

Part 1. Biology, biotechnology and genetics

UDC 575.113.1:636.223.1

ESTIMATION OF INBREEDING DEPRESSION BY CAPN1, CAST, GH, GHR AND CYP3A GENES FOR QUANTITATIVE AND REPRODUCTION TRAITS IN SEVEN ABERDEEN-ANGUS LINES

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Summary. High level of inbreeding has deleterious effects on animal productive and reproductive traits. The effect of inbreeding by *CAPN316*, *CAST282*, *GH L127V*, *GHR F279Y*, *GHR A257G* and *CYP3A28 C994G* markers on reproductive characteristics, weight dynamics (0–5 year age) and exterior traits was studied.

Genealogical analysis showed that population includes seven lines of cattle. For the SNP genotyping, PCR-RFLP methods were set up. Testing deviation from the Hardy-Weinberg equilibrium was performed using Pearson's chi-squared test. The estimation of inbreeding depression by F_{ST} coefficients for SNPs for traits studied was performed via multiple regression models with forward stepwise.

The tested population was analyzed in Herdy-Weinberg equilibrium for all SNPs, except *GHR F279Y*. Lines Bryalhil Sau and Southome Extra considered as the best lines showed the lowest level of heterozygosity. Negative effect of level of inbreeding for different markers were seen for regression coefficients calf birth weight = -1.08 ± 0.30 (*GHR F279Y*), body weight at 8 month = -0.71 ± 0.11 (*CAPN316*), -0.49 ± 0.11 (*GHR F279Y*) and 15 month = -0.54 ± 0.04 (*CAST282*), -0.36 ± 0.06 (*GHR F279Y*). Increased inbreeding had positive influence on regression coefficients for calf average daily gain = 0.86 ± 0.26 (*GH L127V*), weight at 8 and 15 month = 1.43 ± 0.13 , 1.05 ± 0.05 (*GHR A257G*) and exterior traits — shoulder, back and low back, rump and hindquarter = 1.09 ± 0.11 , 0.77 ± 0.22 , and 1.10 ± 0.30 (*CYP3A28 C994G*).

Keywords: Aberdeen-Angus breed, inbreeding, SNPs, *CAPN316*, *CAST282*, *GH L127V*, *GHR F279Y*, *GHR A257G*, *CYP3A28 C994G*

Introduction. Inbreeding has become the classical genetics practice problem since the beginning of the 20th century (Altukhov, 2003). It is defined as the probability that two alleles at any locus are 'identical by descent' and occurs when related individuals are mated (Mc Parland et al., 2008). Inbreeding increases the proportion of homozygous loci in the inbred organisms or population, which can increase the chances of offspring being affected by recessive or deleterious traits. Therefore, the offspring of closely related mates tend to have lower fitness and fitness-related characters because of increased risk of inheriting two copies of recessive deleterious alleles, which would expose the offspring to the full (normally hidden) deleterious effects of those alleles. This effect is called 'inbreeding depression' (Davis and Simmen, 2010).

In many human populations, inbreeding resulting from mating between known relatives is rare due to taboos. Nevertheless, significant positive correlation

of close inbreeding has been shown for diseases including CVS diseases — hypertension and heart disease, oncology diseases, mental disorders — schizophrenia and bipolar disorder (lifetime health problems: -0.29) (Verweij et al., 2014), monogenic genodermatosis — epidermolysis bullosa, ichthyosis ($r=0.99$), sensory system disorders and diseases — isolated neurosensory deafness ($r=0.728$) (Fedota, 2012) and significant decline in child cognitive abilities and mental retardation (verbal, performance and full scale IQ are -22.00 , -26.92 , and -24.47) (Farid and Afzal, 2014a). Children of inbred families either showed decline in mean value for height, weight and BMI (-7.318 , -6.590 , and -2.133 , respectively) (Farid and Afzal, 2014b).

