The effect of selected candidate genes on functional longevity of dairy cattle

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Introduction

Functional longevity is rapidly gaining importance as a selection criterion in dairy cattle. Therefore many scientists have analyzed its relationship with other characters routinely recorded in dairy cattle, such as reproduction traits (Sewalem et al. 2008), udder health traits (Neerhof et al. 2000), level of inbreeding (Sewalem et al. 2006) etc. Our study is focused on the question whether some genes, known to be involved into the physiological determination of milk production, also influence the risk of culling a cow irrespective of her performance level.

Material and methods

Animals. The analyzed data set consisted of 566 Polish Holstein-Friesian cows, daughters of 109 sires. The average number of daughters per sire was 5 and varied between 1 and 67. The cows had their production records in four herds. The distribution of cows among herds was not uniform, with 80% of cows (453) active in the same herd. 65% (368) of the cows were represented by uncensored records, with the average failure time of 1 173 days, varying between 32 and 3 168 days. The remainder of the cows comprised animals with records censored between the 292nd and 3 046th day, with the average censoring time amounting to 1489 days.

Genotypes. The cows were genotyped at 9 functional single nucleotide polymorphisms (SNP) located within 5 genes:

a) the butyrophilin subfamily 1 member A1 gene (BTN1A1, GeneID:282157) located on BTA23: P35Q (Seyfert and Lüthen 1998) and K468R (Taylor et al. 1996);
b) the acyl-CoA:diacylglycerol acyltransferase 1 gene (DGAT1, GeneID:282609) on BTA14: K232A (Grisart et al. 2002; Winter et al. 2002);
c) the leptin receptor gene (LEPR, GeneID:497205) on BTA3: T945M (Liefers et al. 2004);
d) the leptin gene (LEP, GeneID:280836) on BTA4: Y7F (Lagonigro et al. 2003), R25C and A80V (Konfortov et al. 1999), a C/T substitution at position -963 (Liefers et al. 2005);
e) the ATP-binding cassette sub-family G member 2 gene (ABCG2, GeneID:536203) on BTA6: Y581S (Cohen-Zinder et al. 2005).

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Trait. The analysed trait is the length of production life (LPL) defined as the number of days between the first calving and culling (uncensored records) or the last test day (censored records).

Data structure. For this data the following classes, corresponding to the Polish routine genetic evaluation model for functional longevity (National Research Institute of Animal Production, 2010) were considered: year×season - comprising years 1999 to 2009 and 2 seasons: April – September and October – March; lactation number×stage of lactation - comprising the first 5 and pooled later lactations and 4 stages of lactation (1-29, 30-179, 180-304, and >304 day of lactation); relative change of herd size from the current year to the next year at April 1st (<-50%, -50% to -30%, -30% to -10%, -10% to 10%, 10% to 30%, 30% to 50%, > 50%); classes of 305-day fat and protein yield levels relative to herd means, defined separately for the first and later lactations (<-50%, -50% to -40%, -40% to -30%, -30% to -20%, -20% to -10%, -10% to 0%, 0% to 10%, 10% to 20%, 20% to 30%, 30% to 40%, 40% to 50%, > 50%); monthly classes of age at first calving (<20, 21, 22, …, >40 month); 3 classes of SNP genotypes represented by two homozygotes and a heterozygote, respectively comprising the following genotype frequencies: 0.30/0.21/0.49 for P35Q, 0.72/0.02/0.26 for K468R, 0.14/0.36/0.50 for K232A, 0.01/0.80/0.19 for T945M, 0.92/0.00/0.08 for Y7F, 0.23/0.27/0.49 for R25C, 0.50/0.09/0.41 for A80V, 0.28/0.22/0.51 for a C/T substitution at position -963, and 0.97/0.00/0.03 for Y581S.

Statistical models. The analysis was performed using Survival Kit Version 3.12 (Ducrocq and Solkner 1998).The following sequence of functional longevity survival models based on Weibull hazard function was applied to the data:

M_1: $h(t) = h_0(t)\exp[ys(t) + sl(t) + hsize(t) + fat(t) + prot(t) + age]$

M_2-M_{10}: $h(t) = h_0(t)\exp[ys(t) + sl(t) + hsize(t) + fat(t) + prot(t) + age + SNP_i]$

M_{11}-M_{19}: $h(t) = h_0(t)\exp[ys(t) + sl(t) + hsize(t) + fat(t) + prot(t) + age + SNP_{-i}]$

M_{20}: $h(t) = h_0(t)\exp[ys(t) + sl(t) + hsize(t) + fat(t) + prot(t) + age +$
$\mathrm{P35Q} + \mathrm{K468R} + \mathrm{K232A} + \mathrm{T945M} + \mathrm{Y7F} + \mathrm{R25C} + \mathrm{A80V} + \mathrm{CTsub} + \mathrm{Y581S}]$

where $h_0(t)=\rho(t)^{\rho-1}exp[\rho\ log(\lambda)]$ represents a baseline Weibull hazard function with scale parameter λ and shape parameter ρ, $ys(t)$ is a time-dependent fixed effect of year-season, $sl(t)$ is a time-dependent effect of lactation number×stage of lactation, $hsize(t)$ is a time-dependent fixed effect of yearly herd size variation, $fat(t)$ and $prot(t)$ are time-dependent fixed effects of within herd-year-season classes of 305-day fat and protein production level, age is a time-independent fixed effect of age at first calving, SNP_i represents a time independent additive effect of a single polymorphism i ($i \in$ {P35Q, K468R, K232A, T945M, Y7F, R25C, A80V, a C/T substitution at position -963, and Y581S}), SNP_{-i} represents a time independent additive effect of eight of the polymorphisms excluding i.

