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### ANALYSIS OF SNPS *F279Y* AND *S555G* IN GROWTH HORMONE RECEPTOR GENE IN BEEF AND DAIRY CATTLE BREEDS

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**Summary.** Effect of growth hormone on animal growth and metabolism is mediated by interaction with the specific receptor (*GHR*). Marker-assisted selection programs in cattle include SNPs in *GHR* gene regarding their association with fertility and lactation performance. The aim was to analyze the relation between SNPs *F279Y* and *S555G* in *GHR* gene with growth traits in Aberdeen-Angus and to draw comparisons with beef and dairy cattle of other countries.

SNP genotyping was performed with PCR-RFLP methods. Statistical methods included Pearson's chi-squared test, Pearson's correlation coefficient  $r$  and ANOVA.

The allele and genotype frequencies of SNP *F279Y* (*rs385640152*; *g. 914T>A*) are:  $T$  — 0.69 and  $A$  — 0.31;  $TT$  — 62.1%,  $TA$  — 13.8% and  $AA$  — 24.1% ( $n = 58$ ); SNP *S555G* (*rs109300983*; *g. 257A>G*) are:  $A$  — 0.86 and  $G$  — 0.14;  $AA$  — 73.1%,  $AG$  — 25.0% and  $GG$  — 1.9% ( $n = 58$ ). Population is in Hardy-Weinberg equilibrium for *S555G*, contrary to *F279Y*. Animals with  $AA$ -genotype of SNP *F279Y* are characterized by the higher ADG (+40–100 g/day), as well as body weight at 8 month (+10–30 kg) and 2 years (up to +40 kg). In total dairy breeds group the frequency of  $T$ -allele in SNP *F279Y* negatively correlated with milk yield ( $r = -0.713$ ).

**Keywords:** Aberdeen-Angus breed, growth hormone receptor gene, SNP *F279Y*, SNP *S555G*

**Introduction.** Growth hormone (*GH*) is a major regulator of postnatal growth and metabolism in mammals, playing essential role in the fertility and lactation in cows (Hadi et al., 2015). Considering that *GH* exerts its effect due to binding with the growth hormone receptor (*GHR*) protein, structure modification of the receptor can affect all *GH*-mediated functions. Known SNPs *F279Y* and *S555G* in *GHR* gene were proved to be associated with milk performance traits and were included in ongoing marker assisted selection (MAS) for commercial purposes in a few countries (Fontanesi et al., 2007; Oleński, Suchocki and Kamiński, 2010).

*GHR* gene is located on BTA 20. SNP *F279Y* is a  $T>A$  transversion in exon 8, causing the replacement of a phenylalanine ( $F$ ) to tyrosine ( $Y$ ) in a highly conserved transmembrane domain of the *GHR* protein at position 279 (Fontanesi et al., 2007). The reactive hydroxyl group in aromatic ring of tyrosine decreases hydrophobic properties of the *GHR* protein (Viitala et al., 2006). The  $A$  allele of the SNP *F279Y* was shown to be associated with increase of milk yield and lactose content, and decrease

of fat, protein, casein content well as somatic cell score (SCS) in dairy cattle (Rahmatalla et al., 2011; Blott et al., 2003) and with an increase in taste panel-assessed odor (Gill et al., 2009). In beef breeds the SNP *F279Y* had shown no significant association with carcass or weight traits, but selection for  $TT$ -genotype was considered to be advantageous (Tait et al., 2014).

SNP *S555G* is the  $A$  to  $G$  substitution in exon 10 of the *GHR* gene, coding tiny glycine ( $G$ ) instead of serine ( $S$ ) in the *GHR* protein cytoplasmic domain at position 555. Exon 10 was considered to be the 'periphery' of conserved regions, suggesting that the variation does not necessarily have functional or structural importance (Viitala et al., 2006). The  $A$  allele of the SNP *S555G* was shown to have positive effect on milk performance traits — fat yield, protein yield and fat content in dairy breeds. (Oleński, Suchocki and Kamiński, 2010). The relation of SNP *S555G* to growth traits seems to be ambiguous (Waters et al., 2010).

Given the effect of two SNPs on milk performance traits, it is reasonable to assume that this SNP can affect

average daily gain (ADG) during the preweaning period. The aim of our paper was to analyze the relation between SNPs *F279Y* and *S555G* in *GHR* gene with growth traits in Aberdeen-Angus and compare with beef and dairy cattle of other countries.

