Association of insulin-like growth factor I gene polymorphisms (*IGF1*/*Tas*I and *IGF1*/*Sna*BI) with the growth and subsequent milk yield of Polish Holstein-Friesian heifers

M. Szewczuk[1], M. Bajurna[1], S. Zych[2], W. Kruszyński[3]

[1]Laboratory of Molecular Cytogenetics, Department of Ruminant Science, The West Pomeranian University of Technology, Szczecin, Poland
[2]Laboratory of Veterinary Diagnostics LaboWet, Szczecin, Poland
[3]Division of Animal Breeding and Cytogenetics, Department of Genetics, Wrocław University of Environmental and Life Sciences, Wroclaw, Poland

ABSTRACT: The aim of this study was to estimate potential relationships between insulin-like growth factor I gene polymorphisms (*IGF1*/*Tas*I and *IGF1*/*Sna*BI) and the growth parameters of calves as well as their subsequent milk performance. The study involved a total of 191 Polish Holstein-Friesian var. Black-and-White calves. Both polymorphic sites were determined with Amplification Created Restriction Sites-Polymerase Chain Reaction (ACRS-PCR). In the case of the *IGF1*/*Sna*BI polymorphism, the genotype and allele frequencies were as follows: *TT* – 0.27, *CT* – 0.55, *CC* – 0.18, *T* – 0.54, and *C* – 0.46. The *CC* genotype was favourable and associated with higher body weight at the 2nd month of age of calves (WT60) and their daily body weight gains from the 1st to the 2nd month ($P \leq 0.05$) as well as subsequent milk, fat, and protein yield ($P \leq 0.01$). For the *IGF1*/*Tas*I polymorphism, the highest frequency of the *AA* genotype (0.69) was found. Allele frequencies were 0.75 and 0.25 for the *A* and *C* alleles, respectively. In the association study, the *AC* genotype was significantly associated with higher WT60 and average daily gains in the periods from the 2nd to the 3rd month of age and for the whole rearing period ($P \leq 0.05$) as well as subsequent milk, fat, and protein yield ($P \leq 0.01$). Combined genotypes were also included into the analysis. The highest yields of milk as well as fat and protein were found in cows with the *CC/AA* combination. No clear relationships between body weight and genotype combination were found.

Keywords: cattle; body weight; insulin-like growth factors; milk performance

The growth and development of an organism is regulated by both internal (integration of signal pathways) and environmental (mainly supplied from feed) factors (Kišac et al., 2011). There are many reports on the significant relationship between the insulin-like growth factors (IGFs) system and the prenatal growth as well as the growth and differentiation of the mammary gland (Plath-Gabler et al., 2001).

In the postnatal period growth hormone has proven to be the major regulator of growth and metabolism in mammals. The effects of growth hormone (GH) in promoting postnatal body growth and carcass composition are IGF-I dependent (Velloso, 2008). It has also been shown that GH affects the process of aging and reproduction as well as immune response of an organism (Szewczuk et al., 2009) and milk traits (Hradecká et al., 2008).

Gene coding for the bovine IGF-I is located on chromosome 5 (BTA5) (Bishop et al., 1991). The *IGF1* gene expression is regulated both at the transcription and translation levels. In the bovine *IGF1* gene promoter region, three polymorphic sites have been detected and described. The first