In cattle breeding, the moderate level of inbreeding due to using of outstanding sires is considered to be powerful method for concentration of desirable characteristics and creating consistent breeds (Ruban,

Birukova and Basovskiy, 2013). Line breeding enables the perpetuation of founder's commercially valuable traits in progeny, but potentially leads to inbreeding depression in production traits (at high level of inbreeding), increased homozygosity of recessive genetic conditions and reduction in genetic diversity — loss of favorable alleles that may have existed for some traits. Considering the limited number of bulls' seed it is expected that level of inbreeding will increase in separate groups of animals. Some authors have reported that increased inbreeding of the animal is associated with significant reduced birth weight (Hinrichs et al., 2014; Burrow, 1993), post-weaning growth (Burrow, 1993; Davis and Simmen, 2014), milk yield -9.84 kg, fat yield -0.55 kg, fat% -0.0011% (Miglior, Szkotnicki and Burnside, 1992), protein yield -0.66 kg (Rokouei et al., 2010), reproduction traits — fertility (pregnancy rate -6.37%), increased dystocia +1.67% (Gonzalez-Recio, López de Maturana and Gutiérrez, 2007), decreased calving ease, stillbirth rate (Hinrichs et al., 2014) and exterior traits (Rokouei et al., 2010). Therefore, control of inbreeding in livestock populations is of great importance for prevention a rapid loss of genetic variation and adverse phenotypical effects associated with an inbreeding depression.

The aim of our study was to assess the level of inbreeding in 5 loci by SNPs *CAPN316* in calpain gene, *CAST282* in calpastatin gene, *L127V* in growth hormone (*GH*) gene, *F279Y* and *A257G* in growth hormone receptor (*GHR*) gene and *C994G* in *CYP3A28* gene associated with growth, productive, reproduction and exterior traits of commercial value in cattle.

Material and methods. The study object was Aberdeen-Angus breeding herd (n=68) bred at PE 'Agrofirma Svitanok' (Kharkiv region, Ukraine). The Aberdeen-Angus group studied is produced under Canadian selection and predominately includes animals belonging to lines: Bryalhill Sau, Ilinmera Leda, MacHery, Prospector, Raikina, Raimonda, Southome Extra (Kolisnyk et al., 2014). Reproductive traits assessed included weight at 1st calving, age at 1st calving, pregnancy length (P), calving interval (CI), interval between calving and conception (ICC), calf birth weight (CBW) and calf average daily gain (CADG), calculated for pre-weaning period. Evaluation of growth dynamics was conducted via the control weighing at birth, 8, 12, 15 and 18 months, two, three, four and five years age; ADG was calculated for pre-weaning period. Exterior traits were assessed annually until four year age with 100 point scale according 'Guidance on livestock judging of beef breeds' (Ministry of Agrarian Policy of Ukraine, 2002), including maximum scores for body constitution — 15, muscularity — 10, head and neck — 5, chest — 10, shoulder, back and low

back — 15, rump — 10, hind quarter — 10, udder — 15, and extremities — 10.

DNA was extracted from blood samples using DNA extraction kits 'Diatom DNA Prep 100' ('Isogene', Russian Federation). For the SNP genotyping, PCR-RFLP methods were set up, using appropriate primer pairs and amplification modes for *CAPN316* (Miquel et al., 2009), for *CAST282* (Schenkel et al., 2006), for *GH L127V* (Lee et al., 2013), for *GHR F279Y* (Viitala et al., 2006), for *GHR A257G* (Komisarek, Michalak and Walendowska, 2011) and for *CYP3A28 C994G* (Sales et al., 2011). Restriction enzymes used were endonucleases *RsaI*, *BtgI*, *AluI* and *VspI* ('Fermentas', Lithuania). The digested fragments were electrophoresed on 2.0% agarose gel.

The deviation of allele frequencies from Hardy-Weinberg equilibrium was tested using Pearson's chi-squared test. Population heterozygosity was estimated with F coefficient based on ratio between observed and expected heterozygosity indices for all SNPs tested (Zhivotovsky, 1991). The level of inbreeding was assessed by F_{IS} , F_{IT} , F_{ST} coefficients corresponding to measure of inbreeding for individual/subpopulation, individual/total population and subpopulation/total population (Altukhov, 2003). The estimation of inbreeding depression by F_{ST} coefficients for SNPs for traits studied was performed via multiple regression models with forward stepwise (Khalafyan, 2007). When compared three or more groups ANOVA was used. All values were tested on the significance level of 0.05, 0.01 and 0.001.