**Material and methods.** The study object was Aberdeen-Angus breeding herd (n = 58; cows: n = 52, bulls: n = 6) bred at PE 'Agrofirma Svitanok', Kharkiv region, Ukraine. Evaluation of growth dynamics was conducted via the control weighing at 9 time points. Birth weight and ADG data for progeny (n=608; cows: n = 293, bulls: n = 315) of cows tested were included.

DNA was extracted from blood samples using DNA extraction kits 'Diatom DNA Prep 100' ('Isogene', RF). For the SNP genotyping, PCR-RFLP methods were set

up, using primer pairs (Viitala et al., 2006) and restriction endonucleases AluI and VspI ('Fermentas', Lithuania).

The deviation of allele frequencies from Hardy-Weinberg equilibrium was tested using Pearson's chi-squared test. Pearson's correlation coefficient *r* was used to measure the strength of association between two characteristics. Means for more than two groups was compared by ANOVA. The statistical hypotheses were tested on the significance level of 0.05 (Atramentova and Utyevskaya, 2008). The genetic distance between the population studied and data known from the literature was determined according Nei (1972).

**Results.** Allele and genotype frequencies of SNPs *F279Y* and *S555G*, growth traits in groups separated by SNPs *F279Y* and *S555G* for Aberdeen-Angus herd studied are given in Table 1.

**Table 1** — Allele and genotype frequencies and body weight dynamics in Aberdeen-Angus by SNPs *F279Y* and *S555G*,  $\bar{x} \pm s_x$

Parameter	<i>F279Y</i>			<i>S555G</i>		
	<i>T</i>	<i>A</i>		<i>A</i>	<i>G</i>	
Frequency	0.667	0.333		0.856	0.144	
Genotype	<i>TT</i>	<i>TA</i>	<i>AA</i>	<i>AA</i>	<i>AG</i>	<i>GG</i>
n	32	6	14	38	13	1
%	61.5	11.5	27.0	73.1	25.0	1.9
Body weight						
Birth	30.2±0.7	31.7±0.4	31.3±1.9	30.5±0.7	31.6±1.6	24
ADG, g/day	758±14*	718±33*	811±24*	767±14	782±23	814
8 month	211.2±3.9*	193.8±5.7*	222.5±7.3*	212.1±3.5	213.9±8.6	205
12 month	278.7±5.0	262.4±6.0	280.7±6.0	278.0±4.8	277.6±5.2	290
15 month	325.6±4.7	305.0±5.3	325.6±7.7	323.4±4.3	323.5±7.0	338
18 month	368.2±5.0	346.5±9.1	374.5±10.1	367.1±5.3	368.4±7.2	375
2 year	417.8±5.5*	385.2±3.3*	423.8±11.0*	417.8±5.3	410.3±10.5	427
3 year	443.7±6.9	424.7±10.3	461.9±14.5	449.8±7.2	446.9±14.8	450
4 year	484.0±7.4	462.0±1.7	497.1±16.0	490.2±8.0	476.9±14.9	500
5 year	570.9±16.6	652.5±30.0	522.1±15.3	569.3±14.9	586.0±34.3	565

Notes:  $\bar{x} \pm s_x$  — mean ± standard error; \* — differences are significant at  $p < 0.05$

For SNP *F279Y* we found the trend to body weight decrease in all time points  $AA > TT > TA$ . In *AA*-group ADG is significantly higher on 40–100 g ( $p = 0.045$ ), as well as body weight at 8 month ( $p = 0.026$ ) and 2 years ( $p = 0.032$ ). Number of animals in group with

genotype *GG* for *S555G* is very low, therefore it was excluded from the analysis. Differences between groups *AA* and *AG* were not more than 3% or 1–20 kg, therefore we observed no significant association for *S555G*.

Our findings are consistent with the results published before. *S555G* had no effect on slaughter weight, average daily gain and carcass weight (Sherman et al., 2008), no significant association with IGF-1 concentration, weight gain or off-test hip height (Ge et al., 2003). Therefore, *S555G* does not seem to be a useful marker for traits related to growth.