one is $(CA)_n$ dinucleotide repeat polymorphism located in the P1 promoter (Kirkpatrick et al., 1992) within which the A/C transversion was identified at position –977 bp upstream from the ATG codon in exon 1 (GenBank Acc. No. DQ975234)(Zych et al., 2007). Also, the C/T transition (GenBank Acc. No. AF017143) (Ge et al., 2001) was found at position –512 bp. A 4-bp deletion (TTTG) within intron 4 and one SNPs within intron 5 (*IGF1*/*Dpn*II polymorphism) were detected by Lien et al. (2000) (GenBank Acc. No. AF210383-387). Nine novel SNPs within introns and 3'UTR were genotyped by Mullen et al. (2011). In addition, Whole Genome Shotgun (WGS) libraries contain about 100 SNPs and their number still increases. Many researchers have shown an association between the *IGF1* genotypes and milk yield and composition (Curi et al., 2005; Siadkowska et al., 2006; Bonakdar et al., 2010; Mehmannavaz et al., 2010; Szewczuk et al., 2011) as well as growth traits in various cattle breeds (Li et al., 2004; Siadkowska et al., 2006; Reyna et al., 2010). The studies conducted so far have mainly been focused on the milk performance in Holstein-Friesian cattle, whereas there is no information on the association between the *IGF1* gene polymorphism and the growth and development of calves and their subsequent yield as adult individuals.

The aim of this study was to show an association of insulin-like growth factor I gene polymorphisms (*IGF1*/*Tas*I and *IGF1*/*Sna*BI) with body weight and daily body weight gains in Holstein-Friesian calves of Black-and-White strain as well as their subsequent milk yield.

MATERIAL AND METHODS

Data

The study involved a population of 191 Polish Holstein-Friesian (HF) var. Black-and-White calves kept in the West Pomerania Province. Calves after birth stayed with their dams in the calving pens in the barn. Then they were moved to igloo hutches with a stockyard outside the building, where they were reared until 90 days of age. After the period of colostrum feeding until 30 days of age, the calves were fed 2 l of whole milk three times a day, whereas older ones (approx. 30-day-old) were given 10 l in three meals a day. Over time the Milsan milk replacer (Sano, Sekowo, Poland) was given up to 6 l per day (2 × 3 l) until 90 days of age. In the calf feeding, the CJ pelleted mixture was used from 15 days of age, whereas meadow hay was fed *ad libitum* from 3 months of age. Milk, milk replacer, and water (*ad libitum*) were given to the calves from the bucket with a teat.

The cows in barns were managed under confinement system. Water was available from automatic drinkers. The feeding of animals took place twice daily from the Sano forage trailer under Total Mixed Ration (TMR) system, with the division into groups according to the lactation stage and milk yield. In summer, the cows used the outside run with an access to the raised feeding place. Milking took place twice daily with the milking pipeline machine. Milk was cooled to 4°C.

The blood for this study was taken from heifers in the years 2005–2009. The data on the growth, development, and health of calves and subsequent milk performance as dairy cows (only the 1st lactation) were derived from the breeding documentation collected as a part of the milk performance testing.

Genotyping

DNA was isolated with the MasterPure™ Genomic DNA Purification Kit (Epicentre Technologies, Akor, Gdansk, Poland).

The genotyping of all individuals was performed with the Amplification Created Restriction Sites-Polymerase Chain Reaction (ACRS-PCR). The first polymorphic site (rs109763947) is located in the promoter region of the bovine *IGF1* gene and was described by Ge et al. (1997) (transition C→T located at –512 bp from the AUG codon of exon 1). For the *bIGF1*/*Sna*BI analysis, the primer sequences designed by Ge et al. (2001) were used (Table 1). The PCR products were digested with 5U of the *Sna*BI endonuclease (37°C/3h) (MBI Fermentas, ABO Gdansk, Poland) which recognized one TAC↓GTA sequence within the PCR product. The second polymorphic site (A→C, described also as G→T rs133990633 within forward strand in the databases) is located in the 5' flanking region of the *IGF1* gene, within the $(CA)_n$ microsatellite polymorphism described by Kirkpatrick (1992). For the *bIGF1*/*Tas*I analysis, the primer sequences designed by Zych et al. (2007) were used (Table 1). Amplicons were digested with the 5U of the *Tas*I restriction enzyme (65°C/3h) (MBI Fermentas, ABO Gdansk, Poland) which recognized one ↓AATT