Results. Generally, population and each line (subgroup) was in Hardy-Weinberg equilibrium by all SNPs studied, except *GHR F279Y* for total population which showed significant disequilibrium ($\chi^2_{act.}=14.80$, $p<0.001$). The greatest contribution in disequilibrium by SNP *GHR F279Y* was observed for Ilinmera Leda ($\chi^2_{act.}=5.95$) and Southome Extra ($\chi^2_{act.}=5.33$) lines being considered as the best in preliminary genealogical study (Kolisnyk et al., 2014). The disequilibrium suggests that Aberdeen-Angus breeding herd analyzed is likely to be either under focused selection, stratification or inbred. SNP *GHR F279Y* was shown to be associated with milk quality traits (Komisarek, Michalak and Walendowska, 2011). Our results showed association of SNP *GHR F279Y* with dam reproductive characteristics for $CI-F_{act.}=3.3$, $CBW-F_{act.}=6.5$ and $CADG F_{act.}=6.1$, $F_{st.}=3.2$, $p<0.05$. Considering that effect of this is SNP is observed at initial stage of calf evaluation, present disequilibrium suggests that homozygotization increases: observed and expected number of heterozygous individuals are 11.5% and 22.9%. Moreover, both homozygous classes are generally superior by reproductive traits and weight dynamics than heterozygous one.

Genetic variation within population studied was measured with heterozygosity (Table 1). The highest observed frequency of heterozygotes were noted in Raikina and MacHery lines, but deviation factor values for these lines we low. High level of average heterozygosity could be expected to correlate with high levels of genetic variation. These lines showed unstable and inferior weight dynamics compared to other lines (Kolisnyk et al., 2014). Conversely, Bryalhill Sau and Southome Extra lines showed the lowest frequency of

heterozygotes — this circumstance would be indicative of isolation with the subsequent loss of unexploited genetic potential.

Level of inbreeding was characterized by calculation of the F_{IS} , F_{IT} and F_{ST} (Table 1). The highest inbreeding rate (F_{ST}) is observed in Ilinmera Leda line — the level indicating on inbreeding depression. Two lines showed low inbreeding rate suggesting that traits of commercial value are not affected (Gulisija, Gianola and Weigel, 2007).

Table 1 – Population genetics parameters of Aberdeen-Angus herd in Kharkiv region by line

Parameter	Aberdeen-Angus line							
	Bryalhill Sau (n=10)	Ilinmera Leda (n=13)	MacHery (n=9)	Prospectora (n=21)	Raikina (n=3)	Raimonda (n=3)	Southome Extra (n=9)	Total (n=68)
H_{obs}	0.28	0.37	0.42	0.31	0.44	0.39	0.30	0.34
H_{exp}	0.64	0.66	0.71	0.64	0.70	0.54	0.61	0.68
F, %	55.9	44.1	39.9	51.2	36.8	27.6	51.6	49.5
F_{IS} , %	4.7	7.7	-0.4	-3.4	-2.1	2.4	4.1	1.9
F_{IT} , %	3.8	0.6	-1.7	4.2	-0.6	-1.5	2.4	1.0
F_{ST} , %	13.8	27.5	13.1	19.0	3.8	7.3	15.4	14.3

Notes: Heterozygosity: H_{obs} — observed frequency of heterozygotes in the population, H_{exp} — expected frequency of heterozygotes in the population. F — deviation factor calculated as: $F=(H_{exp}-H_{obs})/H_{exp}$. Inbreeding assessment: F_{IS} — for individual relative to subpopulation, F_{IT} — for individual relative to total population and F_{ST} — for subpopulation relative to total population.

Table 2 – Multiple regression coefficients for reproductive characteristics in Aberdeen-Angus herd, $B \pm s_B$ (Beta $\pm s_{Beta}$)

Parameter	Aberdeen-Angus line						
	CAPN316	CAST282	GHL127V	GHR F279Y	GHR A257G	CYP3A28 C994G	Intercept
Weight at 1 st calving, kg	-75.88 (-0.43)	195.08 (1.22)	-113.98 (-0.86)	8.67 (0.06)	3.56 (0.02)	119.84 (1.00)	407.08
Age at 1 st calving, days	346.83 (0.33)	288.44 (0.30)	-846.66 (-1.07)	248.93 (0.29)	49.13 (0.06)	-116.44 (-0.16)	953.04
P, days	19.68±9.36 (1.12±0.53)	-8.69±8.51 (-0.55±0.53)	—	—	—	—	282.35±0.94 ‡
CI, days	—	—	—	-189.88±84.27 (-0.71±0.31)	—	—	465.07±14.64 ‡
ICC, days	157.37±110.26 (0.48±0.40)	—	—	-233.42±90.45 (-0.88±0.34)	—	—	175.51±17.34 ‡
CBW, kg	—	—	3.86±1.55 (0.70±0.28)	-6.39±1.76 * (-1.08±0.30)	4.30±1.72 (0.71±0.28)	—	28.50±0.24 ‡
CADG, kg/day	87.01±34.96 (0.58±0.23)	—	97.93±29.89 * (0.86±0.26)	-84.42±32.97 -0.68±0.27	—	—	729.10±5.46 ‡