Hypothesis testing. The hypothesis of interest was whether some of the considered polymorphisms influence the risk of cow's culling and was tested using the likelihood ratio test: $\lambda = -2\left[lnL\left(\hat{\beta}_0\right) - lnL\left(\hat{\beta}_1\right)\right]$, where $L\left(\hat{\beta}_0\right)$ and $L\left(\hat{\beta}_1\right)$ represent maximum of likelihood functions obtained under the more parsimonious and the less parsimonious model, respectively. In this analysis model parsimony is expressed by the number of polymorphisms considered, while the other model parameters remain the same for all the models.

Asymptotically, λ follows the χ^2 distribution with the degrees of freedom equal to the difference in the number of effects in the compared models.

Results and discussion

Table 1 summarizes model comparison procedure based on λ. Comparisons of the most parsimonious model M_1 with the nine models including a single polymorphism (M_2-M_{10}) as well as comparisons of the full model M_{20} with the nine models with one polymorphism excluded (M_{11}-M_{19}) remain in agreement showing that the only influential SNP is R25C located within the leptin gene. In particular, including the effect of R25C into the model resulted in the significant improvement of fit over the basic model with P=0.0286, while excluding the effect of this polymorphism from the full model resulted in the significantly decreased fit with P=0.0207. Relative risk of culling for cows with genotype TT is much higher than for individuals with the remaining two genotypes. In particular it is 3.14 times higher than for the heterozygous animals.

Table 1: P values of the likelihood ratio test (λ) for comparisons of different models

BTN1A1		DGAT1	LEPR	LEP				ABCG2
P35Q	K468R	K232A	T945M	Y7F	R25C	A80V	C/T	Y581S
no SNP vs. single SNP								
0.6895	0.9374	0.1486	0.6238	0.2173	0.0286	0.1014	0.1596	0.7446
one SNP excluded vs. all SNPs								
0.4631	0.2942	0.1941	0.7075	0.2393	0.0207	0.0527	0.1547	0.8540

Figure 1 summarizes relative risks of culling estimated for all the polymorphisms. It is worth noting that the highest risk differences between animals with different genotypes are observed for polymorphisms located within the leptin gene. Apart from the abovementioned R25C, also TT homozygotes at the Y7F substitution attribute 3.64 times higher risk of culling than the AA homozygotes and TT homozygotes at A80V have 1.83 times higher risk of culling that CC homozygotes. Differences in risks between different genotypes of polymorphisms within the other genes are much smaller.

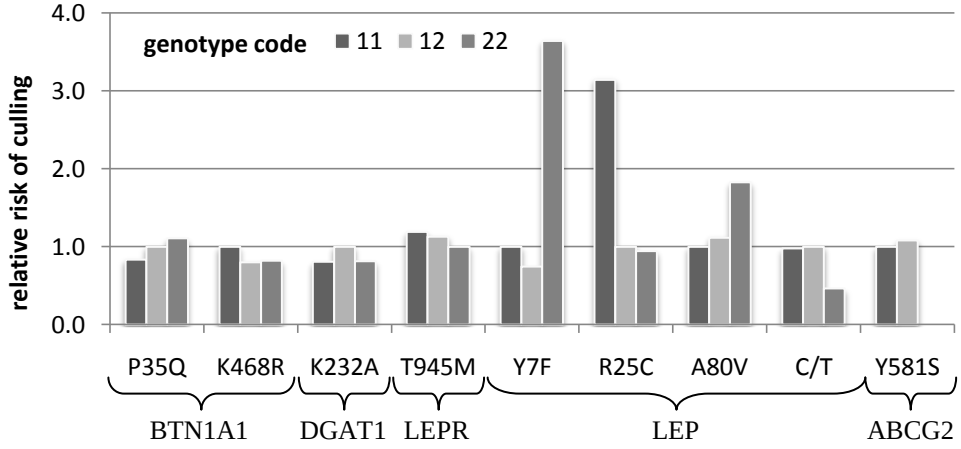

Figure 1: Relative risk of culling for different genotypes estimated based on model M_{20}

Many studies have found significant association of polymorphisms within the leptin gene with production traits (e.g. Banos et al. 2008), but studies analyzing the relation between LEP polymorphism and metabolism or health related traits, which may be components of functional longevity, are much less common and their results are contradictory to each other. Banos et al. (2008) failed to observe a significant association of LEP with body energy traits, but Liefers et al. (2002) reported a borderline significance of the effect of LEP on live weight and feed intake, Oikonomou et al. (2009) detected significant effects of LEP on body energy and blood metabolic traits, Chebel et al. (2008) observed significant associations of LEP with some health traits. The latter studies provide support for our results indicating association between LEP and functional longevity.

Conclusion

Our results indicate association between LEP and functional longevity and are supported by significant associations between LEP and functional and health traits observed in other studies. On the other hand, the reliability of our results is hampered by a moderate size of the data set. Still, in view of the growing importance of functional traits in dairy cattle, LEP polymorphisms should be considered as markers supporting selection decisions.

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