Table 1. Primer sequences used for amplification of the selected gene fragments of the bovine *IGF1* gene using the ACRS-PCR protocols

Polymorphism	Primer	Primer sequence	T_a (°C)	Length of PCR product (bp)	Restriction enzyme
b*IGF1*/*Sna*BI	IGF677F	5'-ATTACAAAGCTGCCTGCCCC-3'	62	249	*Sna*BI (TAC↓GTA)
	IGF897R	5'-ACCTTACCCGTATGAAAGGAATATACGT-3'*			
b*IGF1*/*Tas*I	IgfP1F	5'-TCATCCAGCTGAGAGATTTGAAT-3'	58	146	*Tas*I (↓AATT)
	IgfP1R	5'-TGTGTGTGTGTGTGTGTGTGAAT-3'*			

T_a = annealing temperature
*mismatch is underlined

sequence within the PCR product. The gels were visualized under UV and archived.

Statistical analyses

Statistical analyses of the association between the *IGF1*/*Sna*BI and *IGF1*/*Tas*I polymorphisms and the birth weight (BWT), body weight in the 1st–3rd month of age (WT30, WT60, WT90, respectively), average daily gains (ADG) of calves in different periods of life (ADG from birth (B)–1 month, ADG 1–2 months, ADG 2–3 months), and ADG for the whole rearing period (B–90 days of age; ADG B–3 months) (1) as well as selected milk performance traits (2): milk yield (kg), milk fat and protein yield (kg), milk fat and protein content (%) were carried out using the STATISTICA software (Version 10.0, 2011).

Statistical calculations were performed by using the General Linear Models (GLM) procedure. The following statistical model was applied:

$$Y_{ijkl} = \mu + G_i + S_j + BS_k + P_l + e_{ijkl} \quad (1)$$

where:
Y_{ijkl} = analyzed trait
μ = overall mean
G_i = effect of the *IGF1/Sna*BI or *IGF1/Tas*I genotype (i = 1, ... 3) or combined genotypes (i = 1, ... 5)
S_j = random effect of a sire (j = 1, ... 106; 1, ... 111; 1, ... 100, respectively)
BS_k = effect of birth season (k = 1, ... 4)
P_l = calving ease (l = l, ... 5)
e_{ijkl} = random error

$$Y_{ijkl} = \mu + G_i + S_j + CS_k + \beta\,(x_l - A_l) + e_{ijkl} \quad (2)$$

where:
Y_{ijkl} = analyzed trait
μ = overall mean
G_i = fixed effect of the *IGF1*/*Sna*BI or *IGF1*/*Tas*I genotype (i = 1, ... 3) or combined genotypes (i = 1, ... 5)
S_j = random effect of a sire (j = 1, ... 106; 1, ... 111; 1, ... 100, respectively)
CS_k = fixed effect of calving season (k = 1, ... 4)
β = linear regression coefficient for calving age
x_l = calving age of a cow
A_l = mean calving age
e_{ijkl} = random error

RESULTS AND DISCUSSION

Allelic and genotypic frequencies of the examined population are presented in Table 2. Results of the association study of *IGF1* polymorphisms and combinations with growth traits of calves and subsequent milk production traits are shown in Tables 3 and 4, respectively.

IGF1/*Sna*BI polymorphism

According to Ge et al. (2001), the *IGF1*/*Sna*BI polymorphism may have a direct effect on the expression of the *IGF1* gene and may be associated with IGF-I concentration in blood serum. Digestion of a 249-bp fragment with *Sna*BI enzyme allowed identification of two alleles (*C* and *T*) determining the occurrence of three genotypes: *TT* (223 and 26 bp), *CT* (249, 223, and 26 bp), and *CC* (no digestion of the PCR product – 249 bp) (Figure 1).

