Animal Science Papers and Reports vol. 24 (2006) no. 3, 225-237
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Effect of polymorphism in *IGF-1* gene on production traits in Polish Holstein-Friesian cattle*

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(Received August 10, 2006; accepted September 13, 2006)

Associations were studied between *IGF-1* gene polymorphism and selected beef and milk production traits in Polish Holstein-Friesian (HF) cattle. The *IGF-1* genotype was determined in a total of 662 HF cows, heifers and bulls. In month 8 of life, on 213 young animals of both sexes the 28-days feed intake and conversion test was conducted. Moreover, growth rate and beef production traits were determined on 131 HF bulls slaughtered at the age of 15 months. Referring to *IGF-1* genotype also milk production traits were studied using performance data of 262 HF cows.
Significant differences were found between *IGF-1* genotypes in feed intake and feed conversion for growth. Animals carrying genotype *BB* consumed less dry matter, crude protein and energy per 1 kg body live weight gain than those of *AA* and *AB* genotypes. Moreover, the *BB* genotype appeared favourable for live weight gain during the test. The *AB* genotype was found positively associated with live body weight at slaughter, cold carcass weight, as well as weight of meat and fat in valuable cuts. Cows carrying *AB* genotype yielded daily more FCM and VCM milk and more milk fat and milk protein than those of *AA* and *BB* genotypes.

KEY WORDS: beef / cattle / gene polymorphism / *IGF-1* / milk traits

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. On the cellular level they act through membrane

*Financed by the Ministry of Science and Higher Education, grant PBZ-KBN-113/P06/2005/01 and by the Institute of Genetics and Animal Breeding, project S.I.2.2.

receptors [Baxter 1988]. There are two types of IGF receptors: IGF-R1 and IGF-R2. The former binds both IGF-1 and IGF-2, and in addition weakly binds insulin. The majority of mitogenic and growth-promoting activity of IGF-1 is mediated through IGF-R1. In blood, IGFs are bound to IGF-binding proteins (IGFBPs – 1-6) that can modulate actions of both factors [Ballard *et al*. 1989, Lackey *et al*. 1999, Schams *et al*. 1999]. The *IGF-2* gene is imprinted in mammals, and in most tissues its paternal allele is preferentially expressed [Wrzeska and Rejduch 2004].

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-long [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*. 2003].

In cattle the *IGF-1* gene was localized in chromosome 5 by Miller *et al*. [1991] and Bishop *et al*. [1991]. In all bovine tissues tested, the expression of IGF-1 class 1 transcript was higher than that of transcript 2. The expression of *IGF-1* was shown to be regulated both on the level of transcription and translation [Wang *et al*. 2003].

Due to their role in regulation of cell proliferation and animal growth the IGF-1 and its gene are considered as candidate markers for growth rate and meat production traits in cattle. Significantly higher IGF-1 level was detected in blood of beef type Simmental as compared to dairy Holstein cows. Moreover, a correlation was shown in both breeds between IGF-1 blood level and growth rate [Schlee *et al*. 1994, Sirotkin *et al*. 2000]. Associations between high blood level of IGF-1 and fast growth of cattle were also reported by others [Istasse *et al*. 1990, Yelich *et al*. 1996, Barash *et al*. 1998]. Such positive associations were denied by the results of Davis and Simmen [1997] and Ge *et al*. [2001], who found a negative correlation between IGF-1 level and body weight in Angus cattle.

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 STR (short tandem repeat) polymorphism in the 5'-flanking region, and the SSCP (single strand conformation polymorphism) in intron 3 of the *IGF-1* were reported by Kirkpatrick [1992, 1993]. 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*. 1994, 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-*SnaB*I [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-*SnaB*I 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-*Dpn*I in intron 5. However, the effects of these polymorphisms on beef or milk production traits were not investigated.

The aim of this study was to search for possible associations between a SNP (single nucleotide polymorphism), the C/T transition at position -472 (RFLP-*SnaB*I) in the 5'-noncoding region of the *IGF-1* gene and performance in milk and beef production of Polish Holstein-Friesian cattle.