Preferred alleles for higher fat and protein are *T* and *A* for *F279Y* and *S555G*, respectively, therefore

we can suppose that this alleles are likely to be associated with better preweaning growth dynamics based on better nutritive value of the milk (Rahmatalla et al., 2011; Oleński, Suchocki and Kamiński, 2010). In this regard we studied progeny characteristics (Birth weight and ADG) in cows tested (Table 2). As bulls have higher birth weight and ADG characteristics, than cows groups were analyzed separately.

**Table 2** — Progeny ADG of Aberdeen-Angus cows tested for SNPs *F279Y* and *S555G*,  $\bar{x} \pm s_x$

Parameter	<i>F279Y</i>			<i>S555G</i>		
	<i>TT</i>	<i>TA</i>	<i>AA</i>	<i>AA</i>	<i>AG</i>	<i>GG</i>
All						
Birth weight, kg	28.9±0.2	28.3±0.7	29.3±0.2	28.9±0.2	28.8±0.3	30.3
ADG, g	743±5	749±11	753±10	750±5	736±9	727
Cows						
Birth weight, kg	28.1±0.2	27.3±0.4	28.3±0.4	28.0±0.3	28.0±0.4	29.0
ADG, g	718±9	739±1	743±10	727±9	724±11	767
Bulls						
Birth weight, kg	29.8±0.3	29.7±0.8	30.1±0.3	29.9±0.2	29.7±0.4	31.5
ADG, g	765±8	766±11	777±13	776±7	750±11	698

Note:  $\bar{x} \pm s_x$  — mean  $\pm$  standard error

Significant differences between groups within each SNP were absent. But observed trends for ADG in all groups indicate that *A*-alleles in both SNPs show higher values: *AA*>*TA*>*TT*, *AA*>*AG*>*GG*. *A*-allele of SNP *F279Y* associated with high milk yield and lower somatic cell score (Rahmatalla et al., 2011) and *A*-allele of SNP *S555G* associated with increased fat and protein content probably exert cumulative action in milk quality improvement assessed by ADG values.

Literature data for dairy and beef breeds worldwide are summarized in Table 3 below.

Almost all populations were in Hardy-Weinberg equilibrium, except Aberdeen-Angus group studied for *F279Y* and Holstein group for *S555G* (Hadi et al., 2015). Observed disequilibrium may be a consequence of an unbalanced heterozygous animals number. Essentially all populations within dairy or beef groups considered had similar allelic frequency distribution. Beef breeds

(Aberdeen-Angus, Auliekol, Kazakh White-headed, Beef breeds population) were tended to have lower frequency of *T*-allele by SNP *F279Y*, than dairy breeds.

All cattle groups are located in Northern hemisphere from 64°N to 32°N. Therefore, groups can be formed by location (different breeds, long-term selection within relatively small geographic zone) and by breed (as little literature data for each breed available, we considered two groups — beef and dairy breeds). Analysis failed to show the longitudinal pattern for allele frequencies by each SNP or combined. Considering the given frequencies, we assume importance of the geographic distribution, but it is rather determined by isolation and artificial selection in small groups, than by climatic zone. In general, we consider five groups: 'Western-European' (Germany, Italy, Romania), 'Eastern-European' (Poland, Ukraine), 'Northern-European' (Finland, Scotland and Ireland), 'American' (USA), 'Asian' (Iran/Karakhan for *S555G/F279Y*).

**Table 3** — Genotype and allele frequencies at SNPs F279Y and S555G in cattle populations worldwide by climate zones (longitudinal length)