Notes: * — significant at 0.05 level, † — significant at 0.01 level, ‡ — significant at 0.001 level

It is known that increasing of the inbreeding coefficient value is associated with a reduction of a number of economically important traits in cattle (Miglior, Szkotnicki and Burnside, 1992; Gulisija, Gianola and Weigel, 2007). To assess the influence of inbreeding by each SNP on cattle productive and performance characteristics multiple regressions analysis was performed (Tables 2–4).

Reproductive characteristics of the herd studied are considered to be stable for P, CI, ICC, CBW and ADG (Table 2). It was found negative effect of inbreeding for SNP *GHR F279Y* on CBW and positive effect for SNP *GH L127V* on CADG. CC-genotype of SNP *GH L127V* is associated with higher BW and milk characteristics (Lee et al., 2013) — last can support and justify increased CADG in CC homozygous cows.

Table 3 – Multiple regression coefficients for weight dynamics in Aberdeen-Angus herd, $B \pm s_B$ (Beta $\pm s_{Beta}$)

Parameter	Aberdeen-Angus line						
	<i>CAPN316</i>	<i>CAST282</i>	<i>GH L127V</i>	<i>GHR F279Y</i>	<i>GHR A257G</i>	<i>CYP3A28 C994G</i>	Intercept
AGD, g/day	-192.34 (-0.47)	-82.40 (-0,22)	209.46 (0,68)	-250.89 (-0,75)	447.06 (1,31)	-266.03 (-0,96)	753.99
Birth	—	—	—	9.34±5.25 (0.47±0.26)	—	9.77±4.35 (0.59±0.26)	25.72±0.94 ‡
8 month	-113.02±16.81 † (-0.71±0.11)	—	—	-64.27±13.94 * (-0,49±0.11)	189.80±17.44 * (1,43±0.13)	-12.41±10,76 (-0.11±0.10)	196.01±2.48 ‡
12 month	-113.69 (-0.60)	-16.35 (-0.10)	5.05 (0.04)	-38.08 (-0.25)	229.96 (1.47)	-58.01 (-0.45)	254.70
15 month	—	-91.28±7.41 † (-0.54±0.04)	16.26±7.80 (0.11±0.06)	-54.98±8.58 * (-0.36±0.06)	163.26±8.34 † (1.05±0.05)	—	292.36±1.39 ‡
18 month	9.31 (0.05)	-120.86 (-0.71)	69.22 (0.49)	-91.69 (-0.60)	144.19 (0.92)	-19.00 (-0.15)	339.78
2 year	-183.32 (-0.92)	34.02 (0.19)	79.58 (0.52)	-142.98 (-0.87)	244.96 (1.47)	-57.25 (-0.42)	388.19
3 year	-390.19±154.32 (-1.29±0.51)	222.44±119.38 (0.34±0.81)	—	-181.23±71.36 (-0.73±0.29)	388.27±91,87 (1.55±0.36)	—	398.80±12.22 ‡
4 year	-559.97 (-1.27)	284.41 (0.71)	183.61 (0.55)	-347.16 (-0.96)	552.70 (1.50)	-97.73 (-0.32)	433.67
5 year	450.65 (0.63)	-73.92 (-0.12)	—	469,41 (1.08)	-334.27 (-0.73)	-185.87 (-0.47)	473.93

Notes: * — significant at 0.05 level, † — significant at 0.01 level, ‡ — significant at 0.001 level