Table 2. Numbers and frequencies of the *IGF1*/*Tas*I and *IGF1*/*Sna*BI genotypes and alleles in Polish Holstein-Friesian cows examined

IGF1/*Sna*BI genotypes				Total	Allele	
	TT	*CT*	*CC*		*T*	*C*
n	51	105	35	191	0.5419	0.4581
Frequency	0.2670	0.5497	0.1833	1.0000		
IGF1/*Tas*I genotypes				total	allele	
	AA	*AC*	*CC*		*A*	*C*
n	129	24	34	187	0.7540	0.2460
Frequency	0.6898	0.1283	0.1819	1.0000		

The frequencies of alleles were estimated at 0.5419 and 0.4581 for the *T* and *C* alleles, respectively. They are similar to those observed in Polish Holstein-Friesian cattle (0.48 and 0.52) by Siadkowska et al. (2006). The results obtained by Ge et al. (2001) in Angus breed also indicate a higher frequency of the *T* allele. In the other studies, authors prove a higher frequency of the *C* allele (Curi et al., 2005; Mehmannavaz et al., 2010; Reyna et al., 2010).

In our study, similar BWTs of calves were found irrespective of the genotype. At WT60, statistically significant ($P \leq 0.05$) differences between body weights of calves with the *CT* genotype and the individuals with the *CC* genotype were shown. Similar but non-significant trends were observed at WT30 and WT90. It was found that the individuals with the *CT* genotype were characterized by a lower ADG B–1 month compared with calves with the *TT* genotype (–31 g; $P \leq 0.05$). It was also observed that the *CC* genotype was associated with higher ADG 1–2 months (+ 52 g; $P \leq 0.05$) in comparison with individuals with the *TT* genotype. However, for the whole rearing period the *IGF1*/*Sna*BI polymorphism was not significantly associated with daily body weight gains of calves. In the case of beef cattle, the relationships between genotypes and growth traits of animals as well as carcass quality were also found (Ge et al., 2001; Curi et al., 2005; Reyna et al., 2010). In the case of calves of dairy breeds, the *IGF1*/*Sna*BI polymorphism has not been analyzed so far.

Most studies conducted so far have been focused on the analysis of polymorphisms in respect of milk yield and milk protein and fat content. In the present study, a favourable relationship between the *CC* genotype and milk yield, milk fat, and protein yields ($P \leq 0.01$) was found. An opposite relationship was observed for the milk protein and

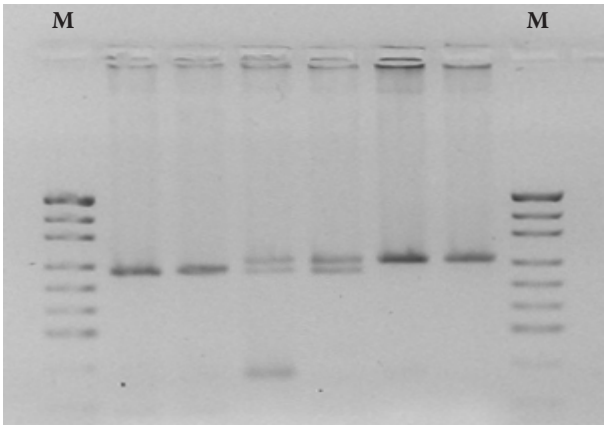

Figure. 1. Agarose gel electrophoresis to detect *Sna*BI restriction fragment length polymorphism in the P1 promoter of the bovine insulin-like growth factor I gene

M = pUC19/*Msp*I DNA mass marker, lanes 2–3 = *TT* genotype, lanes 4–5 = *CT* genotype, lanes 6–7 = *CC* genotype