Breed	Breed characteristics	Country	Longitudinal length	n	Genotypes, %				Alleles	HWE	Reference	D
					TT	TA	AA	T				
<b>GHR F279Y</b>												
Aberdeen-Angus	CLM = 500–700 kg BLM = 750–1000 kg BW = 16–25 kg	Ukraine	49°N	58	62.1	13.8	24.1	0.690	0.310	DE	Present study	-
Finnish Ayrshire	CLM = 500–540 kg BLM = 900–1000 kg BW = 32–36 kg Milk = 7400 kg F% = 4.36% P% = 3.36%	Finland	64°N	1528	-	-	-	0.890	0.110	-	Vitaita et al., 2006	0.059
Commercial beef breeds, Angus 50%	-	Scotland	55°N	438	76.0	21.0	3.0	0.870	0.130	E	Gill et al., 2009	0.05
Group (5 breeds) <sup>1</sup>	-	Ireland	53°N	22	75.0	23.0	2.0	0.870	0.130	E	Waters et al., 2010	0.05
Jersey	CLM = 400–500 kg BLM = 540–820 kg BW = 25–30 kg Milk = 7700 kg F% = 4.84% P% = 3.95%	Poland	52°N	209	74.0	23.0	3.0	0.850	0.150	E	Komisarek, Michalak and Walendowska, 2011	0.042
Holstein	CLM = 600–800 kg BLM = 1100–1200 kg BW = 32–42 kg Milk = 7340 kg F% = 3.6–3.9% P% = 3.1–3.2%	Germany	51°N	1370	69.1	28.8	2.1	0.840	0.160	E	Rahmatalla et al., 2011	0.038
Auliekol	CLM = 540–560 kg BLM = 950–1050 kg	Kazakhstan	48°N	50	-	-	-	0.900	0.100	-	Beyshova, Nametov and Terletskiy, 2016	0.063
Kazakh White-headed	CLM = 540–580 kg BLM = 850–950 kg BW = 27–30 kg	Kazakhstan	48°N	50	-	-	-	0.760	0.240	-	Beyshova, Nametov and Terletskiy, 2016	0.012
Romanian Black-and-White	CLM = 650 kg Milk = 8200–8700 kg F% = 3.93–4.12% P% = 3.28–4.65%	Romania	46°N	60	54.5	45.5	0.0	0.770	0.230	E	Carsai et al., 2013	0.015

Romanian Grey Steppe	CLM = 400–500 kg BLM = 650–850 kg Milk = 1400–2200 kg F% = 4.2–5.0% P% = 3.7–4.1%	Romania	46°N	60	100.0	0.0	0.0	0.0	1.00	0.000	-	Carsai et al., 2013	0.111
Italian Holstein Friesian	CLM = 600–700 kg BLM = 900–1200 kg BW = 38–48 kg Milk = 8000–9000 kg F% = 3.0–3.1% P% = 3.0%	Italy	43°N	108	50.9	43.5	5.6	0.727	0.273	0.005	E	Fontanesi et al., 2007	0.005
Italian Brown	LM = 650–950 kg BW = 45–50 kg	Italy	43°N	104	89.4	10.6	0.0	0.947	0.053	0.085	E	Fontanesi et al., 2007	0.085
Italian Simmental	CLM = 550–900 kg BLM = 850–1300 kg BW = 34–36 kg	Italy	43°N	104	82.7	16.3	0.1	0.909	0.091	0.067	E	Fontanesi et al., 2007	0.067
Jersey	CLM = 400–500 kg BLM = 540–820 kg BW = 25–30 kg Milk = 7700 kg F% = 4.84% P% = 3.95%	Italy	43°N	104	89.4	10.6	0.0	0.947	0.053	0.085	E	Fontanesi et al., 2007	0.085
Reggiana	CLM = 650–700 kg BLM = 900–1000 kg Milk = 5240 kg F% = 3.51% P% = 3.38%	Italy	43°N	108	88.0	8.3	3.7	0.921	0.079	0.073	E	Fontanesi et al., 2007	0.073
Modenese	CLM = 650 kg BLM = 1050 kg Milk = 4700 kg F% = 3.3% P% = 3.4%	Italy	43°N	66	84.8	15.2	0.0	0.924	0.076	0.074	E	Fontanesi et al., 2007	0.074
Rendena	CLM = 490 kg BLM = 500–600 kg Milk = 4733 kg F% = 3.5% P% = 3.36%	Italy	43°N	85	68.2	28.2	3.6	0.824	0.176	0.032	E	Fontanesi et al., 2007	0.032
Beefbreeds population 1 <sup>2</sup>	-	USA	40°N	556	2.5	18.0	79.5	0.115	0.885	0.583	E	White et al., 2007	0.583

