R* genotype ($i= 1, 2$); s_j , random effect of sire ($j= 1, \dots, 53$); BYS_k , fixed effect of birth year/season ($k= 1, \dots, 20$); e_{ijkl} , random error

Age and body weight at first calving,

$$Y_{ijklm} = \mu + G_i + s_j + CYS_k + b_l (cBW - cBW_l) + e_{ijklm} \quad (2)$$

Where; Y_{ijklm} , analyzed trait; μ , overall mean; G_i , fixed effect of *IGF1R* genotype ($i= 1, 2$); s_j , random effect of sire ($j= 1, \dots, 53$); CYS_k , fixed effect of year/season of 1st calving ($k= 1, \dots, 16$); b_l , regression coefficient on birth weight of calves; cBW , mean birth weight of calves; cBW_l , birth weight of a *l*-calf; e_{ijklm} , random error

The chi-square test was used to verify whether each population is in Hardy-Weinberg equilibrium.

3. Results and Discussion

Among all breeds under study, the presence of all three genotypes was observed only for the Angus breed (Table 1). Based on the chi-square test, it was found that genotype frequencies of *IGF1R/TaiI* polymorphism in all breed under study were under genetic equilibrium. The PCR products with cytosine at position 191 (GenBank acc. No JQ715681) were digested by *TaiI* into four fragments of 141, 45, 26 and 24 bp (allele C) while allele T gave a cleavage pattern of 167, 45 and 24 bp (Figure 1). The CC genotype was the most frequent in all investigated breeds (0.7987-0.9904) followed by CT (0.0096-0.1946). Due to the TT homozygote deficiencies, C allele frequency was very high-more than or equal to 0.9 in all population, whereas that of T allele was only equal or less than 0.1.

Table 1- Numbers and frequencies of genotypes and alleles of the *IGF1R/e7/TaiI* polymorphism

Çizelge 1- IGF1R/e7/TaiI polimorfizminin genotip ve allellerdeki sayı ve frekansları

Breed	IGF1R/TaiI genotypes			Total	Allele		
	CC	CT	TT		C	T	
Polish Holstein Friesian	n	124	5	0	129	0.9806	0.0194
	f	0.9612	0.0388	0.0000	1.0000		
Angus	n	238	58	2	298	0.8960	0.1040
	f	0.7987	0.1946	0.0067	1.0000		
Hereford	n	103	1	0	104	0.9951	0.0049
	f	0.9904	0.0096	0.0000	1.0000		
Limousine	n	138	3	0	141	0.9894	0.0106
	f	0.9787	0.0213	0.0000	1.0000		
Total					672		

n, number of cows; f, frequency

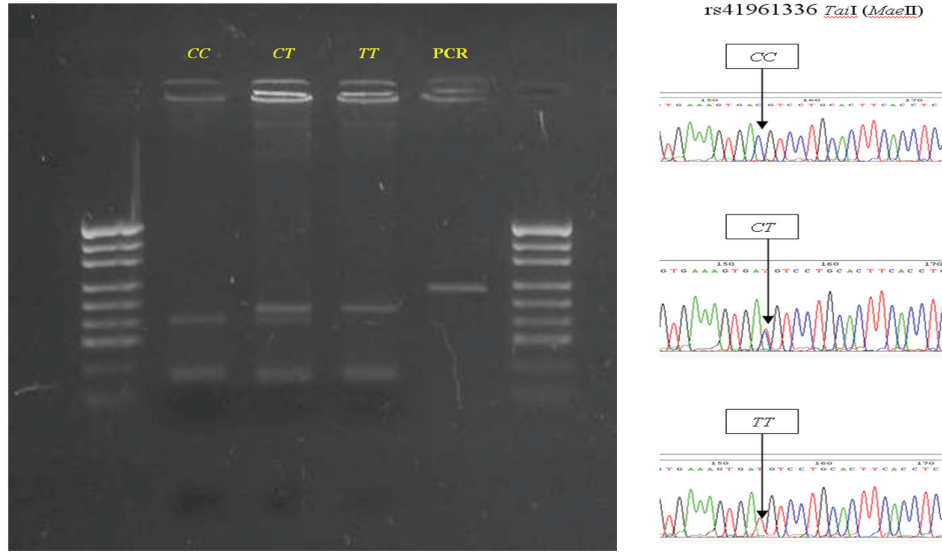


Figure 1- Agarose gel electrophoresis and fluorogram to distinguish *TaiI* restriction fragment length polymorphism in 236-bp fragment of the bovine insulin-like growth factor receptor type 1 gene, lanes 1 and 6 - pUC19/*MspI* DNA mass marker, lanes 2-4 genotypes, lane 5 PCR product without digestion

Şekil 1- 236 bp büyüklüğündeki sığır insülin-benzeri tip 1 büyüme faktörü reseptörü genindeki *TaiI* kesim parçasını ayırtmak için agaroz jel elektroforezi ve fluorogramı, hat 1 ve 6- pUC19/*MspI* DNA belirteci, hat 2-4 genotipler, hat 5 kesimsiz PCR ürünü

Despite the fact that a total of 672 cows of three breeds raised for meat production and one breed used for milk production were genotyped, only Angus cows with two groups of genotypes (*CC* and *CT*) could be selected for further analysis. Due to the low number of individuals in the group ($n=2$), the *TT* genotype group was excluded. Results for association analysis between *IGF1R/TaiI* genotypes

and studied traits in Angus are presented in Table 2. At WWT_{210} , statistically significant differences ($P\leq 0.05$) between body weights of female calves with the *CC* genotype (+5.5 kg) and the female individuals with the *CT* genotype were shown. However, individuals carrying the *CT* genotype had significantly higher body weight at first calving (+10.62 kg; $P\leq 0.05$).