Material and methods

Animals

The study of feed intake and conversion included 213 young Polish Holstein-Friesian (HF) bulls and heifers, sired by 30 HF bulls used in AI. The number of half-sibs varied from 3 to 9. The animals were fed *ad libitum* silage, hay and concentrate up to the age of 15 months. During month 8 of life both growth rate and feed conversion were investigated in a 28-day test during which the only feed used was the concentrate offered *ad libitum*. Two weeks of adaptation to concentrate feeding preceded the test. Body weight at start and at the end of the test was recorded. Moreover, recorded were the mean daily intake of energy, crude protein and dry matter, as well as INRA feeding units (UFV) and protein digested in the small intestine (PDI – INRA). Additionally, net energy and protein intake per kg live body weight gain were calculated. At the age of 15 months 131 bulls were slaughtered, after 24-hours fasting. The carcasses were chilled for 24 hours at 4°C. From the right carcass-sides the valuable cuts (round, shoulder, tenderloin, best ribs + fore ribs) were obtained and dissected into lean, fat and bone [Oprządek *et al*. 2001].

To study the relation between *IGF-1* genotype and milk production traits, 262 HF cows were randomly chosen from the Institute Farm herd yielding on average 8.300 kg milk/cow/year (4.01% fat and 3.45% protein). Only 4-5 cows were sired by one bull. During the whole period the cows were kept in loose barn with outside run. The animals were fed complete TMR (total mixed ration) diet consisting of corn silage, wilted grass silage and concentrates, supplemented with mineral and vitamin mixture, according to the INRA system, and were milked twice a day. Water was available *ad libitum*. Milk samples were taken from each cow once a month during three consecutive lactations, commencing with lactation I.

All procedures carried out with the use of animals were approved by the Local Ethics Commission, permission No 67/2001).

The differences between genotypes were evaluated with Duncan's test. The data were analysed by the SAS General Linear Model procedure [1999] using models shown below.

The association of feed conversion with the IGF-1 genotypes:

$$y_{ijkl} = \mu + Sex_i + G_j + YS_k + \beta(x_{ijkl} - x) + e_{ijkl}$$

where:

y_{ijkl} – mean value of the trait;
μ – general mean;
Sex_i – fixed effect of sex (i = 1,2);
G_j – fixed effect of genotype IGF-1 (j=1,2,3);
YS_k – fixed effect of year and season (k=1,..,10);
$\beta(x_{ijkl} - x)$ – regression on body weight at the age of 7 months;
e_{ijkl} – random error.

The association of carcass traits with the IGF-1 genotypes:

$$y_{ijkl} = \mu + o_i + G_j + YS_k + \beta(x_{ijkl} - x) + e_{ijkl}$$

where:

y_{ijkl} – mean value of the trait;
μ – general mean;
o_i – random effect of sire (i = 1,…,30);
G_j – fixed effect of genotype *IGF-1*(j = 1,2,3);
YS_k – fixed effect of year and season, (k = 1,…,9);
$\beta(x_{ijkl} - x)$ – regression on body weight at slaughter;
e_{ijkl} – random error.

The association of milk traits with the *IGF-1* genotypes:

$$y_{ijkl} = o_i + G_j + L_k + \sum(b_p DIM^p)_{ijkl} + e_{ijkl}$$

where:

y_{ijkl} – mean value of the trait;
o_i – random effect of sire (i = 1,…,83);
G_j – fixed effect of *IGF1*genotype (j = 1,2,3);
L_k – fixed effect of lactation (k =1,2,3);

$\sum(b_p DIM^p)_{ijkl}$ – regression on days between calving and milking (DIM), standardized and converted to Legendre polynomials (LPs) up to 4-th power (p=1,2,3,4);

e_{ijkl} – random error.

The fixed regression on milk yield was used.

DNA isolation from blood

Blood samples for DNA genotyping were collected from the jugular vein by an authorized veterinarian on K2EDTA and stored at -25°C for a few weeks, or at -80°C up to several months. The isolation of DNA from whole blood was performed according to Kanai *et al*. [1994].

***IGF-1* polymorphism**

Detection of restriction fragment length polymorphism (RFLP), based on the polymerase chain reaction (PCR), was carried out according to Ge *et al*. [2001]. The 249-bp fragment of the *IGF-1* gene was amplified using following primers:

forward:5'-ATTACAAAGCTGCCTGCCCC-3', and

reverse: 5'-ACCTTACCCGTATGAAAGGAATATACGT-3'.