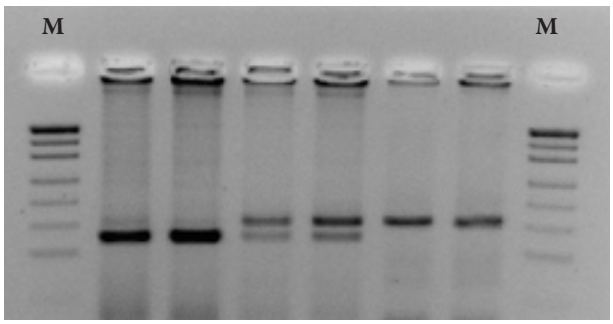

Figure 2. Agarose gel electrophoresis to detect *Tas*I restriction fragment length polymorphism in the 5' region of the bovine insulin-like growth factor I gene

M = pUC19/*Msp*I DNA mass marker, lanes 2–3 = *AA* genotype, lanes 4–5 = *AC* genotype, lanes 6–7 = *CC* genotype

Table 3. Body weight and daily body weight gains of Polish Holstein-Friesian calves depending on *IGF1*/*Sna*BI and *IGF1*/*Tas*I genotypes and their combinations (standard deviations in parentheses)

Polymorphism	Genotype or C.G.	*n*	BWT (kg)	WT30 (kg)	WT60 (kg)	WT90 (kg)	ADG B–1 month (g)	ADG 1–2 months (g)	ADG 2–3 months (g)	ADG B–3 months (g)
IGF1/*Sna*BI	*TT*	51	40.9 (4.16)	60.7 (4.43)	79.1 (4.60)	102.3 (5.79)	662^{a} (97.30)	612^{a} (87.13)	775 (137.53)	683 (61.88)
	CT	105	40.8 (4.80)	59.7 (5.06)	78.7^{a} (4.55)	102.1 (4.41)	631^{a} (117.51)	632 (117.61)	782 (123.34)	682 (56.98)
	CC	35	40.4 (3.89)	60.1 (4.42)	80.0^{a} (5.04)	103.7 (5.84)	654 (95.69)	664^{a} (117.54)	790 (132.54)	703 (59.17)
	total	191								
IGF1/*Tas*I	*AA*	129	40.5 (4.80)	60.2 (4.97)	79.0^{a} (4.78)	101.9 (4.78)	654 (117.56)	627 (106.67)	763^{a} (132.29)	681^{a} (60.86)
	AC	24	41.4 (3.82)	62.0 (3.93)	81.3^{ab} (4.43)	106.0 (5.20)	688 (122.30)	642 (137.00)	825^{a} (120.49)	718^{ab} (61.80)
	CC	34	40.7 (3.94)	59.9 (4.23)	78.3^{b} (4.35)	102.0 (5.38)	640 (92.76)	615 (93.63)	791 (110.80)	682^{b} (55.18)
	total	187								
C.G.	*TT/AA*	24	40.4 (0.86)	60.5 (0.88)	79.6 (0.98)	101.7 (1.23)	671 (22.19)	636 (19.13)	736 (33.39)	681 (14.93)
	TT/CC	17	40.8 (1.08)	60.3 (1.31)	77.8 (1.23)	101.8 (1.46)	649 (18.98)	584^{a} (19.83)	800 (21.77)	678 (11.71)
	CT/AA	69	41.0 (0.62)	60.3 (0.67)	78.6 (0.60)	101.8 (0.54)	642 (14.68)	610^{b} (12.58)	770 (15.36)	674 (6.76)
	CT/CC	14	40.6 (0.89)	59.2 (0.55)	78.6 (0.94)	102.0 (1.25)	619 (29.59)	648 (28.08)	779 (36.58)	682 (17.92)
	CC/AA	28	40.3 (0.67)	60.1 (0.75)	79.4 (0.93)	102.9 (0.99)	642 (18.56)	661^{ab} (22.63)	779 (23.11)	694 (11.27)
	total	152								