Table 2- Frequencies and mean values of the analyzed performance traits of Angus cows with the different *IGF1R* gene variants (standard errors in parentheses)

Çizelge 2- Farklı *IGF1R* gen değişkenliğine sahip Angus sığırlarında analiz edilen performans özelliklerinin ortalama değerleri ve frekansları (standart hatalar parantez içerisinde verilmiştir)

Polymorphism	Genotype	n	f	BWT (kg)	ADG (g)	WWT ₂₁₀ (kg)	Age at first calving (days)	Body weight at first calving (kg)
<i>IGF1R/TaiI</i>	CC	238	0.7987	36.61 (0.20)	992.97 (4.40)	246.91 ^{a*} (1.27)	1067.71 (13.55)	563.86 ^a (2.06)
	CT	58	0.1946	36.81 (0.42)	978.43 (10.48)	241.41 ^a (2.72)	1060.72 (26.44)	574.48 ^a (3.57)

*, means within columns bearing the same letters differ significantly at $P\leq 0.05$; f, frequency

In the present manuscript, there was no association between genotypes of the *IGF1R/Tail* polymorphism and BWT, ADG or age at first calving.

Multiple genes potentially influencing meat and milk production have been investigated in a lot of breeds in order to find interbreed and intrabreed polymorphism and association with production traits. However, without clearly defined conclusions so far. The insulin-like growth factor I receptor (*IGF1R*) has an important effect on growth, carcass, and meat quality traits in many species. In this study, we have designed, optimized and validated protocol capable of detecting rs41961336 SNP within exon 7 of bovine *IGF1R*. In spite of the *IGF1R/Tail* being a SNP in a coding region as a silent mutation, it could be only linked or in linkage disequilibrium with causative polymorphisms associated to phenotype differences. However, in addition to the rs41961336 only few SNPs within bovine exons are known and only one of them is potentially *missense*-rs209595810. Two polymorphic sites are recently described and validated (Szewczuk et al 2013). According to our research carried out in the years 2009-2011 (data not shown), a significant part of submitted SNPs (including unique-*missense* and majority of silent mutations) was not present in breeds under study. This can be explained by the fact that the NCBI database contains submission from whole world often taking into account rare native breeds or frequencies of genotypes. Furthermore, extreme low frequency of minor allele (MAF) of rs41961336 SNP was demonstrated. Only Angus breed (0.010) may be comparable to Brahman cattle (Fortes et al 2013) in this respect. Therefore, low MAF strongly limits the usability of this mutation in the association studies.

Analysis of evolutionary conservation of IGF-I and their receptors had provided insights into essential regions, in which the tyrosine kinase domain is highly conserved among vertebrate species (residues 999-1274) (Le Roith et al 1993) including an activation loop (tyrosines: Y¹¹⁶¹,

Y¹¹⁶⁵ and Y¹¹⁶⁶) (Favelyukis et al 2001). Studies performed on humans indicated that there were important associations of the *IGF1R* gene with growth and development (Inagaki et al 2007). As is shown by Blum et al (2007), the reduced presence of *IGF1R* may have been the underlying cause of dwarfism in calves. The association between SNP within exon 7 and growth traits in beef cattle has not been reported so far. For this reason, it was also the aim of this study to validate this SNP by analyzing the effect of the *IGF1R/Tail* polymorphism on birth weight followed by daily gaining and body weight at different stages of live. It has been limited to Angus breed. Cows with the *CT* genotype with initially lowest WWT_{210} were then heavier at first calving in comparison to *CC* female individuals, despite the fact that first calving was an average of 7 days earlier. In the present work, rs41961336 failed to show association between genotypes and age at first calving. Recent studies show only that rs41961336 did not revealed associations with age of puberty in Brahman cattle (Fortes et al 2013). However, other polymorphism-*IGF1R/MspI* within exon 12-had a significant association with WWT_{210} in Angus cows (Szewczuk et al 2013). No significant differences in growth traits were observed between the genotypes of intronic *IGF1R/TaqI* polymorphism in Nanyang cattle (Zhang & Li 2010). However, evidences suggest the presence of a QTL for growth traits on chromosome 21. Davis et al (1998), Casas et al (2003) and Morris et al (2003) reported a significant *Quantitative Trait Loci* (QTL) for birth weight in the centromeric region of BTA21 with support interval 1-10 cM, where almost exactly in the middle the *Bos taurus IGF1R* gene is localized. On the other hand, Kim et al (2003) and Casas et al (2004) found a QTL for birth weight with support interval 50-63 cM and relative positions at 62 or 56 centimorgans from the beginning of the linkage group (telomeric), respectively. As it can be seen, two QTL for the same trait reside on the same chromosome. This inconsistency across above mentioned studies can partly be explained among other things by the density and kind of the markers and the different breeds used in the studies.

4. Conclusions

Fine mapping around the marker site may eventually lead to the confirmation of some of the underlying genes associated with BW and other growth traits, and this may provide important insights into the biology of growth and development. For this reason, it is reasonable to evaluate the impact of other SNPs (more than 200) within bovine *IGF1R* gene. Once an objective has been defined and appropriate genetic relationships determined, marker-assisted selection may be a cost-effective option in breeding work in a beef herds.

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