The PCR was performed in a reaction volume of 10 μl containing approximately 100 ng of genomic DNA, 0.30 μM of each primer, 0.2 μM dNTPs and 0.8 units of Taq polymerase (PolGen, Poland). The PCR amplification cycles were: 94°C – 1 min, 64°C – 1 min, 72°C – 1 min (31 cycles).

The PCR was carried out in MJ Research PTC-225 Thermal Cycler. The PCR-amplified DNA fragment of the *IGF-1* was digested at 37°C for three hours with five units of *SnaB*I nuclease (NEW ENGLAND BIOLABS, USA). The digestion products were separated on 2% agarose (GIBCO-BRL, England) gels in 1 × TRIS-borate-EDTA (TBE) buffer. The gels were stained with ethidium bromide and visualised and scanned in FX Molecular Imager (Bio-Rad).

Results and discussion

Associations were searched between a SNP (single nucleotide polymorphism), the C/T transition at position -472 (RFLP-*SnaB*I) in the 5'-noncoding region of the *IGF-1* and meat and milk production traits in Polish HF cattle. The polymorphism in question was first reported in Angus cattle by Ge *et al*. [1997] as SSCP, and then identified as a C/T transition at position -472 relative to the start of transcription site (at position 512 bp upstream from the ATG codon; according to the GenBank sequence AF210383) – Ge *et al*. [2001]. As the C→T substitution creates a new *SnaB*I restriction site the polymorphism of interest can be analysed using RFLP techniques. Digestion of the 249 bp PCR product with the restriction *SnaB*I nuclease resulted in two DNA bands

(223 and 26 bp) for homozygote *AA* (TT) and three bands (249, 223 and 26 bp) for the *AB* (CT) heterozygote. The DNA amplified from homozygous *BB* (CC) animals remained undigested with *SnaB*I restrictase (Fig. 1).

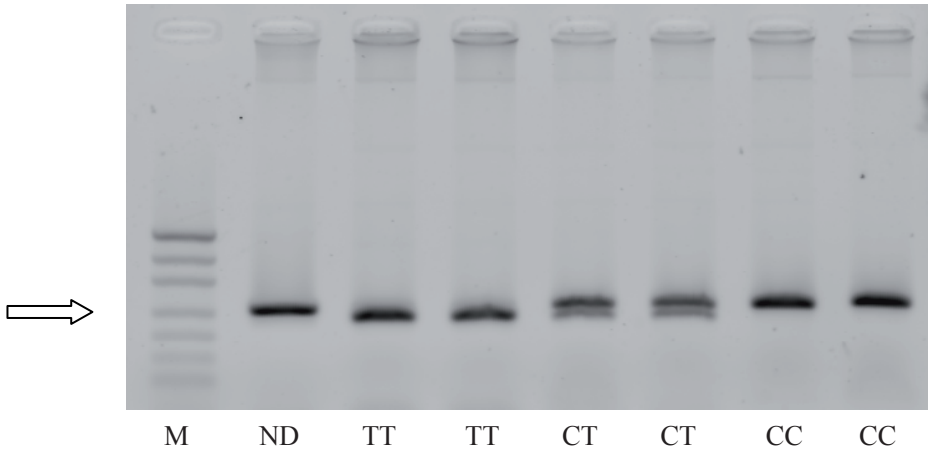

Fig. 1. Agarose gel electrophoresis showing RFLP-*SnaB*I in 5'-noncoding region of the bovine *IGF-1* gene – the C/T transition at position -472. M – DNA length marker (pUC19 *Msp*I digest -26-501 bp); ND – non-digested PCR product (249 bp; arrow); TT (AA); CT (AB); CC (BB) – *IGF-1* genotypes.

Using RFLP-*SnaB*I a cohort was genotyped of 662 Polish HF cattle – dairy cows, heifers and young bulls. The following genotype frequencies were estimated: *AA* (with nt TT) – 0.29, *AB* (nt CT) – 0.47, and *BB* (nt CC) – 0.24. The frequency of alleles *A* and *B* was 0.52 and 0.48, respectively (figures not tabulated).