C.G. = *IGF1 Sna*BI/*Tas*I combined genotypes, BWT = birth weight (kg), WT_{30}, WT_{60}, WT_{90} = body weight (kg) at the 1st, 2nd, and 3rd month of age, respectively, ADG = average daily body weight gain (g), B = birth

means within columns bearing small letter differ significantly at $P \leq 0.05$

fat content, which was the highest in individuals with the heterozygous *CT* genotype ($P \leq 0.05$). Siadkowska et al. (2006) who analyzed relationships between the *IGF1*/*Sna*BI gene polymorphism and selected production traits in the Polish Holstein-Friesian bulls and heifers showed an association between the feed intake, feed conversion, and the *CC* genotype ($P \leq 0.01$). The cows with the *CT* genotype were characterized by a higher daily milk yield, milk fat and protein content ($P \leq 0.01$). Similar results were obtained in other studies (Bonakdar et al., 2010; Mehmannavaz et al., 2010). Polasik et al. (2010) and Szewczuk et al. (2012) did not show any statistically significant association between the *IGF1*/*Sna*BI polymorphism and the milk performance traits in the Polish Holstein-Friesian cows.

IGF1/*Tas*I polymorphism

As a result of the electrophoretic separation of the digestion products for the *IGF1*/*Tas*I polymorphism, restriction fragments of 122 and 24 bp for the *AA* genotype, 146, 122, and 24 bp for the *AC* genotype as well as 146 bp for the *CC* genotype were observed (Figure 2). In the analyzed herd of Polish Holstein-Friesian cattle, the highest frequency for the *IGF1*/*Tas*I polymorphism was found for the *AA* genotype (0.6898). The studies by Zych et al. (2007) and Szewczuk et al. (2011) confirm a higher frequency of the *A* allele in the same breed of cows.

Calves with the *AC* genotype were always characterized by the highest BWT and the highest weight and ADGs in all the analyzed rearing periods. However, only at WT60, ADG 2–3 months and for the whole rearing period, differences were significant ($P \leq 0.05$). Association analyses between the *IGF1*/*Tas*I polymorphism and growth traits of calves have not been studied so far.

In the case of milk performance traits, it was found that the individuals with the *AC* genotype were characterized by the highest milk yield, milk protein and fat yields ($P \leq 0.01$). In other population, Szewczuk et al. (2011) showed that Polish Holstein-Friesian cows with the *CC* genotype of the *IGF1*/*Tas*I polymorphism in the 2nd and 3rd lactation were characterized by the higher milk productivity (+ 515 kg and + 463 kg, respectively) than individuals with the *AA* genotype ($P \leq 0.05$). Similar trends were observed for the milk protein

Table 4. Means and standard errors (in parentheses) for the analyzed milk production traits in Polish Holstein-Friesian cows with different *IGF1* gene variants

Polymorphism	Genotype or C.G.	*n*	Milk yield per lactation (kg)	Fat		Protein	
				kg	%	kg	%
IGF1/*Sna*BI	*TT*	51	7578^{A} (131.18)	305^{A} (6.57)	4.04 (0.06)	253^{A} (4.61)	3.33 (0.03)
	CT	105	7471^{B} (100.33)	303^{B} (4.15)	4.08^{a} (0.04)	249^{B} (3.22)	3.34^{a} (0.02)
	CC	35	8832^{AB} (144.67)	343^{AB} (6.42)	3.90^{a} (0.06)	290^{AB} (4.72)	3.26^{a} (0.03)
	total	191					
IGF1/*Tas*I	*AA*	129	7750^{A} (111.98)	311^{A} (4.34)	4.04 (0.04)	257^{A} (3.58)	3.32 (0.02)
	AC	24	8371^{AB} (262.40)	339^{AB} (13.18)	4.06 (0.08)	278^{AB} (7.93)	3.35 (0.05)
	CC	34	7659^{B} (130.18)	311^{B} (7.36)	4.08 (0.09)	254^{B} (4.56)	3.31 (0.04)
	total	187					
C.G.	*TT*/*AA*	24	7289^{A} (227.94)	300^{a} (10.92)	4.13 (0.11)	244^{a} (7.94)	3.35 (0.05)
	TT/*CC*	17	7863^{B} (156.75)	309 (8.51)	3.95 (0.10)	257 (5.50)	3.27 (0.06)
	CT/*AA*	69	7529^{C} (136.29)	303^{b} (5.42)	4.05 (0.05)	250^{b} (4.26)	3.33 (0.02)
	CT/*CC*	14	7250^{D} (175.12)	302^{c} (12.75)	4.17 (0.15)	245^{c} (8.04)	3.37 (0.06)
	CC/*AA*	28	8803^{ABCD} (167.91)	342^{abc} (7.05)	3.90 (0.07)	291^{abc} (5.20)	3.27 (0.04)
	total	152					