Beef breeds population 2 <sup>3</sup>	Breed characteristics	USA	40°N	n	1.5	17.9	80.6	0.104	0.896	E	White et al., 2007	0.604
Breed	Breed characteristics	Country	Longitudinal length	n	AA	AG	GG	A	G	HWE	Reference	D
<b>GHR S555G</b>												
Aberdeen-Angus	CLM = 500–700 kg BLM = 750–1000 kg BW = 16–25 kg	Ukraine	49°N	58	73.1	25.0	1.9	0.855	0.145	E	Present study	-
Finnish Ayrshire	CLM = 500–540 kg BLM = 900–1000 kg BW = 32–36 kg Milk = 7400 kg F% = 4.36% P% = 3.36%	USA	40°N	472	-	-	-	0.780	0.220	-	Ge et al., 2000	0.006
Group (5 breeds) <sup>1</sup>	-	Finland	64°N	1528	-	-	-	0.870	0.130	-	Virtala et al., 2006	0.000168
Polish Holstein-Friesian	CLM = 600–700 kg BLM = 900–1200 kg BW = 38–48 kg Milk = 8000–9000 kg F% = 3.0–3.1% P% = 3.0%	Ireland	53°N	22	78.0	21.0	1.0	0.880	0.120	E	Waters et al., 2010	0.000485
Holstein	CLM = 600–800 kg BLM = 1100–1200 kg BW = 32–42 kg Milk = 7340 kg F% = 3.6–3.9% P% = 3.1–3.2%	Poland	52°N	872	74.9	23.2	1.9	0.865	0.135	E	Oleński, Suchocki and Kamiński, 2010	0.001
Piedmontese	CLM = 550–600 kg BLM = 700–850 kg BW = 30–45 kg	Germany	51°N	315	91.4	7.3	1.3	0.951	0.049	E	Hradecka et al., 2008	0.007
		Iran	32°N	150	30.0	70.0	0.0	0.640	0.360	DE	Hadi et al., 2015	0.061
		Italy	43°N	-	24.0	50.0	26.0	0.490	0.51	E	Di Stasio et al., 2005	0.22

Notes: CLW — cow live weight, BLW — bull live weight, BW — birth weight; HWE — Hardy-Weinberg equilibrium; E — equilibrium, DE — disequilibrium; D — Nei's genetic distance

<sup>1</sup> Group includes Simmental (n=4), Angus Holstein (n =4), Belgian Blue Holstein (n=6), Holstein (n=4) and Charolais (n=4)

<sup>2</sup> 7 most populous beef breeds in the United States (by annual registration): Hereford, Angus, Red Angus, Simmental, Gelbvieh, Limousin, and Charolais.

<sup>3</sup> Beefmaster, Brangus, Bonsmara, Romosinuano, Hereford, and Angus

Within each group we observe less variation of allele frequency, taking into account the cattle purposes — beef or dairy. The one correlation with the longitude observed for AA and AG genotypes of SNP S555G ( $r=0.834$  and  $r=-0.949$ ,  $p<0.05$ ) and for TT-genotype of the SNP F279Y in dairy breeds group ( $r=-0.751$ ,  $p<0.05$ ). In dairy breeds T-allele of the SNP F279Y negatively correlated with milk yield ( $r=-0.713$ ,  $p<0.05$ ). It is agreed with previously published data (Rahmatalla et al., 2011; Oleński, Suchocki and Kamiński, 2010). Therefore, intra-breed trends can be extended to international cattle population, but extra data are to be included. No trends for growth traits were observed. High percentage of animals with AA-genotype by SNP F279Y in American beef breeds population (White et al., 2007) are indirectly supported by our findings (pattern for live weight AA>TT>TA) or such high frequency of A-allele resulted from using in selection *Bos indicus* breeds; however, data on SNPs studied for any *Bos indicus* breeds are not available.

Nei's genetic distances were not powerful enough to indicate inter-breed differences, while the variation for each SNP was low. Within beef breeds group studied is close to Kazakh White-headed breed by SNP F279Y (Beyshova et al., 2016) and the highest differences, over 0.6, are observed for American population (White et al., 2007), having extremely low T-allele frequency.

**Conclusions.** The desirable allele A frequencies of SNP F279Y and S555G are 0.31 and 0.86. Population is in Hardy-Weinberg equilibrium for S555G, contrary to F279Y. Animals with AA-genotype of SNP F279Y are characterized by the higher ADG (+40–100 g/day), as well as body weight at 8 month (+10–30 kg) and 2 years (up to +40 kg). In total dairy breeds group the frequency of T-allele in SNP F279Y negatively correlated with milk yield ( $r=-0.713$ ).

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