The distribution of genotypes and alleles followed the Hardy-Weinberg rule – no differences were found between expected and estimated values (figures not shown).

Similar frequencies of alleles *A* and *B* at RFLP-*SnaB*I in the bovine *IGF-1* gene were found by Hines *et al*. [1998] who for a population of Holstein cattle reported the estimated frequency of *A* and *B* alleles amounting to 0.55 and 0.45, and by Li *et al*. [2004] for two commercial lines of dairy cattle – 0.56 and 0.44, respectively. However, as reported by Ge *et al*. [2001], in Angus cattle the frequency of both alleles was different – 0.64 for *A* and 0.36 for *B*.

The calculated associations between *IGF-1* genotypes and growth rate, feed intake and feed conversion during the test period (month 7-8 of life) are shown in Table 1. Significant inter-genotype differences were found. Animals of both sexes (young bulls and heifers) carrying the *BB* genotype consumed significantly less feed per live weight gain (as expressed as crude protein and dry matter) than those of the genotype *AB*. Moreover, the *BB* animals digested less protein in small intestine than animals *AB*, and consumed less UFV units for maintenance and meat production. Growth rates

in animals carrying the *BB* genotype were higher than in those of other genotypes, but the difference in the mean daily live weight gain was significant only between *BB* and *AB* genotype (P≤0.01).

Table 1. Least squares means (LSM) and their standard errors (SE) for growth performance parametres (month 8 of life) in young bulls and heifers as referred to *IGF-1* genotypes

Trait	Genotype					
	AA (n=49)		AB (n=103)		BB (n=61)	
	LSM	SE	LSM	SE	LSM	SE
Daily live weight gain (kg)	1.47	0.04	1.44^{A}	0.03	1.54^{A}	0.04
Dry matter intake (kg/kg gain)	4.37	0.11	4.58^{a}	0.08	4.27^{a}	0.1
Crude protein intake (kg/kg gain)	0.66	0.02	0.69^{a}	0.01	0.64^{a}	0.2
Protein digested in the small intestine – PDI (g/kg gain)	432.0	11	447.2^{a}	8.0	419.5^{a}	11
Feed units (UFV/kg gain)	4.55	0.11	4.72^{a}	0.08	4.44^{a}	0.11

n – number of animals.
^{aA}Within rows means bearing the same superscript differ significantly at: small letters – P≤0.05; capitals – P≤0.01.

Table 2. Least squares means (LSM) and their standard errors (SE) for meat production traits in young bulls as referred to *IGF-1* genotype

Trait	Genotype					
	AA (n=33)		AB (n=64)		BB (n=34)	
	LSM	SE	LSM	SE	LSM	SE
Live body weight at the age of 15 months (kg)	459.4	0.99	460.8^{a}	0.74	458.8^{a}	1.01
Cold carcass weight (kg)	232.3^{a}	1.2	235.4^{a}	0.9	233.1	1.2
Dressing percentage cold	52.7	0.27	53.2	0.20	52.8	0.27
Lean of valuable cuts (kg)	48.1^{a}	0.41	49.1^{a}	0.31	48.6	0.42
Fat of valuable cuts (kg)	8.84^{a}	0.40	9.75^{a}	0.32	9.69	0.4
Percent of valuable cuts of a carcass-side	62.46	0.30	62.31	0.24	62.32	0.30
Percent of fat of valuable cuts	12.56^{a}	0.44	13.36^{a}	0.35	13.38	0.44

n – number of animals.
^{a}Within rows means bearing the same superscript differ significantly at P≤0.05.

Associations between *IGF-1* genotype and meat production traits were estimated in 131 HF bulls (Tab. 2). The heterozygous *AB* genotype appeared superior in most of the traits measured, *i.e*. live body weight at slaughter (+2 kg compared to the *BB* genotype), cold carcass weight (+3.1 kg compared to *AA*), weight of lean in valuable cuts, weight of fat in valuable cuts, and per cent of fat in valuable cuts (P≤0.05).