C.G. = *IGF1 Sna*BI/*Tas*I combined genotypes

means within columns bearing the same superscript letters differ significantly at $P \leq 0.01$ (capitals), $P \leq 0.05$ (small letters)

and fat content. However, no association was found between *IGF1* RFLP-*Tas*I and dairy production traits in the 1st lactation.

Combined genotypes

Despite the high numbers of individuals within each genotype, groups of analyzed polymorphisms made it possible to perform association studies for combined genotypes (Tables 3 and 4). Due to the low sample size in some created groups, four combined genotypes (*CT*/*AC* $n = 7$; *TT*/*AC* $n = 6$; *CC*/*AC* $n = 4$; *CC*/*CC* $n = 2$) were excluded from the further analysis. In the case of the body weight of young animals in the analyzed periods, no clear relationships between the parameters under discussion and genotype combination were found (see Table 3). Only in the period from the 1st to the 2nd month of age, significant differences ($P \leq 0.05$) in the daily body weight gains were observed. An association of the milk yield and the content of individual constituents in milk with the afore-mentioned genotype combinations was also determined. The highest yields of milk as well as fat and protein were found in cows with the *CC*/*AA* combination compared to other combinations (Table 4). This can confirm significance of the *CC* genotype of the *IGF1*/*Sna*BI polymorphism in shaping the variation of milk production traits in the analyzed population. Due to the low abundance of potentially the most wanted combination (*CC*/*AC*), this could not be confirmed statistically. In contrast, in the study performed by Szewczuk et al. (2012), where combination of the *IGF1*/*Sna*BI polymorphism and SNP within gene coding its receptor – *IGF1R* was utilized, the $IGF1R^{BB}/IGF1^{AB(CT)}$ genotype combination determined significantly ($P \leq 0.05$) higher milk yield per lactation compared to other combinations.

CONCLUSION

Insulin-like growth factor I is one of the main elements of somatotropic axis. Because of its significant function in the postnatal period and individual's life, it is a good candidate gene for genetic marker. In the association studies on the selected polymorphic sites with regard to calves in individual periods of their rearing, and then in the production period, certain relationships were found between individual genotypes and the growth and development of calves and their subsequent milk yield. The presented results suggest that the *IGF1* genotypes might be used to increase milk, protein, and fat yields with previously normal daily gains for the whole period of rearing. Cows carrying the *CC* genotype of the *IGF1*/*Sna*BI polymorphism and the *AC* genotype of the *IGF1*/*Tas*I polymorphism should be preferred in selection for improving these traits. However, selection on yield traits alone could decrease merit for traits with antagonistic genetic correlations with yield (Němcová et al. 2011). In addition, the results obtained in our study should be confirmed in larger numbers of cows of different breeds representing all possible genotypes and combined genotypes, especially with the *AC* genotype of the *IGF1*/*Tas*I polymorphism.

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Corresponding Author

Małgorzata Szewczuk, Ph.D., The West Pomeranian University of Technology, Department of Ruminant Science, Laboratory of Molecular Cytogenetics, Judyma 10, 71-460 Szczecin, Poland
Tel. +48 914 496 802, e-mail: malgorzata.szewczuk@zut.edu.pl