High level of inbreeding for SNPs *CAPN316*, *CAST282* and *F279Y* negatively correlated with weight until 15 month age, although increase of inbreeding in SNP *GHR A257G* positively correlated with body weight. First is supported by data on beef cattle that inbreeding of the individual has a consistent adverse effect on growth traits from birth to maturity and on maternal traits. More specifically, for every 1% increase in inbreeding coefficient a decrease of 0.06, 0.44, 0.69 and 1.30 kg in live weight at birth, weaning, yearling and maturity respectively. Additionally, inbreeding in the dam decreased weaning and yearling weights by 0.30 and 0.21 kg respectively

for every 1% increase in inbreeding coefficient, probably as a result of decreasing milk yield and reduced maternal value of the inbred dams. (Burrow, 1993). According Davis and Simmen (2010) increased level of inbreeding resulted in lower body weight and average daily gain mediated by IGF-I concentration in blood. The values of inbreeding coefficients in cows and calves (n=3243) were 4.20% and 6.82%, and there was an annual increase for these factors by 0.25% per year and 0.36% per year. The level of inbreeding in the population of the US Angus population was estimated to be in 1985 — 3.3%, in 1995 — 4.7%, in 1999 — 3.5%, and in 2003 — 4,2% (Saatchi et al., 2011).

Table 4 – Multiple regression coefficients for exterior traits in Aberdeen-Angus herd, $B \pm s_B$ ($\text{Beta} \pm s_{\text{Beta}}$)

Parameter	Aberdeen-Angus line						
	CAPN316	CAST282	GH L127V	GHR F279Y	GHR A257G	CYP3A28 C994G	Intercept
Body constitution	-1.78 (-0.36)	3.07 (0.68)	-1.16 (-0.31)	0.11 (0.03)	-0.22 (-0.05)	3.81 (1.13)	11.39
Muscularity	-1.23 (-0.54)	2.25 (1.08)	-0.85 (-0.49)	-0.49 (-0.26)	-0.55 (-0.29)	1.50 (0.97)	8.04
Head and neck	1.15 (0.58)	0.28 (0.15)	0.96 (0.63)	-1.00 (-0.61)	-1.14 (-0.68)	0.70 (0.51)	3.84
Chest	2.69±1.33 (0.63±0.31)	-	-	-1.24±1.11 (-0.35±0.31)	-1.87±1.39 (-0.52±0.39)	3.00±0.86 (1.03±0.29)	7.59±0.20 ‡
Shoulder, back and low back	-	-	-1.45±0.62 (-0.30±0.13)	-1.58±0.62 (-0.30±0.12)	1.17±0.62 (0.12±0.22)	4.74±0.49 * (1.09±0.11)	11.37±0.08 ‡
Rump	-	-	0.40±0.28 (0.38±0.26)	-0.78±0.25 (-0.69±0.22)	-	0.72±0.21 * (0.77±0.22)	7.99±0.04 ‡
Hind quarter	-	-	-1.61±0.99 (-0.49±0.30)	-	-	3.24±0.89 * (1.10±0.30)	8.17±0.14 ‡
Udder	-1.69 (-0.62)	0.25 (0.10)	-1.24 (-0.61)	0.09 (0.04)	0.29 (0.13)	1.87 (1.01)	12.52
Extremities	-	-	-	0.49±0.37 (0.39±0.29)	-	0.66±0.03 (0.63±0.29)	7.76±0.07 ‡
Total	-7.87 (-0.32)	9.87 (0.44)	-4.32 (-0.23)	-5.13 (-0.25)	1.21 (0.06)	19.09 (1.14)	78.78

Notes: * — significant at 0.05 level, † — significant at 0.01 level, ‡ — significant at 0.001 level

Exterior trait composition is considered to be characteristic for each breed; therefore the level of inbreeding had little influence on their performance. F_{ST} for CYP3A28 C994G positively correlated with shoulder, back and low back, rump and hindquarter size and condition.

Conclusion. The population studied is in Herdy-Weinberg equilibrium for all SNPs analyzed, except GHR F279Y. Lines Bryalhil Sau and Southome Extra considered as the best lines showed the lowest level of heterozygosity. Negative effect of level of inbreeding for

different markers were seen for regression coefficients calf birth weight — -1.08 ± 0.30 (GHR F279Y), body weight at 8 month — -0.71 ± 0.11 (CAPN316), -0.49 ± 0.11 (GHR F279Y) and 15 month — -0.54 ± 0.04 (CAST282), -0.36 ± 0.06 (GHR F279Y). Increased inbreeding had positive influence on regression coefficients for calf average daily gain — 0.86 ± 0.26 (GH L127V), weight at 8 and 15 month — 1.43 ± 0.13 , 1.05 ± 0.05 (GHR A257G) and exterior traits — shoulder, back and low back, rump and hindquarter — 1.09 ± 0.11 , 0.77 ± 0.22 , and 1.10 ± 0.30 (CYP3A28 C994G).

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