As shown by Li *et al*. [2004] the *BB* genotype of *IGF-1* (with nucleotides CC) was associated with higher live body weight at weaning in commercial lines of *Bos taurus*. Significant associations of *IGF-1-SnaB*I genotypes with body weight and subcutaneous backfat, and nearly significant with *longissimus dorsi* muscle area, were shown by Curi *et al* [2006] in different genetic groups of beef cattle (including Zebu crosses), genotype *BB* appearing favourable compared to *AB*. Simultaneously, no significant associations were observed between polymorphism in question and live weight gain or dressing percentage.

In the present study the *BB* genotype was found favourable also for feed consumption and conversion. Moreover, the growth rate in bulls carrying the *BB* genotype was higher than in those of other genotypes.

Associations between RFLP-*SnaB*I in the *IGF-1* gene and milk traits were studied in a group of 262 HF cows. Results are shown in Table 3. No differences were found between genotypes in the daily milk yield. However, when milk yield was converted

Table 3. Least squares means (LSM) and their standard errors (SE) for daily milk yield and composition as referred to *IGF-1* genotypes

Trait	Genotype					
	AA (n=1460)		AB (n=2518)		BB (n=1271)	
	LSM	SE	LSM	SE	LSM	SE
Milk (kg)	23.2	0.26	23.0	0.21	22.5	0.27
FCM (kg)	20.86^{a}	0.106	21.17^{a}	0.085	21.12	0.108
VCM (kg)	25.59^{AB}	0.095	26.14^{A}	0.076	25.99^{B}	0.096
Total solids (g)	2737^{A}	10.23	2772^{A}	8.20	2761	10.42
Fat (g)	840.5^{Aa}	6.69	860.8^{A}	5.36	859.0^{a}	6.81
Protein (g)	745.3^{Aa}	2.77	759.8^{A}	2.22	754.5^{a}	2.83
Lactose (g)	1010	1.97	1010	1.58	1010	2.00
Total solids (%)	13.28^{AB}	0.033	13.50^{A}	0.027	13.43^{AB}	0.034
Fat (%)	4.12^{Aa}	0.027	4.26^{A}	0.021	4.21^{a}	0.027
Protein (%)	3.60^{AB}	0.012	3.67^{Aa}	0.009	3.65^{aB}	0.012
Lactose (%)	4.83	0.008	4.82	0.007	4.82	0.009

n – number of milk samples analysed.
^{aA}Means within rows bearing the same letters differ significantly at: small letters – P≤0.05; capitals – P≤0.01.
FCM – fat corrected milk (daily milk yield corrected for fat).
VCM – value corrected milk (daily milk yield corrected for fat and protein).

into FCM and VCM (fat or fat and protein corrected milk, respectively) the *AB* appeared superior to *AA* and *BB* cows. This was obviously due to the higher fat and protein content of *AB* milk. In most traits in question the cows of the heterozygous *IGF-1 AB* genotype appeared superior to those of remaining genotypes. They yielded daily significantly more fat (+20 g) and protein (+14.5 g) than cows carrying the *AA* genotype (P<0.01). The *AB* genotype also appeared favourable for fat and protein content of milk. The difference in protein and fat content between *AB* and *AA* cows reached 0.07 and 0.14 per cent points (pp), respectively (P <0.01). High fat and protein content of *AB* milks also resulted in high content of total solids, which was approximately by 0.2 pp higher in *AB* than in the other genotypes. No association was shown between *IGF-1* genotype of cows and lactose content of milk.

Hines *et al*. [1998] reported no association to exist between *IGF-1* gene RFLP-*SnaB*I and dairy production traits in Holstein cattle. No other papers were found in the literature concerning effects of *IGF-1* polymorphism on milk production traits.

In this report, a computer-aided analysis of the 75-bp fragment of the bovine *IGF-1* gene (from nt -518 to nt -443) containing the polymorphic C/T site performed with both the TESS programme and TRANSFAC database, showed the presence of several putative transcription-factor-binding sequences: Pit1a, PEA3, MCBF and REB1 (Fig. 2). However, none of them co-localized with the polymorphic site at position -472.

AAAATTTTGTGTTGGCTCTGGAATATAAAATTGCTCGCCCATCCTC**C/T**ACGTA

TAAAAT - Pit1a CATCCT - PEA3

TATTCCTTTCATACGGGTAAGGT

ATTCCT - MCBF CGGGTAA - REB1

Fig. 2. A computer-aided analysis of the 75-bp fragment of the bovine *IGF-1* gene (from nt -518 to nt -443) containing the polymorphic C/T site using the TESS programme and TRANSFAC database for the presence of putative transcription factor-binding sequences.

A common assumption in animal breeding is that variation in quantitative traits such as growth or lactation is controlled by many genes. Usually, each of these genes has a small effect. However, the major gene model suggests that few genes may account for a relatively large proportion of genetic variation. Genes involved in the biology of a trait of interest are candidates for association studies, and can be considered as "candidate genes". It was suggested that genes coding for hormones and factors of so-called somatotropic axis, including GH, its receptor GHR, transcription factor STAT5 (mediating actions of GH and prolactin), and insulin-like growth factors 1 and 2, fall into this category [Parmentier *et al.* 1999]. Earlier we showed associations between polymorphisms in the bovine GH, GHR, PIT1, and STAT5A genes and meat and milk production traits [Zwierzchowski *et al*. 2001, Grochowska *et al.* 2002, Flisikowski *et al*. 2003, Maj *et al*. 2004]. The present report shows an association

of the single nucleotide polymorphism in the 5'-noncoding region of the *IGF-1* gene with selected traits of beef production and milk yield and milk composition in Polish Holstein-Friesian cattle. The results speak for the superiority of the heterozygous *AB* genotype (with nucleotides CT at position -472) for milk yield and composition and carcass yield and quality, and of genotype *BB* (nucleotides CC) for growth rate and feed conversion indicators. The *AA* genotype either had no effect on traits under study (feed intake and conversion) or seemed unfavourable (carcass quality indicators, milk production traits).

Previously, strong QTLs for milk [Smaragdov *et al.* 2006] and meat [Casas *et al*. 2000, Macneil and Grosz 2002] production traits were assigned to BTA5, where the *IGF-1* gene is located. However, the C/T transition in the *IGF-1* 5'-noncoding region is obviously not the causative mutation for the traits under study because: (i) the genotype effect is relatively weak, (ii) the predominance of *AB* heterozygotes for most traits indicates that there is no genuine effect of *A* or *B* allele on the animals' performance, and (iii) no causative functional relationship between genotype and phenotype is expected since no co-localization was shown of the polymorphic site and transcription factor binding sequences. Rather, the C/T transition may be considered as a genetic marker, possibly linked to other polymorphism(s) located closely in the same or in another gene.

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Wpływ polimorfizmu genu *IGF-1* na wybrane cechy produkcyjne polskiego bydła holsztyńsko-fryzyjskiego

S t r e s z c z e n i e

Celem przeprowadzonych badań było określenie związku między polimorfizmem genu *IGF-1* a cechami produkcji mięsa i mleka przez bydło. Genotyp *IGF-1* określono u 662 osobników polskiej rasy holsztyńsko-fryzyjskiej (hf). Test żerności przeprowadzono wykorzystując 213 buhajków i jałówek w ósmym miesiącu życia. Użytkowość rzeźną określono na 131 buhajkach, a użytkowość mleczną z wykorzystaniem danych o 262 krowach.

Stwierdzono istotne różnice w wykorzystaniu paszy przez zwierzęta o różnych genotypach *IGF-1*. Zwierzęta o genotypie *BB* pobierały najmniej suchej masy, białka i energii na przyrost 1 kg masy ciała. Genotyp *BB* w *locus IGF-1* związany był wysokoistotnie z większym przyrostem dobowym w czasie trwania testu żerności, natomiast genotyp *AB* okazał się korzystny z punktu widzenia masy ciała przed ubojem, masy tuszy zimnej oraz masy mięsa i tłuszczu w wyrębach wartościowych. Krowy o genotypie *AB* charakteryzowały się lepszymi parametrami użytkowości mlecznej niż krowy o genotypach *AA* i *BB*. Cechowała je większa dzienna wydajność mleka i zawartość tłuszczu i białka w mleku, oraz większa dzienna wydajność mleka skorygowanego na zawartość tłuszczu (FCM) oraz białka i tłuszczu (VCM).